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FACULDADE DE MEDICINA
FUNDAÇÃO OSWALDO CRUZ – FIOCRUZ
INSTITUTO GONÇALO MONIZ

Curso de Pós-Graduação em Patologia Humana e Experimental

TESE DE DOUTORADO

DETERMINANTES CLÍNICOS E EPIDEMIOLÓGICOS DA SUSCEPTIBILIDADE À INFECÇÃO PELO *MYCOBACTERIUM TUBERCULOSIS* E DA RESPOSTA TERAPÊUTICA EM PACIENTES COM TUBERCULOSE

MARÍA BELEN ARRIAGA GUTIÉRREZ

Salvador – Bahia

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MARÍA BELEN ARRIAGA GUTIÉRREZ

Tese apresentada ao Curso de Pós-Graduação em Patologia como parte dos requisitos necessários para a obtenção do grau de Doutor.

Orientador: Prof. Dr. Bruno de Bezerril Andrade

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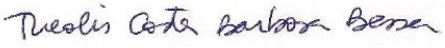

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À minha mãe Rosalía, no céu

Ao meu pai Néstor

Aos meus irmãos Julio, María e Néstor e

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RESUMO

INTRODUÇÃO: A tuberculose (TB), causada pelo bacilo *Mycobacterium tuberculosis,* ainda é um problema de saúde pública mundial. A transmissão da TB acontece pelo ar, quando a pessoa infectada expele os bacilos de Koch através da expulsão de gotículas de *Flügge*, pelo meio da fala, tosse ou espirro, ficando suspenso no ar e podendo ser inalado por outras pessoas. A pessoa exposta pode-se tonar doente ou com a infecção latente (ILTB). Através do tempo, diversas pesquisas e iniciativas no mundo tem sido feitas para controlar a TB, entre eles a Estratégia para o Fim da TB da Organização Mundial da Saúde, cujo objetivo é eliminar a TB até o ano 2035. Apesar da implementação da estratégia, o cenário para o continente americano não tem melhorado muito em razão do incremento da incidência dos casos de TB, sendo o Brasil e o Peru os países com maior carga da doença. A fim de melhorar o panorama atual, são necessários conhecimentos atuais e adicionais da TB para a implementação de novas abordagens nos sistemas de saúde. **OBJETIVO:** Identificar potenciais determinantes clínicos e epidemiológicos da susceptibilidade à infecção pelo *M. tuberculosis* e da resposta terapêutica em pacientes TB. **MÉTODOS:** Foram desenvolvidos onze manuscritos que conformam a tese. **RESULTADOS:** O primeiro estudo utiliza ferramentas estatísticas inovadoras para caracterizar a amostra da coorte do RePORT-Brasil e a compara com a população nacional brasileira de TB e identifica fatores associados aos desfechos desfavoráveis no tratamento anti-TB como o uso de drogas ilícitas, coinfecção por HIV e diabetes (DM) apenas na coorte do RePORT-Brasil. O rastreio de contactantes de casos TB e tratamento para ILTB são importantes para o controle da transmissão da doença, em um dos nossos trabalhos identificamos que não completar a cascata de acompanhamento de ILTB estava associado independentemente com o aumento da idade, baixo status socioeconômico e a coinfecção por HIV. Também demostramos mais uma vez que a DM está associada a um risco aumentado de desfechos desfavoráveis de tratamento, assim como da mortalidade em casos de TB pulmonar e comparamos esses resultados com os do SINAN-TB. Na coorte peruana achamos que a disglicemia persistente está associada também com desfechos desfavoráveis no tratamento. Adicionalmente, identificamos que a presença do HIV não afetou substancialmente a apresentação clínica em pessoas com TBDM. Adicionalmente, os contatos de pacientes com TB e pré-DM apresentaram maior risco de QuantiFERON positivo, no início do estudo e os contatos de pacientes TB-DM tiveram um risco aumentado de ter uma conversão (QuantiFERON negativo no início para positivo no mês 6). Na triagem de DM nos casos de TB, identificamos diferenças quanto aos valores de HbA1c e FPG para diagnóstico da DM nas coortes do Peru (achamos alta prevalência de DM e de pré-DM em casos TB) e do Brasil. Finalmente, na coorte do Peru, a disglicemia (DM e pré-DM) afetou a apresentação lesões pulmonares nos casos de TB e padrões alimentares foram identificados no perfil de ingestão alimentar dos participantes do estudo. **CONCLUSÕES**: Assim, os manuscritos que compõem a tese, adicionam informação relevante na identificação dos determinantes clínicos e epidemiológicos na infecção, transmissão e tratamento da TB, o que visa ser um suporte para a estratégias implementadas no sistema de saúde.

Palavras-chave: Tuberculose. Infecção latente. Transmissão. Tratamento. Resultados. Determinantes.

GUTIERREZ, María B. Arriaga. **Clinical and epidemiological determinants of susceptibility to *Mycobacterium tuberculosis* infection and therapeutic response in people with tuberculosis.** 287 f. il. Tese (Doutorado em Patologia Humana) – Universidade Federal da Bahia. Fundação Oswaldo Cruz, Instituto Gonçalo Moniz, Salvador, 2021.

ABSTRACT

INTRODUCTION: Tuberculosis (TB), caused by *Mycobacterium tuberculosis* is still a worldwide public health problem. The transmission of TB occurs through the air, when the infected person releases the bacilli of Koch through the expulsion of droplets of *Flügge*, through coughing, sneezing or speaking, being suspended in the air and being inhaled by other people. Thus, the exposed person can become sick or with latent infection (ILTB). Over time, several research and initiatives in the world have been carried out to control TB, among them The Strategy for the End of TB of the World Health Organization, whose objective is to eliminate TB by the year 2035. Despite the implementation of the strategy, the scenario for the American region has not improved much due to the increase in the incidence of TB cases, with Brazil and Peru being the countries with the highest burden of the disease. Current knowledge of TB is needed to implement new approaches in health systems. **OBJECTIVE:** To identify potential clinical and epidemiological determinants of susceptibility to *M. tuberculosis* infection and therapeutic response in TB patients. **METHODS:** Eleven manuscripts were developed that form the thesis. **RESULTS:** The first study uses innovative statistical tools to characterize the RePORT-Brasil cohort sample and compares it with the Brazilian national TB population, in addition to identifying factors associated with unfavorable outcomes in anti-TB treatment, such as the use of illicit drugs and co-infection with HIV and diabetes (DM) only in the RePORT-Brasil cohort. Screening contacts of TB cases and prophylactic treatment of those with ILTB are important for controlling disease transmission, we found that not completing the ILTB follow-up cascade was independently associated with increasing age, low socioeconomic status, and HIV co-infection. Furthermore, following the results of the first study, we demonstrated once again that DM is associated with an increased risk of unfavorable treatment outcomes, as well as mortality in patients with pulmonary TB, and we contrasted these results with those of SINAN. In the Peruvian court we find that persistent dysglycemia is also associated with unfavorable outcomes without treatment. Further, we also found that the presence of HIV did not substantially affect the clinical presentation in people with TBDM. Additionally, contacts of patients with TB and pre-DM were at risk of positive QuantiFERON at baseline and contacts of patients who had TBDM were at increased risk of having a conversion (QuantiFERON negative at baseline to positive at month 6). In screening for DM in TB cases, we identified differences regarding HbA1c and FPG values for the diagnosis of DM in the cohorts of Peru (where we found a high prevalence of DM and pre-DM in TB cases) and Brazil. Finally, in the Peru cohort, dysglycemia (DM and preDM) affected the presentation of lung lesions in TB cases and dietary patterns were identified in the food intake profile of the study participants. **CONCLUSIONS:** The manuscripts that make up the thesis add relevant information in identifying the clinical and epidemiological determinants of TB infection, transmission, and treatment, which aims to support strategies implemented in the health system.

Keywords: Tuberculosis. Latent infection. Transmission. Treatment. Results. Determinants.

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LISTA DE ABREVIATURAS

ADA	*American Diabetes Association (*Associacao Americana de Diabetes)
BAAR	Bacilos álcool-ácido resistentes
DPCTB	Dirección de Prevención y Control de la Tuberculosis (Diretoria de Prevenção e Controle da Tuberculose)
DECIT	Departamento de Ciência e Tecnologia
DM	Diabetes Mellitus
DOT	*Directly observed treatment* (Tratamento Diretamente Observado)
ESNPCT	Estrategia Sanitaria Nacional de Prevención y Control de la Tuberculosis (Estratégia Nacional de Saúde para a Prevenção e Controle da TB)
GPJ	Glicose plasmática de jejum
HbA1c	Hemoglobina glicada
HIV	Vírus da Imunodeficiência Humana
IGRA	*Interferon Gama Release Assay* (teste liberação do interferon-gama)
ILTB	Infecção latente por tuberculose
IQR	*Interquartile range*
IMC	Índice de massa corpórea
Mtb	*Mycobacterium tuberculosis*
OMS	Organização Mundial da Saúde
ONG	Organização Não Governamental
PCR	*Polymerase chain reaction* (reação em cadeia da polimerase)
PPD	*Purified protein derivative* (derivado proteico purificado)
Pré-DM	Pré- diabetes
RePORT	*Regional Prospective Observational Research in Tuberculosis*
Rx	Raio X
SCTIE	Secretaria de Ciência, Tecnologia e Insumos Estratégicos
SES	Socios en Salud
SINAN	Sistema de Informação de Agravos de Notificação
TB	Tuberculose
TDO	Tratamento diretamente observado (*DOT*)
TPT	Tratamento preventivo da tuberculose
TST	Tuberculin skin test (teste de tuberculina)

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1 INTRODUÇÃO

1. 1 A TUBERCULOSE: UM PROBLEMA DE SAÚDE PÚBLICA E UM DESAFIO PARA A CIÊNCIA

Em 24 de março de 1882, o Dr. Robert Koch anunciou a descoberta do *Mycobacterium tuberculosis* (Mtb), a bactéria causadora da tuberculose (TB) SAKULA (1979). Essa descoberta é considerada um dos eventos mais importantes para o controle e erradicação da doença (JAMES, 2005), pois foi assim que identificaram a TB com uma doença infecciosa.

Desde aquela descoberta, se passaram mais de 130 anos e numerosas e pesquisas foram realizadas para compreender melhor a TB e as suas repercussões na saúde pública mundial (PAI; BEHR; DOWDY; DHEDA *et al.*, 2016), como resultado dessas pesquisas, atualmente sabemos que, a TB, pode ser transmitida de pessoa a pessoa pelo ar através da expulsão de gotículas de *Flügge* de indivíduos com TB pulmonar ativa (CHURCHYARD; KIM; SHAH; RUSTOMJEE *et al.*, 2017; RILEY, 1983) e que, pessoas expostas à essas gotículas podem ser infectadas por Mtb. Ao entrar em contato com o bacilo o indivíduo pode se tornar doente imediatamente desenvolvendo TB ativa ou os bacilos podem persistir de forma latente sem causar sintomas por décadas, caracterizando a infecção latente pelo Mtb (ILTB) (ZELLWEGER; SOTGIU; CORRADI; DURANDO, 2020).

Pessoas com ILTB têm de 5% a 15% de chance de desenvolver os sintomas da doença (AHMAD, 2010). E, embora o órgão mais afetado na TB ativa seja o pulmão (SNOW; NELSON; SISMANIDIS; SAWYER *et al.*, 2018), outros sítios anatômicos podem ser potencialmente afetados como pleura, gânglios e trato gênito-urinário. Quando ocorre fora do parênquima pulmonar, a TB é caracterizada como extrapulmonar (KETATA; REKIK; AYADI; KAMMOUN, 2015).

A partir dos avanços científicos em relação à TB, foi possível implementar novas técnicas para diagnóstico e tratamento da doença. Assim, na atualidade a TB pode ser prevenida, tratada e curada (AHMAD, 2010; PAI; BEHR; DOWDY; DHEDA *et al.*, 2016). Porém, para o ano 2019, a TB figurava ainda entre as dez principais causas de morte e a principal causa de morte por um único agente infeccioso (acima do HIV / AIDS) (WORLD HEALTH ORGANIZATION, 2020a). Para o 2020, com a chegada da pandemia de Coronavírus – 2019 (COVID-19), os casos fatais aumentaram pela primeira vez em mais de

uma década, totalizando mais de 1,5 milhão de pessoas falecidas, e certamente é esperado que a tendência piore no 2021 e 2022 (WORLD HEALTH ORGANIZATION, 2021).

O Relatório Global da Tuberculose do ano de 2020 (WORLD HEALTH ORGANIZATION, 2020a) disponibilizado pela Organização Mundial da Saúde (OMS) mostrou que houve uma diminuição na taxa de incidência de casos notificados de TB entre os anos 2010 e 2019 no mundo. Contudo, houve um contraste com o continente americano, onde observou-se um incremento da incidência de TB (RANZANI; PESCARINI; MARTINEZ; GARCIA-BASTEIRO, 2021). Dos 46 países que são parte da América, o Brasil e o Peru são os que tem as maiores cargas da doença (pulmonar e extrapulmonar) (RANZANI; PESCARINI; MARTINEZ; GARCIA-BASTEIRO, 2021). Não é coincidência, então, que esses dois países também apresentem frequências elevadas de outros determinantes de risco para desenvolver TB como a diabetes (DM) (CALDERON; ARRIAGA; LOPEZ; BARREDA *et al.*, 2019; DUNCAN; COUSIN; NAGHAVI; AFSHIN *et al.*, 2020) e anemia (GELAW; GETANEH; MELKU, 2021; MACHADO; MALTA; BACAL; ROSENFELD, 2019) entre outros.

Essa tendência de crescimento de incidência tem um agravante, já que diferentes fatores podem influenciar para isso acontecer, como o impacto da doença por COVID-19 (KANT; TYAGI, 2021), incremento de doenças infecciosas e não infecciosas como comorbidades da TB (por exemplo: HIV (MORENO; RAVASI; AVEDILLO; LOPEZ, 2020) e diabetes (DUNCAN; COUSIN; NAGHAVI; AFSHIN *et al.*, 2020), correspondentemente) e adicionalmente o incremento das barreiras que impedem a universalização do atendimento à saúde (G B D UNIVERSAL HEALTH COVERAGE COLLABORATORS, 2020).

A OMS e outras iniciativas, através do tempo, implementaram diferentes estratégias para eliminar a TB (STOP, 2006; WORLD HEALTH ORGANIZATION, 2015). A Estratégia pelo Fim da Tuberculose (WORLD HEALTH ORGANIZATION, 2015) tem como objetivo acabar com a epidemia mundial da TB para o ano 2035 e consideraram-se três pilares fundamentais para conseguir esse propósito: (i) Cuidados e prevenção integrados e centrados no paciente, (ii) Políticas arrojadas e sistemas de apoio) e (iii) Investigação e inovação fortalecidas.

Adicionalmente, é necessário destacar a importância da criação de evidências científicas que obedeçam ao rigor científico em todas as suas etapas. Diante dessa necessidade, a OMS tem como grandes aliadas às redes internacionais de pesquisa, que respondem a determinados

objetivos. Na área da TB temos *Regional Prospective Observational Research for Tuberculosis* (RePORT)-Internacional (Brasil, Índia, África do Sul, China, Indonésia e Filipinas) (HAMILTON; SWAMINATHAN; CHRISTOPHER; ELLNER *et al.*, 2015), TANDEM (Peru, África do Sul, Indonésia, Romênia) (VAN CREVEL; DOCKRELL; CONSORTIUM, 2014), Epidemiologia da tuberculose multirresistente (EPI-Peru) (LUO; SULIMAN; ASGARI; AMARIUTA *et al.*, 2019), *The Caribbean, Central and South America network for HIV epidemiology* (CCASAnet) (MCGOWAN; CAHN; GOTUZZO; PADGETT *et al.*, 2007), *The International epidemiology Databases to Evaluate AIDS Southern Africa collaboration* (IeDEA-SA) (MCGOWAN; CAHN; GOTUZZO; PADGETT *et al.*, 2007).

Porém, apesar do progresso significativo na luta pelo controle da TB, os novos desafios precisam de maiores esforços em conjunto para conseguir a erradicá-la

2 REVISÃO DA LITERATURA

2.1 EPIDEMIOLOGIA DA TUBERCULOSE

A OMS através do Relatório Global da Tuberculose (WORLD HEALTH ORGANIZATION, 2020a) estimou que para o ano 2019, a TB foi a causa mais comum de morte por um único patógeno infeccioso. Mas para o ano 2020, a TB ficou como a décima terceira causa de morte e a doença infecciosa mais mortal, atrás da COVID-19. No 2020, 9,9 milhões de pessoas desenvolveram TB e houve cerca de 1,2 milhão de mortes por TB entre pessoas HIV-negativas e 214.000 mortes adicionais entre pessoas com vivendo com HIV (PVHIV). Do total de casos com TB, os adultos representavam 88.9% e as crianças menores de 15 anos, 11.1% (WORLD HEALTH ORGANIZATION, 2021).

No mesmo ano, a carga da TB estava concentrada nas regiões do Sudeste Asiático (43%), África (25%) e Pacífico Ocidental (18%), com porcentagens menores no Mediterrâneo Oriental (8,2%), Américas (3%) e Europa (2,3%). Oito países representam o 66% da carga total mundial de TB: Índia (26%), China (8,5%), Indonésia (8,4%), Filipinas (6,0%), Paquistão (5,8%), Nigéria (4,6%), Bangladesh (3,6%) e África do Sul (3,3%)(WORLD HEALTH ORGANIZATION, 2021).

Os países mais desenvolvidos economicamente, como a maioria dos países da Europa Ocidental, Canadá, Estados Unidos, Austrália e Nova Zelândia têm as taxas mais baixas de TB ativa, normalmente com menos de 10 casos por 100.000 habitantes por ano. Em contraste, os países de baixa renda apresentam taxas mais altas de TB (**Figura 1**).

A taxa de incidência mundial de TB está diminuindo, porém, não o suficiente para atingir a primeira meta da Estratégia pelo Fim da TB, uma redução de 20% entre 2015 e 2020 (WORLD HEALTH ORGANIZATION, 2015). No mundo, a redução cumulativa de 2015 a 2019 foi de 9% (de 142 a 130 novos casos por 100.000 habitantes), incluindo uma redução de 2,3% entre 2018 e 2019. A Região Europeia quase atingiu a marca de 2020, com uma redução de 19% entre 2015 e 2019, e a Região Africana tem avançou bastante, com redução de 16%. Reduções em outras regiões da OMS foram 3,5% na Região do Mediterrâneo Oriental, 8,7% na Região do Sudeste Asiático e 6,1% na região do Pacífico Ocidental. Na região das Américas que compreende 46 países, a incidência está aumentando lentamente, devido a tendência de alta no Brasil (WORLD HEALTH ORGANIZATION, 2015) e no Peru (RANZANI; PESCARINI; MARTINEZ; GARCIA-BASTEIRO, 2021).

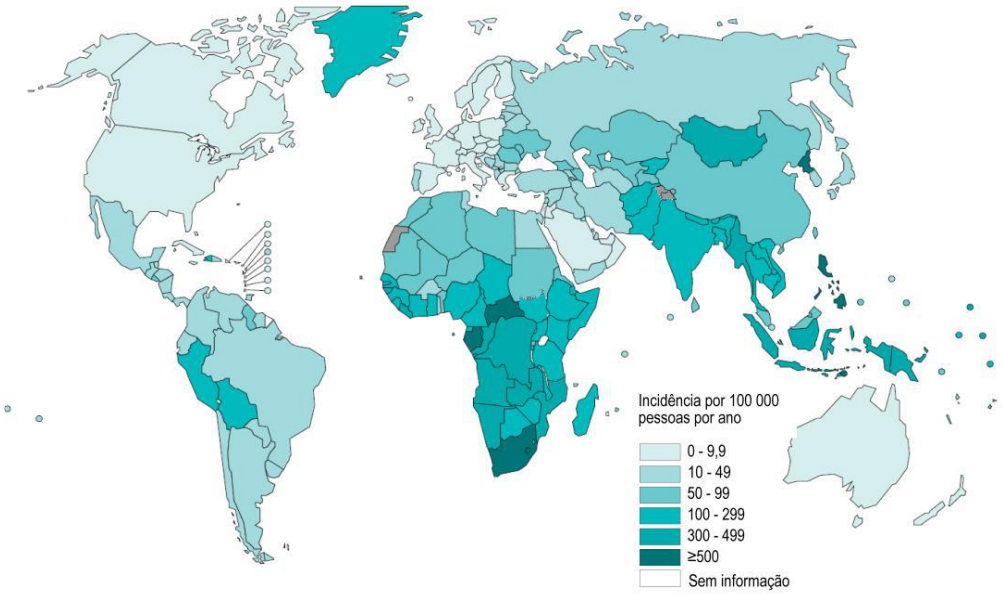


Figura 1 - Incidência global da tuberculose pulmonar e extrapulmonar para o ano de 2020
Fonte: Global Tuberculosis Report 2021(WORLD HEALTH ORGANIZATION, 2021).

2.2 PERFIL EPIDEMIOLÓGICO DA TUBERCULOSE NO BRASIL

Para o ano 2019, 73 864 casos novos de TB foram notificados o que significou um coeficiente de incidência de 37,4 casos por 100 mil habitantes (BRASIL. SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2020). Em 2020 o Brasil registrou 66.819 casos de TB, o que representa a 31,6 por 100 mil habitantes. (BRASIL. SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2021) Isso mostra uma queda atípica de 16% em relação ao ano 2019, o que estaria relacionado com a decorrência da pandemia de COVID-19. (BRASIL. SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2021)

Apesar de que entre os anos 2010 e 2106 houve uma tendência de queda na incidência, o coeficiente de incidência da TB no Brasil aumentou nos anos de 2017 e 2019. Nesses anos, houve uma tendência de queda na incidência entre os maiores de 65 anos, e de aumento na incidência nos menores de 10 anos e entre os de 10 - 64 anos (BRASIL. SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2020). No ano de 2018, a incidência de casos TB-rifampicina Resistente/ Multirresistente foi de 1,2. por 100.000 habitantes (PAN AMERICAN HEALTH ORGANIZATION, 2020).

Entre os anos 2015 e 2019 a apresentação da TB nos estados brasileiros foi heterogênea, porém, com o maior número de notificações de casos de TB foi identificado nos estados do São Paulo, Rio de Janeiro, Rio Grande do Sul, Pernambuco e Bahia (BRASIL.

SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2016; 2017; 2018; 2019; 2020). Para o ano 2020, mais casos do sexo masculino foram notificados (69%) e a forma mais frequente de TB foi pulmonar (BRASIL. SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2021).

Um estudo indicou que no Brasil, os profissionais de saúde pouco ou raramente se apropriam do regime de tratamento diretamente observado (TDO) como um instrumento para o controle e tratamento dos casos de TB, assim no ano 2019, dentre os casos novos de TB pulmonar, 41,9% foi realizado o TDO (OLIVEIRA BONFIM; LIMA FERREIRA; CABRAL SIQUEIRA; OLIVEIRA BARROS, 2021).

Os casos com a comorbilidade TB-HIV representaram 8.4% do total, sendo a porcentagem mais baixa desde o ano de 2010, além disso, a OMS reportou o Brasil dentro dos 8 países com maior carga de TB e carga de HIV (WORLD HEALTH ORGANIZATION, 2021). Por outro lado, no ano 2019 os casos de TB-DM chegaram ao 7.92%, (BARRETO-DUARTE; ARAUJO-PEREIRA; NOGUEIRA; SOBRAL *et al.*, 2021). Aqui existe a possibilidade de uma subnotificação dos casos, porque não existe uma conexão direta entre os dados dos programas de TB e DM no Brasil.

A taxa de mortalidade da TB caiu cerca de 8% nos últimos 10 anos, de forma que o número de óbitos variou de 4881 a 4490 entre 2008 e 2018 (BRASIL. SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2020). Assim, o coeficiente de mortalidade no 2018 foi de 2,2 óbitos/100 mil habitantes e nove estados apresentaram coeficientes de mortalidade por TB próximo ou superior ao coeficiente do Brasil, esses estados são: Amazonas, Rio de Janeiro, Pernambuco, Rio Grande do Sul, Pará, Maranhão, Rio Grande do Norte, Ceará e Acre (BRASIL. SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2020; 2021).

2.3 PERFIL EPIDEMIOLÓGICO DA TUBERCULOSE NO PERU

No 2019, foram notificados 32.970 casos de TB, com 36,8 casos novos de TB por 100.000 habitantes, esse número desceu para 28,5 no ano 2020 (DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS). Em 2016 a TB ocupava no Peru o 10° lugar entre as causas de morte e atingiu predominantemente as camadas sociais mais pobres das grandes cidades do pais (ALARCON; ALARCON; FIGUEROA; MENDOZA-

TICONA, 2017). A TB pulmonar foi o tipo de TB mais reportada com um 81,57% do total. Dos casos notificados de TB, 63,62% foram do sexo masculino 74% eram jovens ou adultos. As cidades peruanas com coeficientes elevados de incidência são: Loreto, Ucayali, Madre de Dios, Lima, Ica e Tacna (DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS). No ano 2018, a incidência de casos TB-rifampicina Resistente/ Multirresistente foi de 10 por 100.000 habitantes, sendo que o Peru é o país do continente americano com mais casos de TB resistente à rifampicina ou multirresistente (PAN AMERICAN HEALTH ORGANIZATION, 2020).

A Diretoria de Prevenção e Controle da Tuberculose (DPCTB), através da Estratégia Nacional de Saúde para a Prevenção e Controle da Tuberculose (ESNPCT) do Peru, informou que os óbitos durante o tratamento (por qualquer causa) em 2019 apresentaram uma incidência de 4,4 por 100.000 habitantes, sendo o coeficiente mais elevado nos últimos 5 anos (DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS). Em geral no ano 2019 houve um incremento dos casos de TB notificados, casos novos e na taxa de mortalidade quando comparado com os últimos 5 anos.

Em 2019, foram identificados 32.970 casos de TB, 1.464 correspondem a casos de TB multirresistente (MDR); enquanto 116 pertencem ao grupo de TB extremamente resistente (XDR)(DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS). Em 2018, o Ministério da Saúde do Peru conseguiu reduzir para 6% os casos de abandono de tratamento de tuberculose sensível; enquanto isso, para 2019, essa redução atingiu 3,6% (DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS).

No território peruano, no ano 2019 a proporção de pessoas com a comorbidade TB-HIV foi de 6.9% e no 2020 6.6% (DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS). E a proporção de casos TB-DM entre no ano 2019 foi de 9.9 e no 2020 foi de 11.9% (DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS ; UGARTE-GIL; CURISINCHE; HERRERA-FLORES; HERNANDEZ *et al.*, 2021). A tendência dessas comorbidades foi similar à do Brasil, a proporção de pessoas com TB-HIV diminuiu nos últimos 5 enquanto anos e a de TB-DM aumentou.

No Sistema de Informação de Gestão da Tuberculose (SIGTB) do Peru, observa-se que para o ano de 2017, 86,8% dos contatos identificados foram investigados para descartar a TB (DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS), esse percentual vem aumentando para o ano de 2018 (92,5%) e 2019 (93,4%). Dentro desta percentagem, são também considerados os contatos <5 anos, que em 2019 eram 6705 crianças, das quais 55,2%

receberam o tratamento preventivo para TB (TPT) (DIRECCIÓN DE PREVENCIÓN Y CONTROL DE LA TUBERCULOSIS).

2.4 2.4 TRANSMISSÃO E INFECÇÃO DA TUBERCULOSE

A TB é causada principalmente pela Mtb, mas existem outras microbactérias que podem causar a TB em humanos como por exemplo *M. bovis* e *M. africanum*. Nesta tese os estudos estão focados em Mtb. Diferentes autores descreveram o processo de transmissão do Mtb (MATHEMA; ANDREWS; COHEN; BORGDORFF *et al.*, 2017; RILEY, 1983; WELLS, 1934; YATES; KHAN; KNIGHT; TAYLOR *et al.*, 2016) e, ao longo do tempo, o progresso nas áreas da ciência melhorou a compreensão da transmissão do Mtb.

Indivíduos com TB pulmonar ativa expelem gotículas com Mtb ou aerossolização das gotículas (RILEY, 1983), colocando as pessoas expostas em risco de infecção. A aerossolização pode ser por meio da fala, espirros, tosse, entre outros. Alguns experimentos mostraram que após a aerossolização das gotículas, elas podem permanecer suspensas na corrente de ar até serem inaladas ou ventiladas externamente (FENNELLY; JONES-LOPEZ; AYAKAKA; KIM *et al.*, 2012).

O indivíduo susceptível pode ficar com uma infecção latente (ILTB), assintomática e não transmissível (MATHEMA; ANDREWS; COHEN; BORGDORFF *et al.*, 2017) e potencialmente pode desenvolver a doença no futuro. Alguns pacientes são portadores de TB subclínica, chamados assim porque tem a doença ativa com cultura positiva, mas são assintomáticos (BARRY; BOSHOFF; DARTOIS; DICK *et al.*, 2009).

Quando o bacilo é inalado, ingressa até os pulmões chegando ao espaço alveolar, onde os macrófagos alveolares atuam como a primeira linha de defesa (YATES; KHAN; KNIGHT; TAYLOR *et al.*, 2016). Se os bacilos não são eliminados, a bactéria invade o tecido pulmonar, seja pelos próprios mecanismos ou pelos macrófagos infectados. As células dendríticas e os monócitos quando infectados transportam a Mtb até os gânglios linfáticos pulmonares, onde consequentemente há uma mudança de microambiente com a liberação de citocinas que vão atrair as células T e B para o local, formando um granuloma (BARRY; BOSHOFF; DARTOIS; DICK *et al.*, 2009). As bactérias iniciam a replicação dentro do granuloma e, caso este seja rompido, as bactérias podem se espalhar para outros órgãos (PAI; BEHR; DOWDY; DHEDA *et al.*, 2016). Ao chegar à corrente sanguínea ou no trato

respiratório, o hospedeiro infectado se torna infeccioso, é um caso de TB ativa (PAI; BEHR; DOWDY; DHEDA *et al.*, 2016). **(Figura 2)**.

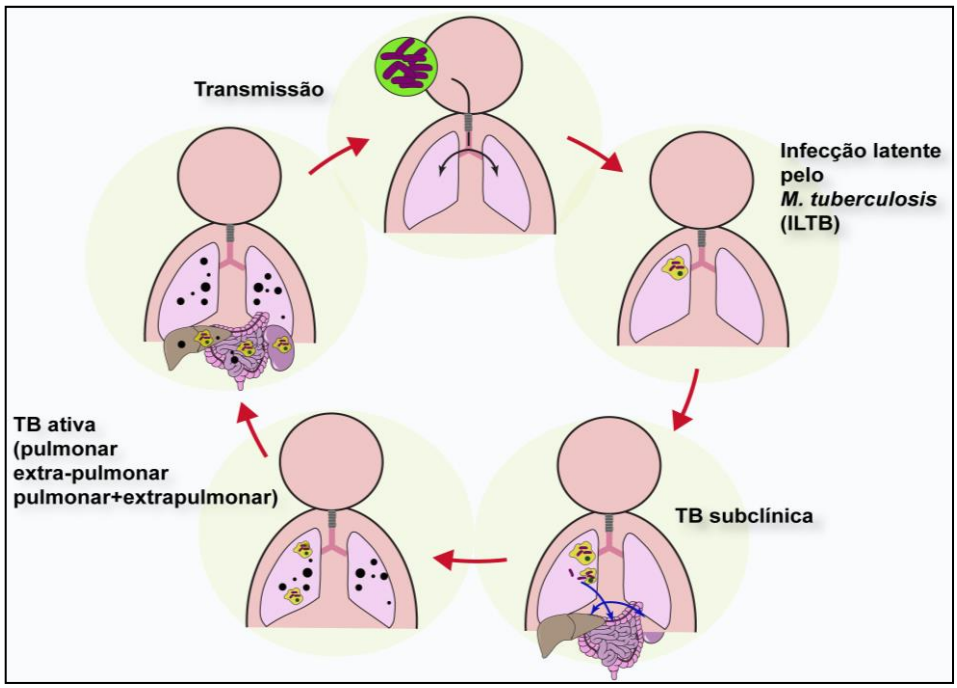


Figura 2 - Transmissão e infecção pela *Mycobacterium tuberculosis*
Fonte: Adaptação do esquema apresentado no artigo *Tuberculosis* (PAI; BEHR; DOWDY; DHEDA *et al.*, 2016). Abreviações: TB: tuberculose

O primeiro contato da Mtb com o hospedeiro leva a uma série de manifestações conhecida como TB primária. Na TB primária ou infecção inicial o foco da infecção é um granuloma subpleural acompanhado pela infecção granulomatosa dos linfonodos hilares, que quando agrupados formam o complexo de *Ghon* (ADIGUN; SINGH, 2021). Em quase todos os casos, esses granulomas controlam a disseminação da infecção, caracterizando a TB latente (ADIGUN; SINGH, 2021; KAWABATA, 1998). Uma pequena proporção de pessoas desenvolveria a doença ativa após a primeira exposição, esse caso é chamado de TB progressiva (ADIGUN; SINGH, 2021). A TB secundária é observada principalmente em adultos como reativação de uma infecção anterior (ou reinfecção), e em geral acontece após de vários meses ou anos desde a infecção primaria (KAWABATA, 1998). Geralmente, os lobos superiores do pulmão são os mais afetados e quando a inflamação granulomatosa é muito disseminada, há presença de cavitações (ADIGUN; SINGH, 2021; KAWABATA, 1998).

2.5 DETERMINANTES NA TRANSMISSÃO DA TUBERCULOSE

Vários fatores estão envolvidos no processo de transmissão da Mtb, entre eles a infecciosidade (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2019; MATHEMA; ANDREWS; COHEN; BORGDORFF *et al.*, 2017; PAI; BEHR; DOWDY; DHEDA *et al.*, 2016). Como foi mencionado antes, o indivíduo com TB ativa expulsa gotículas carregadas de Mtb, e alguns experimentos demostraram que indivíduos com TB pulmonar mais grave podem expulsar gotículas em maior número e contribuir mais com a transmissão (FENNELLY; JONES-LOPEZ; AYAKAKA; KIM *et al.*, 2012). Outro fator é a duração, proximidade e frequência de exposição do contactante ao paciente infeccioso, que acrescentam o risco de infecção (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2019).

O fator administrativo no sistema de saúde e a busca de atendimento do paciente têm um papel importante no tempo do diagnóstico e no início do tratamento, o que caso demorem aumentam a probabilidade de transmissão (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2019; PAI; BEHR; DOWDY; DHEDA *et al.*, 2016). Também estão os fatores ambientais que facilitam a transmissão, estar em espaços fechados, com pouca circulação do ar e insuficiente exposição à luz ultravioleta, que formam o lugar ideal para as partículas de ar contaminadas com Mtb (CENTERS FOR DISEASE CONTROL AND PREVENTION, 2019).

Além disso, outro fator é a susceptibilidade do hospedeiro que está condicionada pela imunidade. Para os indivíduos com ILTB sem fatores de risco adicionais, o risco de desenvolver uma TB ativa é de 5% nos primeiros dos anos após a infecção e quase 10% ao longo da vida (MATHEMA; ANDREWS; COHEN; BORGDORFF *et al.*, 2017). Nos indivíduos ILTB-DM é de 3 vezes maior ou 30% ao longo da vida (JEON; MURRAY, 2008) e no caso dos indivíduos com ILTB-HIV o risco varia entre 7% e 10% (CORBETT; STEKETEE; TER KUILE; LATIF *et al.*, 2002) Dentre os contatos menores de 5 anos de pacientes com TB ativa pulmonar, aqueles infectados por HIV têm maior risco de desenvolver TB (THOMAS, 2017). Outros fatores de risco no hospedeiro são o tabagismo (CHAN; KINNEY; HONDA; BISHWAKARMA *et al.*, 2014), consumo de álcool e drogas ilícitas

(NGUIPDOP-DJOMO; RODRIGUES; SMITH; ABUBAKAR *et al.*, 2020) e a desnutrição (KANT; TYAGI, 2021; MARTIN; SABINA, 2019) entre outros.

Apesar do grande número de investigações realizadas para o entendimento dos determinantes para infecção e desenvolvimento da TB, o conhecimento atual ainda não é suficiente para a erradicação da doença, de forma que existem fatores não estudados por completo como a influência comorbidades da TB, como a diabetes e hipertensão, assim como o uso de fármacos nos contactantes. Nesta tese exploramos mais detalhadamente essas associações.

2.6 O ESPETRO CLÍNICO DA TUBERCULOSE

2.6.1 O espetro clínico na infecção latente pela TB (ILTB)

A exposição à Mtb pode ter dois resultados: a eliminação da bactéria mediada pela resposta imunitária inata (o resultado do IGRA e TST podem ser negativos) ou a persistência como consequência da resposta imunitária adaptativa (IGRA e TST com resultado positivo ou negativo). Alguns indivíduos conseguirão eliminar a bactéria, mas conservarão uma forte resposta de células T de memória e serão TST ou IGRA positivos. Os indivíduos com ILTB e resultado positivo no IGRA ou TST em sua grande maioria não apresentam sintomas, tem escarro e cultura negativa e não são infecciosos, porém têm a recomendação de iniciar o TPT que consiste em 6 a 9 meses de isoniazida e máximo de 12 meses, o que reduz o risco de adoecimento de TB em 60% a 90% (BRASIL. SECRETARIA DE VIGILÂNCIA EM SAÚDE. MINISTÉRIO DA SAÚDE, 2016).

2.6.2 O espetro clínico da tuberculose pulmonar ativa

Estudos experimentais e estudos observacionais de pacientes com TB ativa são o suporte para compreender o espectro clínico da doença. Assim, os sinais e sintomas da TB dependem do lugar afetado. Pacientes com TB pulmonar ativa experimentam sintomas como tosse, produção de escarro, perda de apetite, febre, sudorese noturna, perda de peso e hemoptise (LAWN; ZUMLA, 2011). Também há achados de bacilos álcool-ácido resistentes (BAAR) nos exames de microscopia no escarro ou em amostra biológica. Adicionalmente, é

frequente encontrar anomalias nas radiografias de tórax, porém, no caso da radiografia esses achados não são específicos para TB (LODDENKEMPER; LIPMAN; ZUMLA, 2015). Na **Tabela 1**, são mostradas em resumo as características diferenciais no espectro clínico dos indivíduos com ILTB e TB ativa.

Tem sido relatado em muitas pesquisas o espectro da TB, mas ainda há um déficit na exploração do espectro clínico em pacientes que além da TB têm outras condições. Um claro exemplo são as pesquisas em pacientes com TB-DM, que revelam leves variações na apresentação das manifestações radiográficas (GIL-SANTANA; ALMEIDA-JUNIOR; OLIVEIRA; HICKSON *et al.*, 2016), Porém existem outros estudos com achados diferentes, onde houve uma piora das manifestações radiográficas em pacientes com a comorbilidade (KREISEL; PASSANNANTE; LARDIZABAL, 2019).

Tabela 1 - Características diferenciais no espectro clínico dos indivíduos com infecção pela TB (ILTB) e TB ativa.

Característica	Infecção tuberculosa (ILTB)	TB ativa
Sintomas	Não	Na maioria de casos tose, perda de peso, febre e sudoração noturna
Teste tuberculínico	Positivo	Geralmente positiva
Teste de liberação do interferon-gama (IGRA)	Positivo	Geralmente positiva
Baciloscopia em escarro	Negativa	Geralmente positiva
Radiografia de tórax	Normal	Geralmente anormal
Contagiosidade (Infecciosidade)	Não	Frequentemente sim (sem tratamento)
Caso de TB	Não	Sim
Tratamento recomendado	Tratamento preventivo da TB	Tratamento anti-TB

Fonte: Adaptado do artigo *Tuberculosis infection control in resource-limited settings in the era of expanding HIV care and treatment* (BOCK; JENSEN; MILLER; NARDELL, 2007). Abreviações: TB: tuberculose.

2.7 RESISTÊNCIA AOS FÁRMACOS ANTI-TB

Em 1948 foi a primeira vez que foi descrita a farmacorresistência durante um ensaio clínico em humanos, e desde aquela vez, tem sido descritas cepas resistentes. A resistência aos fármacos anti-TB pode-se apresentar (MINISTÉRIO DA SAÚDE DO BRASIL; SECRETARIA DE VIGILÂNCIA EM SAÚDE, 2013): i) resistência natural, que surge naturalmente no processo de multiplicação do bacilo, são resistentes sem ter sido exposto ao fármaco anti-TB; ii)Resistência primária, em pacientes nunca tratados para TB, contaminados por bacilos previamente já resistentes; iii) resistência adquirida ou secundária, em pacientes com tuberculose inicialmente sensível, que se tornam resistentes após a exposição aos medicamentos; iv) resistência cruzada, fenômeno conhecido que ocorre entre os grupos farmacológicos mais importantes no tratamento. Na prática por exemplo resulta que um caso de TB resistente à rifampicina tem uma chance superior à 80% de sê-lo também à rifabutina.

A resistência aos fármacos anti-TB é determinada com o uso de testes de sensibilidade que mostram que os isolados infectados de Mtb crescem in vitro na presença de um ou mais medicamentos anti-TB (SEUNG; KESHAVJEE; RICH, 2015) . A OMS classifica em quatro categorias de resistências aos fármacos anti-TB (SEUNG; KESHAVJEE; RICH, 2015):

- **Monorresistência:** Resistência à apenas um medicamento anti-TB.
- **Polirresistência:** Resistência à mais de um medicamento anti-TB, mas que não seja a combinação de isoniazida e rifampicina.
- **Tuberculose Multirresistente (TB-MDR):** Resistência à pelo menos isoniazida e rifampicina sem ou com combinação de resistência a outros medicamentos anti-TB.
- **Tuberculose Extremamente Resistente (TB-XDR):** Resistência a pelo menos isoniazida e rifampicina, a qualquer fluoroquinolona e a pelo menos um dos 3 medicamentos injetáveis de segunda linha (Amicacina, Canamicina ou Capreomicina).

A evolução das variantes da Mtb resistentes aos fármacos tem sido atribuída à implementação inadequada de medidas de controle, interrupção do fornecimento de fármacos, fármacos de baixa qualidade e falta de adesão dos pacientes entre outros. Entretanto, está cada vez mais claro que esses fatores por si só são insuficientes para explicar a evolução da resistência aos medicamentos na TB (CAMINERO, 2008).

2.8 MANEJO DA TUBERCULOSE

O manejo da tuberculose visa reduzir os casos de TB desde distintos pontos e estão dirigidos para a prevenção, controle e tratamento. Entre esses pontos estão a cascata do cuidado da ILTB, o diagnóstico da TB e o tratamento antituberculose.

2.8.1 Cascata de cuidado da ILTB

O manejo da ILTB é considerado uma das intervenções eixo para a eliminação da TB (ALSDURF; HILL; MATTEELLI; GETAHUN *et al.*, 2016). Está amplamente demostrado que a identificação dos contatos de pacientes diagnosticados com TB (busca ativa) poderia reduzir a reativação da TB que é responsável dos 80% de casos incidentes de TB (ALSDURF; HILL; MATTEELLI; GETAHUN *et al.*, 2016).

Para iniciar a cascata é necessário definir os contactantes dos pacientes diagnosticados com TB. Os contactantes são indivíduos (incluindo crianças) que compartilham espaço aéreo em casa ou outro ambiente com um paciente com TB pulmonar. O tempo e frequência varia em cada pesquisa, podendo ser maior a 15 horas na semana ou maior de 180 horas no total, durante o período infeccioso (aproximadamente desde 3 meses antes do caso TB ter uma cultura positiva no escarro) (REICHLER; KHAN; STERLING; ZHAO *et al.*, 2018).

O gerenciamento de ILTB é um processo complexo de várias etapas que inicia com a identificação dos potenciais indivíduos que deverão ser testados para diagnosticar ILTB, após disso e se tiver um resultado positivo no IGRA o TST, é recomendado começar e concluir o tratamento preventivo para TB. Este processo foi denominado cascata de cuidado de ILTB (ALSDURF; HILL; MATTEELLI; GETAHUN *et al.*, 2016).

2.8.2 **Diagnóstico da TB**

O diagnóstico oportuno rápido e confiável pode ajudar no controle da TB, mas isso pode ser afetado pelo retardo do paciente em procurar consulta médica ou o sistema de saúde. Vários fatores estão relacionados com o diagnóstico tardio, uma vez que os pacientes comparecem para o atendimento (STORLA; YIMER; BJUNE, 2008). Isso inclui a presença de comorbilidades pulmonares, sintomas menos graves, incluindo a ausência de hemoptise, tuberculose extrapulmonar, infraestrutura precária de saúde e a falta de ferramentas diagnósticas apropriadas (STORLA; YIMER; BJUNE, 2008). Além disso, as comorbidades como HIV, diabetes e a pandemia pelo COVID-19, dão novos desafios no diagnóstico da TB (VISCA; ONG; TIBERI; CENTIS *et al.*, 2021). Os países do Brasil e o Peru adotaram as recomendações da OMS (WORLD HEALTH ORGANIZATION. 2007A, 2015) para diagnostico de ILTB e para o diagnóstico de TB ativa (MINISTÉRIO DA SAÚDE DO BRASIL; SECRETARIA DE VIGILÂNCIA EM SAÚDE, 2013; MINISTERIO DE SALUD-PERÚ, 2013). Aqui um breve repasso pelos médios diagnósticos.

Para o diagnóstico de ILTB, a OMS (WORLD HEALTH ORGANIZATION, 2018) recomenda a realização do TST ou IGRA e a realização de radiografia de tórax em todos os casos, o diagnóstico considera os resultados: TST≥5mm: positivo para ILTB, PT<5mm: negativo para ILTB, IGRA: positivo, negativo ou indeterminado.

O TST com o recombinante derivado proteico purificado (PPD da sigla em inglês) atual (PPD IC-65) é apresentado em 1965 na Romênia e desde então é usado como ensaio in vivo para a vigilância da infecção por Mtb e o diagnóstico de TB.

Os estudos mostram que a eficácia do PPD IC-65 era igual ao PPD RT23, a tuberculina mais usada ao nível mundial para as preferências locais (SKJOT; OETTINGER; ROSENKRANDS; RAVN *et al.*, 2000). Os antígenos proteicos presentes no filtrado do cultivo de Mtb, inclua a proteína do filtrado do cultivo de 10 kDa (CFP10), a data do antígeno secretor temprano de 6 kDa (ESAT-6) e a proteína imunogênica MPT 64 (MPT64), que distinguem os pacientes com TB dos vacinados com BCG(SKJOT; OETTINGER; ROSENKRANDS; RAVN *et al.*, 2000). O TST é realizado pelo método de Mantoux, que consiste na administração de sobrino0,1 mL de PPD na região antebraço. Os resultados do teste são lidos dentro de 48 a 72 h após a administração de PPD.

O IGRA foi desenvolvido como alternativa ao teste cutâneo da tuberculina. Atualmente, o FDA (Food and Drug Adinistration) aprovou dois IGRAs comerciais para o diagnóstico de infecção por Mtb (HERRERA; PERRY; PARSONNET; BANAEI, 2011): o Teste QuantiFERON-TB Gold In-Tube (QFT-GIT) (Cellestis Limited, Carnegie, Victoria, Austrália, aprovado em 2007); Teste T-Spot (Oxford Immunotec Limited, Abingdon, Reino Unido, aprovado em 2008). Sangue total ou células mononucleares de sangue periférico (PBMC) são estimuladas com antígenos de Mtb e a liberação de interferon gama estimulada é medida (HERRERA; PERRY; PARSONNET; BANAEI, 2011). A OMS não recomenda o uso de IGRA em ambientes endêmicos ou para o diagnóstico de TB ativa (WORLD HEALTH ORGANIZATION, 2018).

A coloração de BAAR com o método Ziehl-Neelsen tem sido o eixo do diagnóstico da TB, é um método económico e tem uma sensibilidade para o diagnóstico de TB, em torno de 60 % (DAVIS; CATTAMANCHI; CUEVAS; HOPEWELL *et al.*, 2013), contudo a sensibilidade pode variar pela gravidade da doença, comorbidade como HIV ou o tempo desde que foi coletada a amostra (GETAHUN; HARRINGTON; O'BRIEN; NUNN, 2007). A OMS recomenda a coleta de pelo menos duas amostras de escarro consecutivas para o diagnóstico.

A cultura de micobactérias tem sido tradicionalmente realizada em meio sólido, geralmente Lowenstein-Jensen. A cultura tem maior sensibilidade que de BAAR no esfregaço, mas é requerido de 4 a 6 semana para ter um resultado, o que é uma limitante na utilidade já que não auxilia na decisão inicial de tratar o caso de TB (SHAW; WYNN-WILLIAMS, 1954). A cultura também pode diferenciar entre micobactérias tuberculosas e não tuberculosas, que são indistinguíveis ao microscópio (SHAW; WYNN-WILLIAMS, 1954).

O uso da técnica de reação em cadeia de polimerase (PCR) para diagnóstico da TB é das implementações mais recentes. O teste rápido molecular ou Gene XPERT detecta o ácido desoxirribonucleico (DNA) da Mtb, bem como a resistência à rifampicina. A pesquisa é feita em uma amostra de escarro, sendo o resultado disponibilizado em duas horas o que é uma grande vantagem (LAWN; NICOL, 2011). Em contraste ainda os estudos reportam diferentes sensibilidades, pode ser devido as coortes de estudo e protocolos de coleta (DAVIS; CATTAMANCHI; CUEVAS; HOPEWELL *et al.*, 2013), porém, a capacidade de detectar em menos tempo pacientes com esfregaço negativo leva que o início da terapia seja mais rápido, reduzindo o atraso de 56 para 5 dias (BOEHME; NICOL; NABETA; MICHAEL *et al.*, 2011).

2.8.3 **Tratamento antituberculose**

Junto com o diagnóstico da TB, o início oportuno do tratamento interromperá o ciclo de transmissão da TB, também reduzirá as taxas de morbidade e mortalidade. No entanto, o tratamento não é livre de complicações. Isso é mais evidente no tratamento da tuberculose associada ao HIV (GOPALAN; CHANDRASEKARAN; SWAMINATHAN; TRIPATHY, 2016), onde há consideráveis interações medicamentosas entre os antirretrovirais e os medicamentos antituberculose, e um risco aumentado de desenvolver doenças mais graves.

2.8.4 **Tratamento para ILTB**

O tratamento para ILTB é considerado um componente fundamental na Estratégia para o Final da TB (WORLD HEALTH ORGANIZATION, 2018). De acordo com as diretrizes da OMS, o tratamento para ILTB é recomendado para grupos específicos com risco de progressão para TB ativa (WORLD HEALTH ORGANIZATION, 2018). Nos países de baixa e mediana renda é indicado o tratamento em:

- Pessoas infectadas pelo HIV;
- Menores de 5 anos de idade que têm contato com casos de TB ativa;

- E pessoas que após avaliação clínica apropriado, a TB ativa está descartada, mas apresentam ILTB.

Os tratamentos recomendados pela OMS para ILTB são:

- Isoniazida por 6 meses ou isoniazida por 9 meses, ou;
- Rifapentina mais isoniazida semanalmente por 3 meses, ou;
- Isoniazida mais rifampicina por 3 a 4 meses ou rifampicina sozinha por 3 a 4 meses.

No Brasil, a indicação de tratamento da ILTB depende do resultado do TST ou do IGRA, idade (crianças menores de 10 anos de idade, contatos de casos de TB pulmonar), probabilidade de ILTB e risco de adoecimento e pessoas infectadas com HIV(MINISTÉRIO DA SAÚDE DO BRASIL; SECRETARIA DE VIGILÂNCIA EM SAÚDE, 2013). Os esquemas indicados para ILTB são: isoniazida por 6 ou 9 meses e rifampicina por 4 meses (MINISTÉRIO DA SAÚDE DO BRASIL; SECRETARIA DE VIGILÂNCIA EM SAÚDE, 2013)

No Peru o esquema recomendado e baseado apenas com isoniazida durante 6 meses em contatos de casos de TB pulmonar menores de 5 anos, pessoas entre 5 e 19 anos com TST igual ou maior a 10 mm, pessoas com infecção por HIV e conversão no TST em pessoal de saúde e população privada de liberdade (MINISTERIO DE SALUD- PERÚ, 2013). Em pessoas com infecção por HIV o tratamento com isoniazida é por 12 meses acompanhado de piridoxina (MINISTERIO DE SALUD- PERÚ, 2013).

2.8.5 **Tratamento para TB ativa**

Atualmente os medicamentos para o tratamento da TB, segundo a proposta da OMS, estão classificados em 4 grupos. No Grupo 1, os fármacos de primeira linha (pela eficácia e boa tolerância), No Grupo 2, os fármacos injetáveis, no Grupo 3, fármacos de segunda linha (usados em caso de TB resistente de forma prolongada), e no Grupo 4, medicamentos sem uma função clara no tratamento de TB MDR.

Embora esses regimes sejam amplamente aplicáveis, o tratamento deve ser sempre individualizado com base na situação clínica de cada paciente. Nestas considerações é importante conhecer o peso e a idade dos pacientes, para a indicação das doses dos fármacos.

Existem outros fatores que regulam a efetividade do tratamento, como:

a) A administração do tratamento;

b) Seguimento e avaliação do tratamento;

c) Aderência ao tratamento anti-TB, A terapia da TB requer uma adesão elevada (> 90%) para facilitar a cura. Boa aderência resulta na ausência de descumprimento do tratamento.

Tratamento diretamente observado (DOT da sigla em inglês), o componente DOT é uma tentativa de melhorar a aderência através da monitorização ativa e do registo do consumo de cada dose de fármaco por um "observador" aceitável para o paciente. Para o sistema de saúde tem sido amplamente utilizada como padrão de prática em muitos programas de tuberculose. O DOT foi significativamente associado com o sucesso do tratamento melhorado (a soma dos pacientes curados e os pacientes que completaram o tratamento) e com o aumento da conversão.

a) Uso de doses fixas combinadas;

b) Manejo de eventos adversos;

No Brasil o esquema de tratamento para TB sensível está descrito na **Tabela 2**. A diferença do Peru, no Brasil é usado a doses-fixas combinadas desde o ano 2010. Com essa nova implementação esperou-se aumentar o sucesso terapêutico e evitar o aumento da multirresistência (resistência à isoniazida + rifampicina).

Tabela 2 - Esquema básico para o tratamento da TB sensível em adultos e adolescentes no Brasil

Regime	**Regime**	**Duração**	**Faixa de Peso**	**Unidade/dose**
2 RHZE Fase Intensiva	RHZE 150/75/400/275 Comprimido em DFC	2 meses	20 Kg a 35 Kg	2 comprimidos
			36 kg a 50 Kg	3 comprimidos
			> 50 Kg	4 comprimidos
4 RH Fase de Manutenção	Comprimidos de 150/75	4 meses	20 Kg a 35 Kg	2 comprimidos de 150/75
			36 kg a 50 Kg	3 comprimidos de 150/75
			> 50 Kg	4 comprimidos de 150/75

Fonte: Manual de Recomendações para o controle da tuberculose no Brasil. Fonte: (MINISTÉRIO DA SAÚDE DO BRASIL; SECRETARIA DE VIGILÂNCIA EM SAÚDE, 2013). A doses são administradas de acordo com o peso do paciente. Abreviaturas: R: Rifampicina; H: Isoniazida; Z: Pirazinamida; E: Etambutol

No Peru o esquema básico para TB sensível (**Tabela 3)** foi implementado entre os anos 1970 e 1980 e as variações do esquema são para condições especificas indicadas nas guias peruanas para o controle da TB.

Tabela 3 - Esquema básico para o tratamento da TB sensível em adultos e adolescentes no

Fase	**Regime**	**Duração**	**Frequência**	**Medicamento e dose**	**Número de cápsulas/ comprimidos**
1°	2 RHZE Fase Intensiva	02 meses (50 doses)	Diária, não domingos e feriados	Rifampicina x 300 mg	2
				Isoniazida x100 mg	3
				Pirazinamida x 500 mg	3
				Etambutol x 400 mg	3
2°	4 RH Fase de Manutenção	04 meses (32 doses)	Três vezes por semana	Rifampicina x 300 mg	2
				Isoniazida x100 mg	8

Fonte: Norma técnica de salud para el control de la tuberculosis. (MINISTERIO DE SALUD- PERÚ, 2013). A doses são administradas de acordo com o peso do paciente. Abreviaturas: R: Rifampicina; H: Isoniazida; Z: Pirazinamida; E: Etambutol

Nas Definições e Estrutura de Informação para a Tuberculose da OMS (WORLD HEALTH ORGANIZATION, 2020b), desde o ano 2013, são considerados os seguintes desfechos para o tratamento anti-TB:

- **Cura:** Paciente com TB pulmonar, bacteriologicamente confirmada no início do tratamento e que apresentou baciloscopia ou cultura negativa no último mês de tratamento e em pelo menos uma ocasião anterior;
- **Tratamento completo:** Paciente com TB que completou o tratamento sem evidência de falha, mas sem nenhum registro para mostrar que os resultados da baciloscopia ou cultura no último mês de tratamento e em pelo menos uma ocasião anterior foram negativos, porque os testes não foram feitos ou porque os resultados não estão disponíveis;
- **Falha no tratamento**: Paciente com tuberculose cuja baciloscopia ou cultura é positiva no mês 5 ou posterior durante o tratamento;
- **Óbito:** Paciente com TB que morre por qualquer motivo antes de iniciar ou durante o curso do tratamento;

- **Perda do seguimento**: Paciente com TB que não iniciou o tratamento ou cujo tratamento foi interrompido por 2 meses consecutivos ou mais;
- **Não avaliado**: Paciente com TB para o qual não foi atribuído nenhum resultado do tratamento. Isto inclui casos "transferidos" para outra unidade de tratamento ou como casos para os quais o resultado do tratamento é desconhecido para a unidade de relatório;
- **Tratamento com sucesso**: A soma de tratamento curado e completo.

O resultado do tratamento é um indicador importante dos programas de controle da tuberculose. (WORLD HEALTH ORGANIZATION. 2007A, 2015), o que torna importante estabelecer sistemas de dados dinâmicos que permitam o monitoramento e avaliação dos resultados do tratamento.

Os resultados do tratamento podem ser influenciados por diferentes fatores, uma revisão sistemática (CHAVES TORRES; QUIJANO RODRÍGUEZ; PORRAS ANDRADE; ARRIAGA *et al.*, 2019) com 151 estudos publicados entre os anos 2014 e 2019 mostrou que fatores como idade, sexo, consumo de álcool, tabagismo, não conversão do esfregaço de escarro aos dois meses de tratamento e HIV afetam os resultados do tratamento da TB. No Brasil, outro estúdio (BARRETO-DUARTE; ARAUJO-PEREIRA; NOGUEIRA; SOBRAL *et al.*, 2021) revelou que ausência de DOT, história de TB, raça (negra ou parda), localização da doença tuberculosa e infecção por HIV foram fatores de risco para resultados desfavoráveis, sujeito à faixa etária. No Peru, um estudo (LACKEY; SEAS; VAN DER STUYFT; OTERO, 2015) prospectivo em uma coorte de 1294 pacientes reportou que o uso de drogas ilícitas, a multirresistência, indivíduos sem o teste de HIV, consumo de álcool, baixo peso e não ter acabado o ensino médio foram fatores de risco para não completar o tratamento.

2.9 A COMORBIDADE TUBERCULOSE E DIABETES

Diabetes Mellitus (DM) engloba um conjunto de distúrbios metabólicos caracterizados por hiperglicemia na ausência de tratamento, que se apresenta em dois principais tipos: tipo 1 (DM1) e tipo 2 (DM2). A etiopatologia da DM pode estar associada a defeitos na secreção de insulina, à ação ineficaz da insulina, e a distúrbios do metabolismo de carboidratos, gorduras e proteínas (AMERICAN DIABETES ASSOCIATION, 2020).U m dos testes para o

diagnóstico de DM é a medição da hemoglobina glicada (HbA1c) no sangue total dos pacientes. Um valor de HbA1c considerado normal é inferior a 5,7%, enquanto valores acima de 6,5% caracterizam o diagnóstico de DM. Caso a medição fique entre 5,7-6,4%, os pacientes são considerados para o diagnóstico de pré-DM (AMERICAN DIABETES ASSOCIATION, 2020)

Por se tratar de uma doença crônica, algumas complicações surgem a longo prazo em indivíduos com DM, a exemplo de neuropatias, nefropatias e retinopatias. Além disso, esses indivíduos apresentam risco aumentado de desenvolver outras patologias, como doenças cardíacas, oculares e metabólicas, assim como também ficam mais susceptíveis a infecções, como por Mtb (JEON; MURRAY, 2008).

A susceptibilidade à tuberculose em pacientes com DM tem sido atribuída a vários fatores, incluindo efeitos diretos relacionados à hiperglicemia e resistência à insulina e efeitos indiretos relacionados à função de células como macrófagos e linfócitos (KUMAR NATHELLA; BABU, 2017). A resposta imunológica alterada em pacientes com DM facilita a infecção primária com TB ou a reativação da TB latente.

Um estudo experimental demostrou que a função dos macrófagos alveolares infectados com Mtb foi alterada em ratos hiperglicêmicos, resultando em expressão reduzida de sinais e quimiocinas que recrutam macrófagos, CDs, neutrófilos e linfócitos. Além disso, produz uma barreira à transmigração de leucócitos (MARTINEZ; KORNFELD, 2014). O interferon (IFN)γ também determina a ativação de macrófagos, mediada pela liberação de interleucina (IL) -1 β, IL-12 e IL-18 a partir de células apresentadoras de antígenos após estimulação com Mtb. Deste modo, pacientes com DM2 podem ser caracterizados pela diminuição na secreção de IL-1β, IL-12 e IL-18 e responder com menos IFNγ após estimulação, o que aumenta a suscetibilidade à T B (LEE; HA; KIM; CHRISTIANI *et al.*, 2003).

As células T helper 1 (Th1) desempenham um papel central na defesa do hospedeiro, induzindo a produção de IFN γ, que aumenta a atividade destrutiva dos macrófagos, enquanto a IL-2 é uma citocina essencial para o desenvolvimento e a proliferação de células T, Th1 e CD8 +, e células T, e as células Th17 secretam IL-17 e IL-23 que atuam na resposta inflamatória da TB, portanto a alteração da função das células Th no DM seria um fator importante para o desenvolvimento da tuberculose (YAMASHIRO; KAWAKAMI; UEZU; KINJO *et al.*, 2005).

A associação TB-DM é altamente frequente ao redor do mundo, de forma que atualmente mais pacientes com TB vivem com DM do que com coinfecção por HIV (GIRARDI; SANE SCHEPISI; GOLETTI; BATES *et al.*, 2017). Pacientes com DM têm um

risco três vezes maior se comparados aos indivíduos sem DM de desenvolver TB ativa. Esse risco pode sofrer uma variação de acordo com as características da população de estudo, variando de 1.16-7.83. Essa grande variação pode estar relacionada a heterogeneidade das populações, principalmente no que diz respeito à idade, acesso aos serviços de saúde, controle glicêmico e comorbidades (JEON; MURRAY, 2008).

O perfil dos pacientes com TB-DM é notavelmente distinto dos pacientes apenas com TB, apresentando maior idade, obesidade, abuso de álcool, maior consumo de drogas ilícitas e coinfecção por HIV. Além disso, a literatura mostra que esses pacientes também apresentam menor escolaridade e maior desemprego, o que pode estar associado a um inadequado controle glicêmico (ABDELBARY; GARCIA-VIVEROS; RAMIREZ-OROPESA; RAHBAR *et al.*, 2016).

A hiperglicemia crônica pode influenciar não só na ativação da TB, mas também na susceptibilidade à infecção e no desfecho do tratamento anti-TB. Um estudo conduzido em Atlanta, EUA, com refugiados sem diagnóstico prévio de TB ou ILTB que realizaram o teste de HbA1c e IGRA, mostrou que aqueles com DM apresentaram um risco de 2,3 vezes maior de ILTB que aqueles que não apresentavam disglicemia. Para pacientes com pré-DM, esse risco foi de 1,7 vezes, mostrando que a hiperglicemia pode estar associada a uma maior susceptibilidade à infecção (HENSEL; KEMPKER; TAPIA; OLADELE *et al.*, 2016). Já durante o tratamento anti-TB, aqueles com TB-DM mantém a baciloscopia positiva por mais tempo e apresentam maior taxa de resistência a medicamentos. Em contrapartida, esses pacientes possuem uma menor taxa de abandono e morte se comparados aos sem DM (ABDELBARY; GARCIA-VIVEROS; RAMIREZ-OROPESA; RAHBAR *et al.*, 2016), possivelmente associada a um acompanhamento mais preciso justamente pela existência da comorbidade.

2.10 COINFECCAO ENTRE TUBERCULOSE E HIV

O HIV (Vírus da Imunodeficiência Humana) é um lentivírus que pertence à família dos retrovírus, e é o agente causador da AIDS. O tipo HIV-1 predomina em todo o mundo, enquanto o tipo HIV-2 é mais comum em África Ocidental. O HIV tem predileção por células do sistema imunológico, principalmente linfócitos T-CD4, aos quais se adere na sua superfície por meio de receptores CCR5 ou CXCR4, introduzindo seu RNA que se torna

DNA pró-viral na presença da enzima transcriptase reversa (PAWLOWSKI; JANSSON; SKOLD; ROTTENBERG *et al.*, 2012). Essa transformação permite que entre no núcleo da célula hospedeira, acoplando-se ao seu material genético onde pode permanecer latente por tempo indeterminado. Quando a célula hospedeira se replica, o vírus executa um processo de transcrição criando RNAs mensageiros que formam proteínas que, pela enzima protease, são cortados em cadeias curtas, formando os novos vírions, assim eles adquirem seu revestimento da membrana da célula hospedeira (PAWLOWSKI; JANSSON; SKOLD; ROTTENBERG *et al.*, 2012).

Dentre os fatores associados ao desenvolvimento da TB ativa, a infecção pelo HIV é um dos mais importantes, com impacto bidirecional em muitos casos. Por um lado, leva ao declínio dos linfócitos CD4, afetando a reativação da TB latente; e, por outro, aumenta a carga viral, acelerando a progressão da infecção pelo HIV para a AIDS e, portanto, para o óbito (PAWLOWSKI; JANSSON; SKOLD; ROTTENBERG *et al.*, 2012).

Em 2020, a OMS estimou que 37,7 milhoes de pessoas vivem com HIV no mundo, 214.000 pessoas morreram de TB associada à infecção pelo HIV (UNAIDS, 2021). Quase 25% das mortes entre as pessoas infectadas pelo HIV são causadas pela tuberculose e é a África Subsaariana que tem dois terços (67%) das pessoas que vivem com HIV (UNAIDS, 2021).

As infecções bacterianas representam, sem dúvida, a primeira causa de morte em pacientes com infecção pelo HIV, sendo muitas vezes o evento terminal em pacientes com AIDS; também são responsáveis por uma parte importante das infecções oportunistas de fases iniciais da doença.

A TB ativa desenvolve-se numa fase relativamente precoce da infecção pelo HIV, podendo representar um dos primeiros sinais clínicos de infecção por este vírus (BRUCHFELD; CORREIA-NEVES; KALLENIUS, 2015). Considerando a diferença de transmissão, a TB provavelmente representa a maior ameaça à saúde da população em geral. A combinação de infecção pelo HIV e TB é letal, pois uma acelera a progressão da outra. Embora a prevalência seja semelhante a outros grupos de risco, aumenta de 20 a 30 vezes mais chances de desenvolver TB ativa (TEWELDEMEDHIN; ASRES; GEBREYESUS; ASGEDOM, 2018).

Combinações de medicamentos antirretrovirais (HAART) são usadas para tratar a AIDS. Eles são agrupados em quatro classes: análogos de nucleosídeos e nucleotídeos, inibidores de protease e inibidores de fusão (LAMBERT; SANDESARA; HIRSH; SHAW *et al.*, 2016). Existem vários esquemas, que são modificados de acordo com os resultados. É

necessário adicionar que, além do tratamento antirretroviral, os pacientes devem receber tratamento para infecções oportunistas associadas à síndrome (LAMBERT; SANDESARA; HIRSH; SHAW *et al.*, 2016).

2.11 INTERELAÇÃO ENTRE TUBERCULOSE E NUTRIÇÃO

A nutrição é um eixo fundamental para a saúde em todas as fases da vida porque age nas estruturas celulares o que permite um estado funcional em equilíbrio (WORLD HEALTH ORGANIZATION, 2003). Uma melhor nutrição está relacionada a uma melhor qualidade de vida, a um sistema imunológico forte e menor risco de doenças no transmissíveis e infecções. (WORLD HEALTH ORGANIZATION, 2003). O sistema imunológico depende do estado nutricional para funcional corretamente. A imunidade inata e o metabolismo dos nutrientes são sistemas biológicos complexos que devem trabalhar juntos para manter e preservar a vida (CHANDRA, 1997).. As células efetoras do sistema imune inato dependem de nutrientes essenciais para gerar energia, produzir precursores metabólicos para a biossíntese de macromoléculas e ajustar suas respostas aos agentes infecciosos. Portanto, as alterações no estado nutricional têm um impacto substancial na competência imunológica e podem resultar em aumento da suscetibilidade à infecção durante a deficiência de nutrientes ou inflamação crônica associada à distúrbios nutricionais (CHILDS; CALDER; MILES, 2019).

Na TB existe uma interação com a desnutrição, a TB pode provocar perda de peso ou caquexia e a desnutrição é um fator de risco para TB. No primeiro caso, os pacientes com TB perdem peso porque existe um maior gasto de energia para manter a função corporal causada pelo incremento da taxa metabólica basal, embora, como foi mencionado antes, a desnutrição pode levar a um deterioro do sistema imunológico. Um estudo (CHAN; TANAKA; MANNION; CARROLL *et al.*, 1997) demostrou como a desnutrição proteico-calórica pode alterar a interação entre macrófagos e linfócitos T, células fundamentais na resposta imune à infecção pela Mtb.

A avaliação do estado nutricional é feita através do estúdio antropométrico completo e uma avalição dietética que reporta os hábitos alimentares e a ingestão de rotina de cada indivíduo (WORLD HEALTH ORGANIZATION, 2003). Também parâmetros bioquímicos como níveis de ferro, vitaminas, colesterol, triglicérides entre outros, são usados na avalição nutricional.

Um dos marcadores para a avaliação antropométrica é o IMC (Índice de Massa Corpórea). Vários estúdios relatam que valores baixos de IMC são um fator de risco para desenvolver a TB ativa (CEGIELSKI; MCMURRAY, 2004; EDWARDS; LIVESAY; ACQUAVIVA; PALMER, 1971), e outras pesquisas identificaram uma associação entre valores de IMC elevados e um risco reduzido para TB (LEUNG; LAM; CHAN; YEW *et al.*, 2007; YEN; HU; LEE; KU *et al.*, 2017). Porém, a obesidade tem relação com a DM, condição que é um fator de risco para TB (JEON; MURRAY, 2008). A explicação poderia se fundamentar no papel do tecido adiposo e a sua participação na liberação de fatores pro-inflamatórios e anti-inflamatórios o que influencia a susceptibilidade às infecções (YEN; HU; LEE; KU *et al.*, 2017).

O IMC e a DM também são componentes relacionados do perfil nutricional das populações, enquanto a DM aumenta o risco de TB pulmonar (KUBIAK; SARKAR; HORSBURGH; ROY *et al.*, 2019), um IMC mais alto protege, mas a DM é mais comum entre pessoas com sobrepeso. Para aumentar a complexidade da sindêmia TB-DM, a distribuição do IMC, a prevalência de DM e a incidência de TB na população variam por idade e sexo e diferem entre áreas rurais e urbanas (KUBIAK; SARKAR; HORSBURGH; ROY *et al.*, 2019).

Apesar de o estado nutricional guiado pelo IMC seja uma boa ferramenta para auxílio no acompanhamento dos pacientes, essa é uma técnica limitada já que leva em consideração peso e altura, não levando em conta a composição corporal e os padrões alimentares dos indivíduos.

Recentemente uma nova abordagem propõe usar o padrão alimentar (MUMME; CONLON; VON HURST; JONES *et al.*, 2020) para explorar melhor o estado nutricional de populações tão complexas como é a sindêmia TB-DM O padrão alimentar é definido como um conjunto de alimentos frequentemente consumidos por indivíduos e populações (MUMME; CONLON; VON HURST; JONES *et al.*, 2020) Essa abordagem permite avaliar a dieta desde um aspecto global. Além disso, essa proposta supera algumas limitações como incapacidade de detectar os efeitos de nutrientes e dificuldades da avaliação de interações entre os nutrientes e fatores sociodemográficos (MUMME; CONLON; VON HURST; JONES *et al.*, 2020).

Publicações anteriores (ANDRADE; DE SANTANA; FUKUTANI; QUEIROZ *et al.*, 2019; ANDRADE; SANTANA; FUKUTANI; QUEIROZ *et al.*, 2020) mostraram como o padrão alimentar se relaciona fortemente com o espectro da doença apresentada, sendo uma estratégia interessante a ser futuramente empregada para melhor compreensão do estado

nutricional global dos doentes. Ademais, junto com o padrão alimentar, as técnicas estadísticas multidimensionais (ANDRADE; DE SANTANA; FUKUTANI; QUEIROZ *et al.*, 2019; ANDRADE; SANTANA; FUKUTANI; QUEIROZ *et al.*, 2020) conseguiram visualizar o quanto a alimentação está associada a outros fatores clínicos e epidemiológicos. e consequentemente compreender a população mais vulnerável a apresentação de doença.

3 JUSTIFICATIVA

Apesar do grande empenho em combater a TB a partir de planos estratégicos como o END-TB da OMS, os 10 milhões de casos e 1,4 milhão de mortes anuais demonstram que essa doença continua sendo um grande problema de saúde pública e uma das 10 principais causa de morte globalmente. Além disso, estima-se que um quarto da população mundial esteja infectada por Mtb em um estágio latente. O Brasil é o 22º país do com maior incidência de TB e o primeiro das Américas, com uma taxa nacional de 46 casos por 100 mil habitantes. Assim, é fundamental caracterizar e avaliar a população brasileira com TB, a fim de compreender quais os fatores determinantes para a transmissão e desfecho terapêutico anti-TB. Entretanto um estudo com um grande número amostral que acompanhe detalhadamente estes pacientes torna-se de difícil execução, dado o custo operacional elevado, grande número populacional e extensa distribuição geográfica do Brasil. Assim, de forma geral são realizados estudos com um número limitado de participantes, como o RePORT-Brasil, cujos resultados são extrapolados para a população.

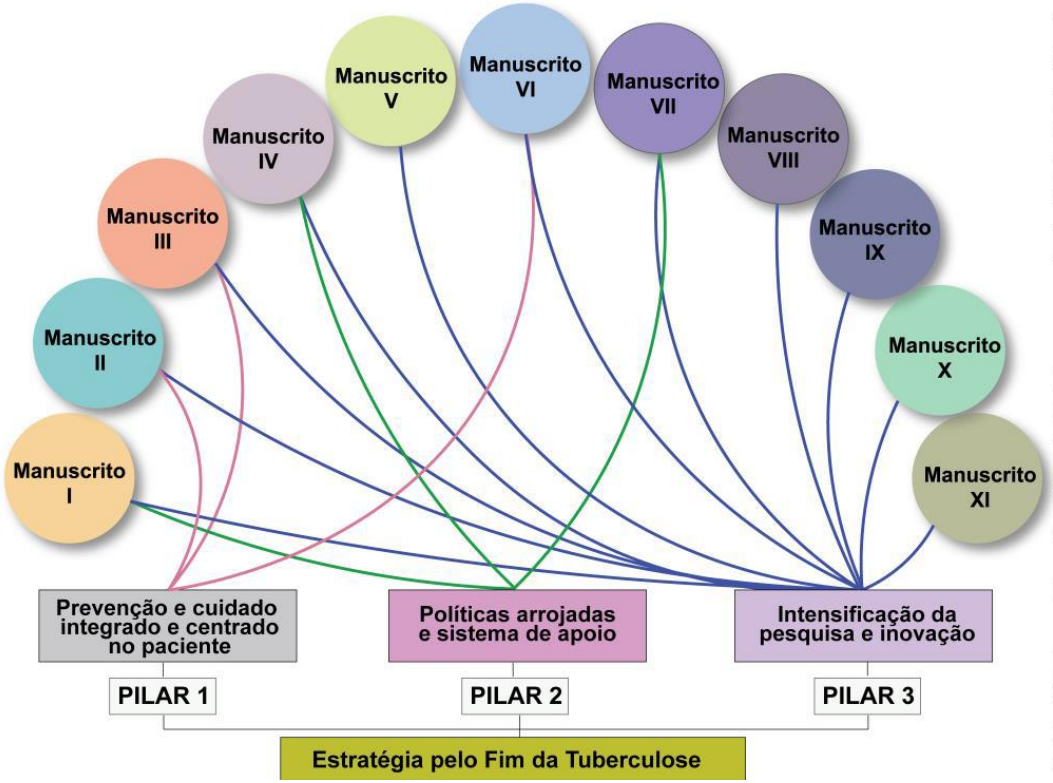
A investigação em TB tem um papel fundamental na geração de conhecimento que orienta as estratégias de tomada de decisão. No entanto, diferentes componentes do desenho do estudo podem incluir fatores de confusão e vieses, que podem afetar a representatividade do estudo população e limitar a generalização dos resultados. Isso pode resultar em estimativas errôneas e, consequentemente, levar à adoção de ações ou estratégias inadequadas. Assim, é de fundamental importância avaliar a representatividade de uma população de estudo, e se os resultados do estudo população reflete o que acontece na população em geral. No Manuscrito I utilizamos ferramentas estatísticas inovadoras para caracterizar a amostra populacional atendida no RePORT-Brasil e a compara com a população nacional de TB.

Dentre todos os fatores cruciais para o controle da TB, está o rastreio e acompanhamentos de indivíduos contactantes de pacientes com TB, o tratamento preventivo para TB para todos os contatos de TB com resultado positivo no teste de liberação de interferon gama (IGRA) ou no teste tuberculínico (TST). Porém, no Brasil, são escassos os

dados conjuntos sobre os desfechos de tratamento em coorte de paciente com TB pulmonar e a cascata diagnóstica e terapêutica de ILTB em seus contatos. Isto demostra que são necessários mais estudos para caracterizar essa população de pacientes e os contactantes a fim de identificar quais são os determinantes clínicos e epidemiológicos que estão associados a um abandono do tratamento preventivo da TB e a susceptibilidade à infecção, para que futuramente possam guiar as políticas públicas no sistema de saúde. Dois estudos do nosso grupo, apresentados nesta tese, visaram identificar os momentos cruciais de perda de acompanhamento dos contactantes (Manuscritos II e III) e outros dois estudos abordaram como a disglicemia (DM e pré-DM) (Manuscrito IV) e disglicemia persistente (Manuscrito V) estão associadas a desfechos desfavoráveis de tratamento. Além disso, o nosso grupo se propôs também a preencher algumas lacunas no estudo da TB-DM, como a prevalência de DM, pré-DM e HIV em pacientes com TB no Brasil (Manuscrito VI) e que fatores clínicos como pré-DM e DM nos casos TB podem estar associados a um maior risco de transmissão da Mtb nos contatos (Manuscrito VII).

Um fator importante bastante conhecido na susceptibilidade à Mtb, é a DM, que aumento em até 3 vezes a chance de desenvolver TB ativa. Entretanto, existem divergências sobre a melhor abordagem para triagem da DM em pacientes com TB em diferentes países. A fim de expandir as análises, nós também avaliamos uma coorte do Peru, o segundo país com maior incidência das Américas que juntamente com o Brasil possuem 45% dos casos de TB ativa do continente. O manuscrito VIII aqui apresentado comparou os níveis de HbA1C e FPG em pacientes e contatos de TB no Brasil e no Peru, a fim de identificar os melhores marcadores de diagnóstico para essas populações. Além disso, estimamos a prevalência de DM, pré-DM no Peru (Manuscrito IX) e as manifestações radiológicas mais graves em pacientes com TB (Manuscrito X).

Por fim, ainda avaliamos com metodologias inovadoras quais são os padrões alimentares de pacientes com TB-DM (Manuscrito XI), tendo em vista que nutrição é um importante fator com potencial influencia em desfechos clínicos da TB. Todos os trabalhos aqui apresentados objetivaram a compreensão de aspectos importantes para o diagnóstico e acompanhamento da TB, desde a sua forma latente até o desenvolvimento da TB ativa e associada a DM. Os resultados produzidos neste trabalho encontram suporte nos lineamentos da Estratégia pelo Fim da TB **(Figure 3)** e podem ser de grande valia para a tomada de decisões realizada pelos poderes públicos e influenciar na melhora do desenvolvimento do sistema único de saúde (SUS no Brasil) ou no sistema integral de saúde (SIS no Peru) no combate a TB, visando o controle e posterior erradicação da doença.



Manuscrito I. *Novel stepwise approach to assess representativeness of a large multicenter observational cohort of tuberculosis patients: The example of RePORT Brazil (2020)*

Manuscrito II. *Determinants of losses in the latent tuberculosis cascade of care in Brazil: A retrospective cohort study (2020)*

Manuscrito III. *Determinants of losses in the latent tuberculosis infection cascade of care in Brazil (2021)*

Manuscrito IV. *The Effect of Diabetes and Prediabetes on Anti-tuberculosis Treatment Outcomes: A Multicentric Prospective Cohort Study (2021)*

Manuscrito V *Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru (2022)*

Manuscrito VI. *Prevalence and Clinical Profiling of Dysglycemia and HIV infection in Persons with Pulmonary Tuberculosis in Brazil (2022)*

Manuscrito VII. *The Effect of Diabetes and Prediabetes on Mycobacterium tuberculosis Transmission to Close Contacts (2021)*

Manuscrito VIII. *Divergence in Accuracy of Diabetes Screening Methods in Tuberculosis Patients: A Cross-Sectional Study from Brazil and Peru (Pre-print 2021)*

Manuscrito IX. *High prevalence and heterogeneity of Dysglycemia in patients with tuberculosis from Peru: a prospective cohort study (2019)*

Manuscrito X. *Severe pulmonary radiological manifestations are associated with a distinct biochemical profile in blood of tuberculosis patients with dysglycemia (2020)*

Manuscrito XI. *Systems Nutrology of persons with tuberculosis identifies specific dietary profiles associated with dysglycemia (Pre-print 2021)*

Figura 3. **Manuscritos da tese e os pilares da Estratégia pelo Fim da TB**

Fonte: Estratégia pelo Fim da TB (WORLD HEALTH ORGANIZATION, 2015) e WHO's new End TB strategy (UPLEKAR; WEIL; LONNROTH; JARAMILLO *et al.*, 2015). Entre parêntesis os anos de publicação do artigo, exceto os manuscritos VI e IX que são os anos de publicação do pré-print. As linhas mostram a relação dos manuscritos que compõem a tese e os pilares da Estratégia pelo Fim da TB. **Pilar 1:** Prevenção e cuidados integrados centrados na pessoa com TB, com os princípios de: Diagnosticar precocemente todas as formas de TB, com oferta universal de cultura e teste de sensibilidade, incluindo o uso de testes rápidos; tratar de forma adequada e oportuna todos os casos diagnosticados de TB visando à integralidade do cuidado; intensificar as atividades colaborativas TB-HIV e intensificar as ações de prevenção. **Pilar 2**: Políticas arrojadas e sistemas de apoio, com os princípios: Fomentar ações para garantir a realização das atividades de cuidado e prevenção da doença com recursos adequados (humanos, infraestrutura e financeiros); fortalecer a articulação intra e intersetorial para garantia dos direitos humanos e cidadania nas ações de controle da doença; fortalecer a participação da sociedade civil nas estratégias de enfrentamento da doença; melhorar a qualidade dos sistemas informatizados de registro de casos para tomada de decisão mais oportuna. **Pilar 3**: Intensificação da Pesquisa e Inovação, com os princípios: Estabelecer parcerias para fomentar a realização de pesquisas no país em temas de interesse para saúde pública e promover a incorporação de iniciativas inovadoras para aprimorar o controle da TB.

4 OBJETIVOS

4.1 OBJETIVO GERAL

Identificar os determinantes clínicos e epidemiológicos da susceptibilidade à infecção pelo *Mycobacterium tuberculosis* e a resposta terapêutica em pessoas com tuberculose (TB).

4.2 OBJETIVOS ESPECIFICOS

- Avaliar a representatividade em uma coorte brasileira prospectiva de pessoas com TB pulmonar (Regional Prospective Observational Research in Tuberculosis (RePORT) - Brasil), em comparação aos casos de TB notificados no Sistema Nacional de Notificação de Agravos (SINAN);
- Avaliar as características clínicas e demográficas dos casos de TB cadastrados no RePORT-Brasil e notificados ao Programa Nacional de TB;
- Avaliar a cascata de atenção infecção latente pelo *Mycobacterium tuberculosis* (ILTB) em uma coorte brasileira prospectiva e em outra coorte retrospectiva de contatos de pacientes com tuberculose pulmonar confirmada por cultura e identificar fatores associados a perdas em cada fase da cascata;
- Avaliar o efeito da disglicemia (diabetes ou pré-diabetes) nos desfechos do tratamento antituberculose em uma coorte brasileira prospectiva de pessoas com TB pulmonar do RePORT -Brasil, e o efeito da diabetes entre os casos de TB notificados no SINAN.
- Avaliar o efeito da disglicemia (diabetes ou pré-diabetes) persistente nos desfechos do tratamento antituberculose em uma coorte peruana prospectiva de pessoas com TB pulmonar;
- Identificar e caracterizar a prevalência do HIV e sua associação com o estado glicêmico entre pessoas com TB pulmonar ativa na coorte do RePORT-Brasil e nos casos notificados ao SINAN;
- Investigar se os contatos de pessoas com TB pulmonar e disglicemia estavam em maior risco de infecção por *Mycobacterium tuberculose* em comparação com os contatos de pessoas com TB pulmonar normoglicêmicos;
- Investigar o desempenho de hemoglobina glicosilada (HbA1c) e glicose no plasma em jejum na identificação de casos de pré-diabetes e diabetes entre pessoas com TB

pulmonar de duas coortes dois países da América do Sul com alta carga para TB e diabetes, Brasil e Peru;

- Determinar a prevalência real de DM ou pré-DM em pacientes com TB e seus contatos domiciliares, numa coorte de Lima, Peru;
- Identificar se a manifestação radiográfica da TB pulmonar é afetada pela disglicemia em termos de tipos e número de lesões numa coorte de Lima, Peru;
- Caracterizar com uma abordagem de nutrologia de sistemas os padrões alimentares em pessoas com TB pulmonar e disglicemia em uma coorte de pessoas com TB em Lima, Peru.

5 MÉTODO

Para os manuscritos que são parte desta tese foram usadas três coortes de indivíduos diagnosticados com tuberculose e dois cortes de contatos de casos de TB. Duas coortes brasileiras que correspondem a RePORT-Brasil e SINAN, e uma coorte peruana de SES-Peru. O número de participantes varia em cada estudo e é detalhado em cada manuscrito. A seguir descreveremos as coortes estudadas na tese.

5.1 PESQUISA OBSERVACIONAL PROSPECTIVA REGIONAL EM TUBERCULOSE (RePORT)-Brasil

O consórcio RePORT-Brasil foi criado em agosto de 2013 com financiamento do Departamento de Ciência e Tecnologia (DECIT) - Secretaria de Ciência e Tecnologia (SCTIE) do Ministério da Saúde do Brasil e do *National Institutes of Health* dos Estados Unidos (HAMILTON; SWAMINATHAN; CHRISTOPHER; ELLNER *et al.*, 2015). O objetivo principal do RePORT-Brasil é descrever os resultados clínicos do tratamento da TB no Brasil, e a ocorrência de infecção por *M. tuberculosis* e doença de TB entre contatos próximos desses casos fonte de TB (HAMILTON; SWAMINATHAN; CHRISTOPHER; ELLNER *et al.*, 2015).

Os centros de estudo do RePORT-Brasil estão localizados em Manaus, Salvador e Rio de Janeiro, estados brasileiros com altas cargas de TB. No total são cinco unidades de saúde: Instituto Nacional de Infectologia Evandro Chagas (Rio de Janeiro), Clínica da Família Rinaldo Delamare (Rio de Janeiro), e Secretaria de Saúde de Duque de Caxias (Rio de Janeiro), Instituto Brasileiro para Investigação da Tuberculose (Bahia) e Fundação de Medicina Tropical Doutor Heitor Vieira Dourado (Amazonas) (HAMILTON; SWAMINATHAN; CHRISTOPHER; ELLNER *et al.*, 2015).,

Todos os dados foram inseridos no REDCap e armazenados no centro de coordenação de dados do RePORT-Brasil no *Vanderbilt University Medical Center*. O banco de dados é monitorado continuamente quanto à qualidade e integridade dos dados e atualizado conforme apropriado.

RePORT-Brasil: casos diagnosticados com TB ativa e os seus contatos

Entre junho de 2015 e junho de 2019, 1.060 individuos ≥ 18 anos com TB pulmonar nova ou recorrente (com ou sem doença extrapulmonar) e escarro com cultura positiva (meio Lowenstein-Jensen ou BD BACTEC MGIT) foram arrolados na coorte do RePORT-Brasil. As informações clínicas e epidemiológicas foram coletadas durante as visitas do estudo no início, durante e no final do tratamento e, além do acompanhamento até 24 meses após o recrutamento. Além disso, foram realizados testes de hemoglobina glicada (HbA1c), raio-X de tórax, teste de sensibilidade para medicamentos anti-TB e contagem de CD4 (se teve resultado de HIV positivo). No RePORT-Brasil, o resultado do tratamento foi notificado na última visita do estudo (24 meses após o início do tratamento) (**Figura 4A)**

Após do arrolamento do caso índice, os contatos próximos foram convidados a serem entrevistados e examinados nas unidades de saúde do RePORT-Brasil. Os contatos elegíveis que compareceram aos sítios do RePORT-Brasil foram abordados pela equipe do estudo para participar na coorte do RePORT-Brasil e investigados para ILTB. Contatos próximos foram definidos como indivíduos que tinham >4 horas de contato/semana com o caso do índice de TB em qualquer momento nos últimos 6 meses. Os contatos foram avaliados em duas visitas: arrolamento e 6 meses após de ingressar no estudo e contatados por telefone nos meses 12, 18 e 24, para investigar se desenvolveram TB ativa. Os contatos foram avaliados presencialmente no início do estudo e 6 meses após do arrolamento; avaliações subsequentes a cada 6 meses foram feitas por telefone. (**Figura 4B).**

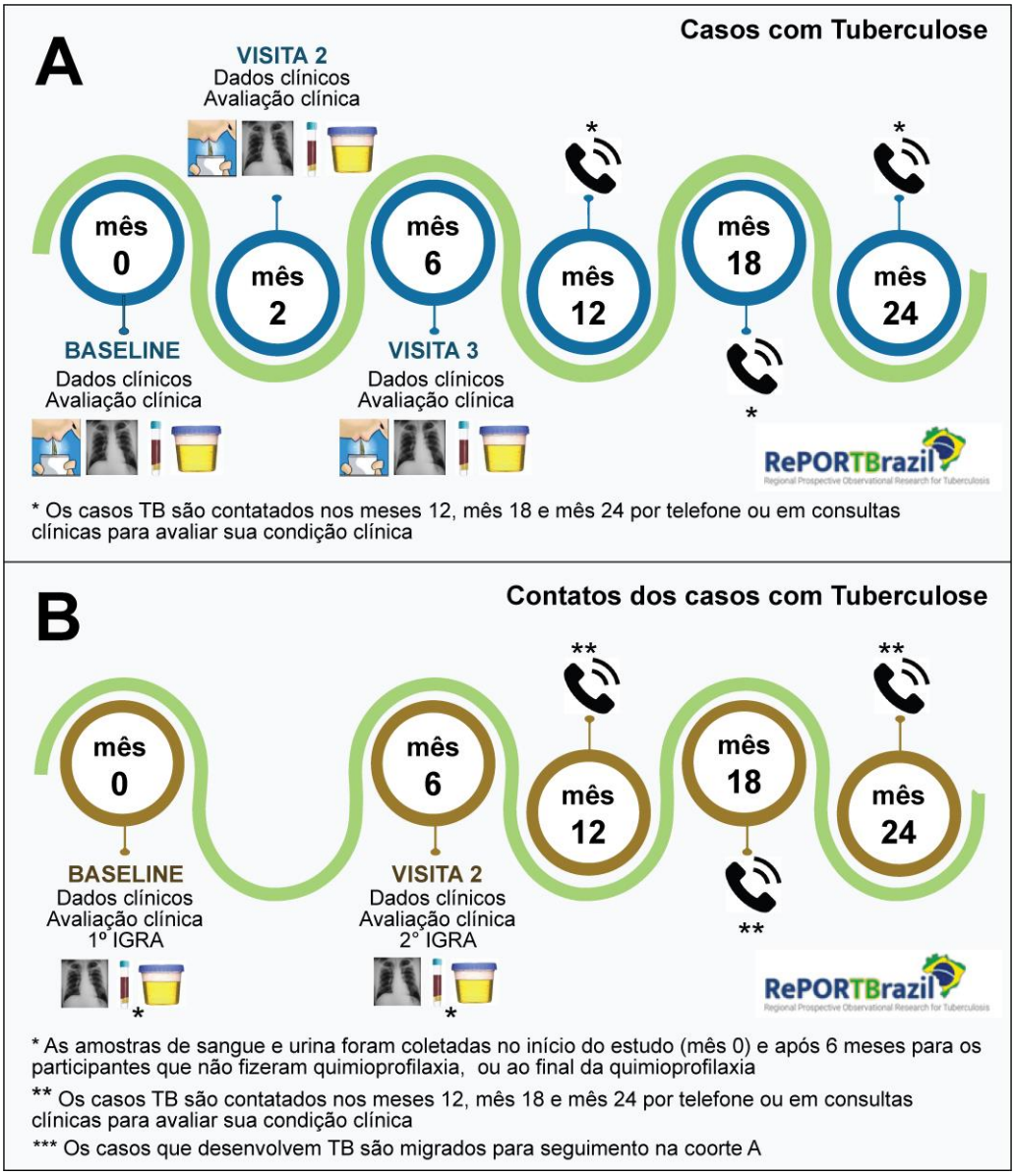


Figura 4. Esquema de visitas e procedimentos nos participantes de RePORT-Brasil **(A)** Visitas e procedimentos nos casos diagnosticados com tuberculose e **(B)** nos contatos dos casos com tuberculose. Abreviações: TB: tuberculose, IGRA: *Interferon-gamma release assay* (teste liberação do interferon-gama).
Fonte: Elaborado pela autora

Dos 2483 contatos que se apresentaram à clínica e foram convidados a participar do estudo, 1901 concordaram em participar, forneceram consentimento informado e foram investigados para ILTB. Foi realizada uma avaliação clínica, radiografia de tórax e coleta de sangue para testes de IGRA e HIV. Complementarmente, os dados clínicos e demográficos foram coletados por meio de formulários padronizados de relato de caso.

5.3 SISTEMA DE INFORMAÇÃO DE AGRAVOS DE NOTIFICAÇÃO (SINAN)

O SINAN é um sistema de notificação e investigação de doenças transmissíveis implementado, apoiado e mantido pelo Ministério da Saúde do Brasil (ROCHA; BARTHOLOMAY; CAVALCANTE; MEDEIROS *et al.*, 2020). A notificação dessas doenças, incluindo a TB, é obrigatória nos municípios e estados brasileiros desde 1993. Para cada caso notificado, são coletados dados epidemiológicos e clínicos. As informações são fornecidas sem identificação do paciente e disponíveis no site do SINAN. Dados de 455.873 pacientes com TB foram notificados ao SINAN entre 2015 e 2019. Os casos de TB foram diagnosticados por um ou mais dos seguintes critérios: (a) fatores clínicos e epidemiológicos (diagnóstico presuntivo), (b) bacteriologia (esfregaço de escarro positivo) ou positivo cultura (sólida ou líquida), (c) GeneXpert Mtb RIF, (d) radiografia de tórax ou (e) no caso de TB extrapulmonar por histopatologia (os detalhes do diagnóstico estão descritos no Manual de Recomendações para o Controle da TB em Brasil) (ROCHA; BARTHOLOMAY; CAVALCANTE; MEDEIROS *et al.*, 2020). Após o diagnóstico de TB, as informações coletadas na entrevista de avaliação e os resultados laboratoriais foram registrados em formulário padronizado que incluía a forma clínica da TB, características individuais (sexo, idade, raça, escolaridade, etilismo, uso de drogas ilícitas, tabagismo, condições e doenças associadas), presença de coinfecção TB-HIV e resultados de exames, entre outros. Informações sobre o resultado do tratamento anti-TB também foram fornecidas.

5.4 SOCIOS EN SALUD (SES): COORTE DO PERU

SES é uma Organização Não-Governamental (ONG), que entre outras atividades realiza pesquisas epidemiológicas sobre questões relacionadas à TB, HIV e outros problemas importantes de saúde pública, com o propósito de entender as lacunas de conhecimento e propor soluções por meio de uma abordagem social e equitativa, que ajudem as populações mais afetadas (PARTNERS IN HEALTH, 2006).

Nesta coorte, 136 indivíduos diagnosticados com TB e 138 dos seus contatos domiciliares foram arrolados entre fevereiro e novembro de 2017 em Lima, Peru.

O estudo foi realizado no Hospital Público Sergio Bernales e nos Centros de Saúde Ambulatoriais dos municípios de Carabayllo e Comas, localizados em Lima Norte. Foram incluídas pessoas com TB pulmonar ativa com 16 anos ou mais de idade diagnosticados pelos Programa de Controle de Tuberculose dos postos de saúde públicos. Os contatos foram definidos como indivíduos maiores de 12 anos ou mais que compartilha pelo menos a casa

onde dormia ou fazia suas refeições (pelo menos uma por dia) com um paciente de TB do estudo. Os critérios de exclusão foram pacientes ou contatos com diagnóstico de HIV, gestantes, que não residiam permanentemente na área de jurisdição do estudo e pacientes que apresentavam infecção ou doença por microbactéria não tuberculosa. O acompanhamento desses pacientes foi realizado entre 6 a 12 meses após o recrutamento.

Uma amostra de escarro de cada paciente foi isolada para investigação de esfregaço (bacilos álcool-ácido resistentes, BAAR) e culturas sólidas de Mtb. A medição de HbA1c em amostras de sangue total foi realizada pelo uso da plataforma TRI-stat ™ (*Trinity Biotech, Irlanda*) e a glicose sérica rápida ou o teste oral de tolerância à glicose foram realizados seguindo métodos padrão. Todos esses testes de TB foram realizados no Laboratório SES, localizado em Lima.

Também foram realizadas avaliações clínicas por especialista, entrevistas para coleta de informações sociodemográficas e clínicas, revisão de prontuários, para obtenção de informações clínicas relevantes sobre comorbidades, como pressão arterial, pulso, frequência respiratória, condições imunossupressoras, entre outras. As informações demográficas e clínicas foram registradas no software *Socios En Salud Informatic System* (SEIS) (Lima, Peru).

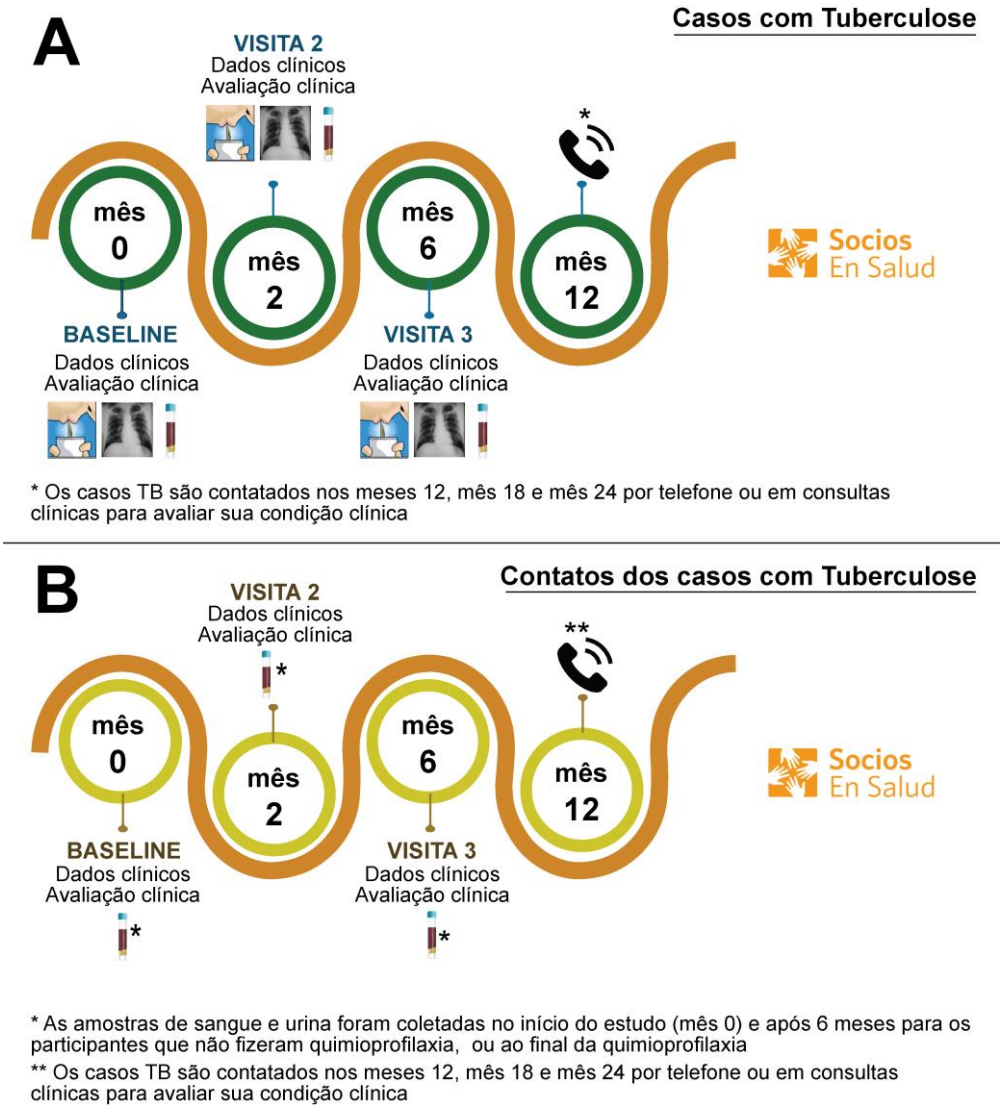


Figura 5 - Esquema de visitas e procedimentos nos participantes de Socios En Salud

(A) Visitas e procedimentos nos casos diagnosticados com tuberculose e **(B)** nos contatos dos casos com tuberculose. Abreviações: TB: tuberculose.

Fonte: Elaborado pela autora

6 MANUSCRITOS

6.1 MANUSCRITO I

Novel stepwise approach to assess representativeness of a large multicenter observational cohort of tuberculosis patients: The example of RePORT Brazil.

Um dos principais objetivos de estudos epidemiológicos da TB é obter resultados que possam ser generalizados para a população geral, principalmente no que tange aos determinantes dos desfechos do tratamento. Esse trabalho compara as características clínicas e demográficas iniciais, assim como os determinantes dos desfechos do tratamento anti-TB entre participantes da Coorte Regional de Pesquisa Prospectiva Observacional em Tuberculose (RePORT)-Brasil entre junho de 2015 e junho de 2019, e o registro de casos de TB notificados SINAN no mesmo período.

Resumo dos resultados: Fazendo uso de novas e inovadoras ferramentas estatísticas, foram identificados importantes semelhanças nas características demográficas das coortes, como sexo, idade e baciloscopia inicial positiva, assim como se identificou semelhanças nos determinantes dos desfechos clínicos não favoráveis entre a coorte RePORT-Brasil e o registro nacional de casos de TB (SINAN), como o uso de drogas ilícitas e co-infecção com HIV, comprovando a representatividade da coorte do RePORT-Brasil e facilitando a generalização dos resultados dos estudos nela realizados. Neste estudo a diabetes também foi achado um fator determinante para os desfechos clínicos não favoráveis na coorte do RePORT-Brasil.

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Novel stepwise approach to assess representativeness of a large multicenter observational cohort of tuberculosis patients: The example of RePORT Brazil

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ABSTRACT

Background: A major goal of tuberculosis (TB) epidemiological studies is to obtain results that can be generalized to the larger population with TB. The ability to extrapolate findings on the determinants of TB treatment outcomes is also important.
Methods: We compared baseline clinical and demographic characteristics and determinants of anti-TB treatment outcomes between persons enrolled in the Regional Prospective Observational Research in Tuberculosis (RePORT)-Brazil cohort between June 2015 and June 2019, and the registry of TB cases reported to the Brazilian National TB Program (Information System for Notifiable Diseases [SINAN]) during the same time period. Multivariable regression models adjusted for the study site were performed using *second-generation* p-values, a novel statistical approach. Associations with unfavorable treatment outcomes were tested for both RePORT-Brazil and SINAN cohorts.
Findings: A total of 1,060 culture-confirmed TB patients were enrolled in RePORT-Brazil and 455,873 TB cases were reported to SINAN. *Second-generation* p-value analyses revealed that the cohorts were strikingly similar with regard to sex, age, use of antiretroviral therapy and positive initial smear sputum microscopy. However, diabetes, HIV infection, and smoking were more frequently documented in

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RePORT-Brazil. Illicit drug use, the presence of diabetes, and history of prior TB were associated with unfavorable TB treatment outcomes; illicit drug use was associated with such outcomes in both cohorts. *Conclusions:* There were important similarities in demographic characteristics and determinants of clinical outcomes between the RePORT-Brazil cohort and the Brazilian National registry of TB cases.

Introduction

Tuberculosis (TB) is a major cause of death worldwide, particularly in people living with HIV (PLWH) (World Health Organization, 2019). The World Health Organization (WHO) estimated that in 2018, ten million people developed TB, and of those, 1.5 million died (including 251,000 PLWH) (World Health Organization, 2019). The WHO, through the End TB Strategy, (World Health Organization, 2017) has proposed two essential pillars to improve TB control worldwide: (i) robust, coordinated data systems, prioritizing existing systems where possible, and (ii) support systems that promote research and innovation (World Health Organization, 2017). Routinely collected TB data allow for monitoring and calculating epidemiological and operational indicators, which are important for TB control (World Health Organization, 2018). However, to be useful and effective, frequent data updates and quality control are essential for accurate data (Agency for Healthcare Research and Quality (US), 2014).

TB research has a vital role in generating knowledge that guides decision-making strategies (World Health Organization, 2017). However, the different components of study design (e.g., eligibility criteria, recruitment and enrollment, and retention) can include confounders and biases, which may affect the representativeness of the study population and limit generalizability of the results (He et al., 2016). This can result in erroneous estimates, and consequently lead to the adoption of inappropriate actions or strategies (Kukull and Ganguli, 2012). Thus, it is of critical importance to evaluate the representativeness of a study population and whether results from the study population reflect what occurs in the larger population (Jaehn et al., 2020; Kukull and Ganguli, 2012).

In Brazil, the National TB Program (NTBP) implemented, in 1993, the collection of detailed demographic and clinical data on all TB patients. Importantly, the notification of all TB cases and reporting of such information is mandatory, and occurs through an electronic system referred as the Notifiable Disease Information System (SINAN) (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2020b). This system is critical for monitoring the epidemiology of TB in all Brazilian regions, guiding governmental investments and policy changes to optimize patient care, minimizing the occurrence of drug-resistance, and leading to better TB outcomes and control. SINAN is also a unique source of data for scientists interested to test the generalizability of their research populations and results.

Although national TB datasets are useful, often the amount and detail of clinical and demographic data that can be collected are limited, and patient follow-up is passive rather than active. Prospective observational cohorts with active participant follow-up for TB treatment outcomes are valuable, but their cost usually limits the cohort size. Regional Prospective Observational Research in Tuberculosis (RePORT) Brazil is a multicenter cohort study with enrollment sites in 3 major regions in Brazil (Hamilton et al., 2015; Regional Prospective Observational Research for Tuberculosis, 2020). However, it is unclear whether the RePORT-Brazil cohort reflects TB epidemiology and treatment outcomes nationally. We therefore evaluated the representativeness of RePORT-Brazil by comparing epidemiological variables and operational indicators with those in the SINAN dataset. In addition, clinical and epidemiological determinants of unfavorable TB treatment outcomes were also compared between the two cohorts. We also assessed whether data and variables collected in RePORT-Brazil could improve the utility of SINAN.

Materials and methods

Overall study design

We compared baseline clinical and sociodemographic characteristics, and the determinants of anti-TB treatment outcomes among persons with TB enrolled into RePORT-Brazil and those reported to SINAN, both between June 2015 and June 2019. The primary hypothesis was that the overall characteristics of TB patients enrolled into RePORT-Brazil and reported to SINAN were similar.

The regional prospective observational research in tuberculosis (RePORT)-Brazil

The description of RePORT sites is presented in Supplementary Methods and in (Regional Prospective Observational Research for Tuberculosis, 2020). Between June 2015 and June 2019, 1060 persons ≥18 years old with new or recurrent pulmonary TB (with or without extrapulmonary disease) and culture-positive sputum (Lowenstein–Jensen medium or BD BACTEC MGIT) were enrolled. Epidemiological information was collected during study visits at baseline, during and at the end of treatment, and up to 24 months after enrollment. This included sex, age, self-reported race, weight, height, education level, the consumption of alcohol, use of illicit drugs and smoking, presence of comorbidities, and HIV status. Additionally, glycated hemoglobin testing (HbA1c), chest X-ray, drug susceptibility testing for anti-TB drugs, and CD4 count (if HIV positive) were performed. In RePORT-Brazil, the treatment outcome was recorded at the last study visit (24 months after the start of treatment). For this study, 434 participants had not yet completed their 24-month visit, so the analysis of treatment outcomes did not include these participants. All data were entered into a REDCap database (Harris et al., 2009) and stored at the RePORT-Brazil data coordination center at Vanderbilt University Medical Center. The database was continuously monitored for data quality and completeness and updated as appropriate.

Notifiable diseases information system (SINAN), Brazilian Ministry of Health

SINAN is a system for the notification and investigation of transmissible diseases that has been implemented, supported, and maintained by the Brazilian Ministry of Health (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2007). The description of SINAN is presented in Supplementary Methods. Data from 455,873 TB patients were reported to SINAN between 2015 and 2019. TB cases were diagnosed by one or more of the following criteria: (a) clinical and epidemiological factors (presumptive diagnosis), (b) bacteriology (sputum smear positive) or positive culture (solid or liquid), (c) GeneXpert MTB RIF, (d) chest

radiography or (e) in the case of extrapulmonary TB by histopathology (the details regarding the diagnosis are described in the Manual of Recommendations for the Control of TB in Brazil) (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2013). After TB diagnosis, the information collected in the evaluation interview and the laboratory results were recorded on a standardized form that included the clinical form of TB, individual characteristics (sex, age, race, education, alcohol consumption, illicit drug use, smoking habits, and associated conditions and diseases), the presence of TB-HIV coinfection and test results, among others (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2013). Information regarding the anti-TB treatment outcome was also provided.

Outcome definition

For this study, a favorable treatment outcome was defined as cure or completed treatment and an unfavorable outcome was defined as treatment failure, lost to follow-up, or death during treatment. The definitions for clinical and bacteriological cure, failure, lost to follow-up, and death for both cohorts corresponded with those in the Manual of Recommendations for the Control of TB of Brazil (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2013). The definitions of treatment outcomes for RePORT-Brazil and SINAN are described in Supplementary Table 1.

Operational indicators

We also evaluated operational indicators for TB, which monitor the performance of TB Control Programs (Arakawa et al., 2015). The list of indicators is shown in Supplementary Figure 1.

Data analysis

All analyses were prespecified. Categorical variables were compared using a two-sided Pearson's chi-square test (with Yates correction) or the Fisher's two-tailed test in 2×3 or 2×2 tables, respectively. Quantitative variables were compared using the Mann Whitney *U* test. LASSO (Least Absolute Shrinkage and Selection Operator) (Trevor et al., 2009) regression analysis and mixed effects models (Gelman and Hill, 2006) were performed, in RePORT-Brazil and SINAN cohorts, to identify independent associations between clinical characteristics of TB patients and anti-TB treatment unfavorable outcomes. In LASSO regression, the optimal parameters were found by a cross-validation step, which was repeated 100 times to stabilize the results. The mixed effects model included the variable "Brazilian states" as a random effect (to avoid possible selection bias, because RePORT-Brazil participants were also reported to be part of the SINAN dataset). Results from both regressions approaches were presented in terms of point estimates and 95% confidence intervals (95% CI). P-values <0.05 were considered statistically significant. In addition to the p-value, the *second-generation* p-value (pδ-value) and the *delta-gap* (Δ) (when applicable) were calculated (Blume et al., 2018) as described in Supplementary Methods and Supplementary Figure 2.

Results

Tuberculosis epidemiology in Brazil and RePORT-Brazil sites

Brazil has 26 states and a federal district, all allocated to five macro-regions. RePORT-Brazil has sites located in the cities of Manaus, Salvador, Rio de Janeiro, and Duque de Caxias (Figure 1A). Between 2015 and 2019, Sao Paulo was the state with the highest number of notified TB cases, followed by Rio de Janeiro and Rio Grande do Sul; the states of Bahia and Amazonas were in the top 10 (Figure 1B). The top 10 cities in the number of TB cases documented during the same period included all of the cities that had RePORT sites, including Rio de Janeiro (1), Manaus (3), Salvador (4), and Duque de Caxias (10) (Figure 1B). On the evaluation of TB incidence per 100,000 persons in the Brazilian states where RePORT-Brazil has sites, different patterns were detected. Bahia had a trend in TB incidence that was similar to that observed in the whole country, whereas Amazonas had a substantially higher incidence over time, followed by Rio de Janeiro (Figure 1C, left panel). Similarly, Manaus city displayed the highest TB incidence among the cities that contained RePORT-Brazil sites, followed by Rio de Janeiro, Duque de Caxias, and Salvador. (Figure 1C, right panel). Figure 1D compares the number of cases notified to SINAN and the number of cases in RePORT Brazil in each year of the study period. The number of cases enrolled in RePORT-Brazil (1060 TB cases) represented 0.23% of the total registries in SINAN (455,873 TB cases). These analyses indicate that RePORT-Brazil sites are located in regions of Brazil that account for a significant TB burden of the country.

Characteristics of the TB cases in RePORT-Brazil and SINAN

Population characteristics of TB cases in both datasets were then compared (Table 1). In both datasets, the majority of patients were male, and the age distributions were similar (second-generation p-values not significant). The frequencies of self-reported race were somewhat similar between the two cohorts (second-generation p-value indeterminate: pδ-value = 0.5). The RePORT cohort had a higher proportion of literate persons (95.3% as compared to 83% in SINAN; ($p < 0.001$, $p\delta = 0$; and $\Delta = 14.9$). Compared to the national dataset, the RePORT cohort also had a higher proportion of health care workers (4.3% vs. 1.3%), proportion with no comorbidities (82.9% vs. 74.1%), prevalence of diabetes (24% vs. 8%) and HIV infection (21% vs. 13.5%), alcohol consumption (83.9% vs. 19.5%), use of illicit drugs (34.2% vs. 15.6%), smoking (52.4% vs. 24.3%), abnormal chest x-ray (97% vs. 93.3%), presence of extrapulmonary TB (11% vs. 3%) and drug-resistant *Mycobacterium tuberculosis* (17.3% vs. 9.7%), all with $p < 0.001$ and $p\delta = 0$; Table 1).

In both cohorts, the most frequent treatment outcome was cure (69.5% in RePORT and 66.9% in SINAN). Treatment failure was more frequently documented in the RePORT cohort (4.2% vs. 1.9%), whereas patients who were transferred out to health care facilities of higher complexity were more commonly observed in the SINAN dataset (7.3% vs. 1.9%). When all categories of treatment outcomes were compared between the datasets, a statistically significant difference was observed between RePORT and SINAN ($p < 0.001$ and a $p\delta = 0$; Table 1).

Additional comparisons are shown in Figure 2. The analyses of the second-generation p-values detected in the comparisons of the age distribution between patients stratified by sex ($p\delta = 0.135$), diabetes comorbidity ($p\delta = 0$, with a delta gap of 14.4), and HIV status ($p\delta = 0.245$), indicated that there were marginal differences (except for diabetes) in age distributions within each of these subpopulations between the datasets (Figure 2A). Of note, the majority of the TB patients were new cases (treatment naive), with a similar profile between the datasets ($p\delta = 0.5$; Table 1 and Figure 2B). The populations from the two distinct datasets exhibited similar proportions of positive acid-fast bacilli (AFB) in sputum smears ($p\delta = 0.5$ and Figure 2C). In contrast, the proportions of TB cases with abnormal chest radiographs and positive sputum culture results were substantially higher in the RePORT cohort than SINAN (all $p\delta = 0$ and Figure 2C); a positive sputum culture was required for enrollment in RePORT-Brazil. TB patients from RePORT-Brazil more frequently reported smoking

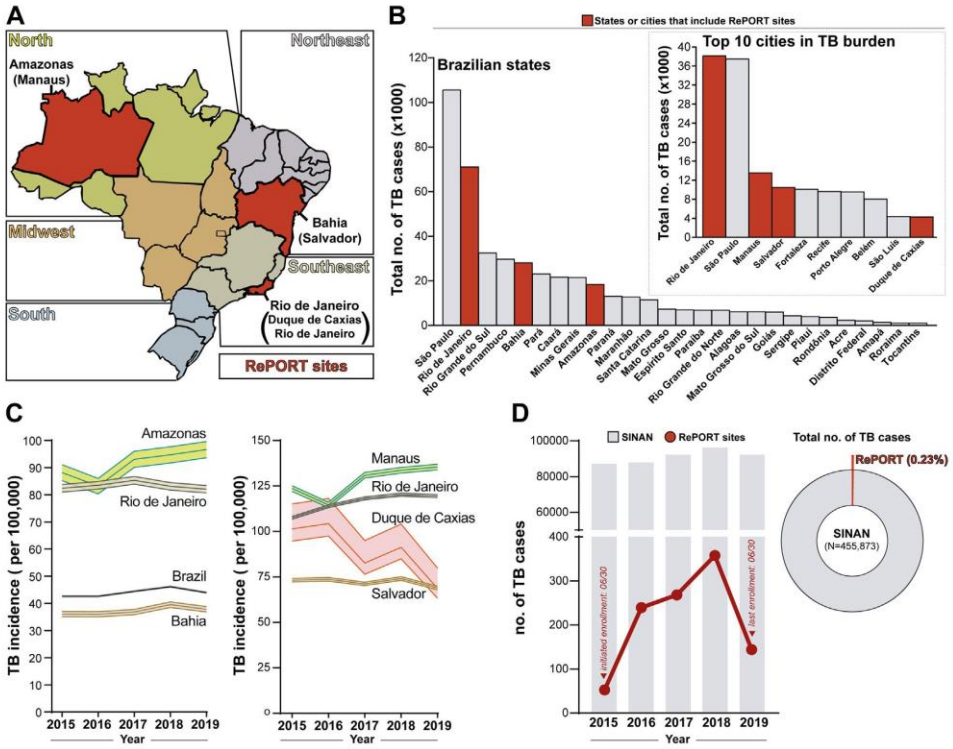

Figure 1. Overview of tuberculosis epidemiology in Brazil (2015–2109).
(A) Political map of Brazil shows the different 26 Brazilian states and one federal district colored according to the 5 macroregions (geopolitical subdivision). The states that include RePORT research centers are displayed in red. (B) Total number of tuberculosis cases reported in each Brazilian state, between 2015 and 2019. The states that include RePORT research centers are indicated by red bars. The upper right panel shows the total number of tuberculosis cases between 2015 and 2019 in the top 10 Brazilian cities with the highest number of tuberculosis cases reported within the study period. The cities where RePORT has research centers are highlighted by red bars. (C) Tuberculosis incidence (per 100,000 person-years) for the years 2015–2019, in Brazil the states (left panel) or in the cities (right panel) that host RePORT sites are shown. Data represent incidence and 95% confidence interval. Data were obtained from the National Plan for the End of Tuberculosis as a Public Health Problem (*Plano Nacional pelo Fim da Tuberculose como Problema de Saúde Pública*) (Ministério da Saúde do Brasil, 2017) (D) Total number of TB cases reported by the Brazilian Notification Information System (SINAN; gray bars) and by RePORT sites (red dots and connecting lines), in the study period. Right panel shows a donut pie chart illustrating the percentage that the TB cases recruited in the RePORT Brazil protocol represents among the total number of cases reported in SINAN between 2015 and 2019.
Abbreviations: TB: Tuberculosis, RePORT: Regional Prospective Observational Research for Tuberculosis, and SINAN: Sistema de Informação de Agravos de Notificação.

and alcohol consumption and more commonly had diabetes, than patients from SINAN ($p\delta = 0$ and Figure 2D).

Characteristics associated with unfavorable tuberculosis treatment outcomes

In RePORT-Brazil, the patients who experienced an unfavorable treatment outcome were more frequently male (75.4%), *pardo* (57.6%), and had diabetes (31.1%) and/or HIV infection (44%). In addition, alcohol consumption (92.1%), the use of illicit drugs (47.6%), and smoking (63.4%) were also associated ($p < 0.001$ in all) with unfavorable anti-TB treatment outcomes (Supplementary Table 3). Similarly, in the SINAN cohort, male sex (72.3%), *pardo* race (53%), HIV infection (24.9%), alcohol consumption (27.6%), illicit drug use (23.3%), and smoking (30.2%) were all associated with unfavorable outcomes. In addition, increasing age, previous TB (30.5%), and positive sputum culture (69.9%) also characterized individuals who had unfavorable outcomes (Supplementary Table 4). Comparisons of clinical characteristics and treatment outcomes between Report-Brazil and SINAN patients in the cities of Duque de Caxias, Manaus, Salvador, and Rio de Janeiro are shown in Supplemental Tables 5–8.

To define the specific associations with unfavorable treatment outcomes in each cohort, LASSO regression (model 1) and mixed effects (model 2) were utilized. The LASSO regression model showed that prior TB, diabetes, illicit drug use, and HIV coinfection were all independently associated with the occurrence of unfavorable treatment outcomes in the RePORT-Brazil cohort (Figure 3, left panel), whereas increased age, male sex, alcohol consumption, illicit drug use, prior TB, and HIV coinfection were associated with increased odds of such outcomes in patients from the SINAN cohort (Figure 3, right panel). In the mixed effects model, diabetes comorbidity (OR:1.81; 95% CI: 1.11–2.94, $p\delta = 0$; and $\Delta = 1.0$) and the use of illicit drugs (OR: 2.28; 95% CI:1.36–3.82; $p\delta = 0$; and $\Delta = 2.2$) were associated with an unfavorable outcome in RePORT-Brazil (Figure 3, left panel). Likewise, in the SINAN cohort, the use of illicit drugs (OR:1.85; 95% CI: 1.80–1.91; $p\delta = 0$; and $\Delta = 5.1$) was also associated with an unfavorable result, along with prior TB (OR: 1.96; 95% CI: 1.95–1.97; and $p\delta = 7.5$), HIV positive (OR: 2.81; 95%CI: 2.74–2.90; $p\delta = 0$; and $\Delta = 9.6$), and alcohol consumption (OR: 1.42; 95% CI:1.38–2.53; $p\delta = 0$; and $\Delta = 2.4$) (Figure 3, right panel).

Table 1
Characteristics of the study participants.

Characteristics	RePORT-Brazil (n = 1,060)	SINAN (n = 455,873)	p-value	pδ-value
Sex–no. (%)			0.027	0.744
Male	702 (66.3)	316693 (69.5)		
Female	358 (33.7)	139149 (30.5)		
Age–median (IQR)	36 (25–49)	37 (26–52)	0.001	1.0
Race/Ethnicity–no. (%)			0.002	0.5
White	214 (20.2)	136446 (32.4)		
Black	271 (25.6)	58061 (13.8)		
Asian	6 (0.6)	3314 (0.8)		
Pardo	551 (52.1)	218312 (51.9)		
Indigenous	16 (1.5)	4817 (1.1)		
Literate–no. (%)	1008 (95.3)	254989 (83.0)	<0.001	0 (Δ = 14.9)
Health worker–no. (%)	45 (4.3)	5572 (1.3)	<0.001	0 (Δ = 7.0)
Comorbidities[a]–no. (%)			<0.001	0 (Δ = 0.38)
Cancer	10 (1.0)	3933 (0.9)		
Chronic Obstructive Pulmonary Disease/Emphysema	6 (0.6)	650 (0.1)		
Kidney disease	5 (0.5)	328 (0.1)		
Hypertension	81 (8.2)	46668 (10.2)		
Others	66 (6.7)	66568 (14.6)		
No comorbidity	817 (82.9)	337715 (74.1)		
Diabetes–no. (%)	250 (24.0)	33961 (8.0)	<0.001	0 (Δ = 11.3)
HIV infection–no. (%)	220 (21.0)	49046 (13.5)	<0.001	0 (Δ = 11.3)
Antiretroviral therapy (ART)[b]–no. (%)	193 (87.7)	16592 (33.8)	<0.001	0.5
Alcohol consumption–no. (%)	889 (83.9)	82842 (19.5)	<0.001	0 (Δ = 31.2)
Illicit drug use–no. (%)	361 (34.2)	64919 (15.6)	<0.001	0 (Δ = 12.5)
Smoking–no. (%)	555 (52.4)	102030 (24.3)	<0.001	0 (Δ = 14.7)
Prior TB–no. (%)	170 (16.2)	88266 (19.4)	0.010	0.5
Abnormal chest x-ray–no. (%)	1027 (97.0)	323940 (93.3)	<0.001	0 (Δ = 4.8)
Type of TB[c]–no. (%)			0.001	0 (Δ = 13.6)
Pulmonary	936 (88.4)	384709 (84.4)		
Extrapulmonary	0 (0.0)	57301 (12.6)		
Pulmonary and Extrapulmonary	123 (11.6)	13629 (3.0)		
Positive AFB–no. (%)	852 (80.8)	225900 (67.9)	<0.001	0.5
Positive culture–no. (%)	1053 (99.9)	93668 (69.1)	<0.001	0 (Δ = 47.8)
Drug-susceptibility testing (DST)–no. (%)			<0.001	0 (Δ = 14.5)
Rifampicin resistance	5 (0.5)	674 (1.3)		
Isoniazid resistance	51 (4.9)	1774 (3.4)		
Rifampicin-Isoniazid resistance	26 (2.5)	1264 (2.4)		
Any drug resistance[d]	98 (9.4)	1444 (2.7)		
Sensitive	859 (82.7)	47785 (90.3)		
Directly observed treatment (DOT)–no. (%)	740 (70.3)	150016 (48.7)	<0.001	0 (Δ = 10.7)
Treatment Outcome[e]–no. (%)			<0.001	0 (Δ = 13.6)
Cure	435 (69.5)	258355 (66.9)		
Failure	26 (4.2)	7343 (1.9)		
Relapse	9 (1.4)	9039 (2.3)		
Death	52 (8.3)	32972 (8.5)		
Lost to follow-up	92 (14.7)	50228 (13.0)		
Transferred out	12 (1.9)	28198 (7.3)		

Table note: Data represent no. (%) or median with interquartile range (IQR). pδ-value: second-generation p-value. Δ = *delta-gap*. See the Supplemental Figure 2 for the interpretation of the pδ-value. Details of the total data available in the Report-Brazil and SINAN bases in the Supplementary Table 2.
Alcohol consumption: Past or current, any consumption of alcohol. Smoking: Past or current, cigarette smoker. Illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin, or crack).
Abbreviations: TB: Tuberculosis, SINAN - Sistema de Informação de Agravos de Notificação (Brazilian Notification Information System), AFB: acid fast bacilli, and ART: Antiretroviral therapy.
[a] It did not include DM and HIV.
[b] ART frequency was calculated among the persons living with HIV.
[c] All individuals from the RePORT cohort had a diagnosis of pulmonary tuberculosis, in some cases with presence in other anatomical sites.
[d] Any drug (anti-TB) resistance except rifampicin and isoniazid: Pyrazinamide, ethambutol, streptomycin, kanamycin, and ethionamide.
[e] In RePORT-Brazil study, the results of anti-TB treatment are recorded at the last study visit (24 months after the start of treatment). By the time the present analyses were performed, 434 participants had not yet completed the last visit, and analyses of treatment outcomes did not include such participants.

Epidemiological and operational indicators of tuberculosis cases in RePORT-Brazil and SINAN

Finally, the epidemiological and operational indicators were compared between the cohorts (Supplementary Figure 1A–L). Among the 11 operational indicators, significant differences were identified between RePORT-Brazil and SINAN, during each year in the study period. The frequency of new cases of pulmonary TB diagnosed through Xpert -MTB/-RIF, smear, culture, or drug susceptibility testing among the total pulmonary TB cases was lower in each year in the SINAN cohort, likely due to RePORT inclusion criteria ($p < 0.01$, in each year) (Supplementary Figure 1B). In turn, this difference was also reflected by higher proportions of each type of TB screening test compared (Supplementary Figure 1F, and H). The coverage of HIV testing was also different between the datasets, with 70% in SINAN and 95% in RePORT ($p < 0.001$), also likely due to RePORT inclusion criteria. The ART initiation and cases receiving DOT was also significantly higher in RePORT-Brazil.

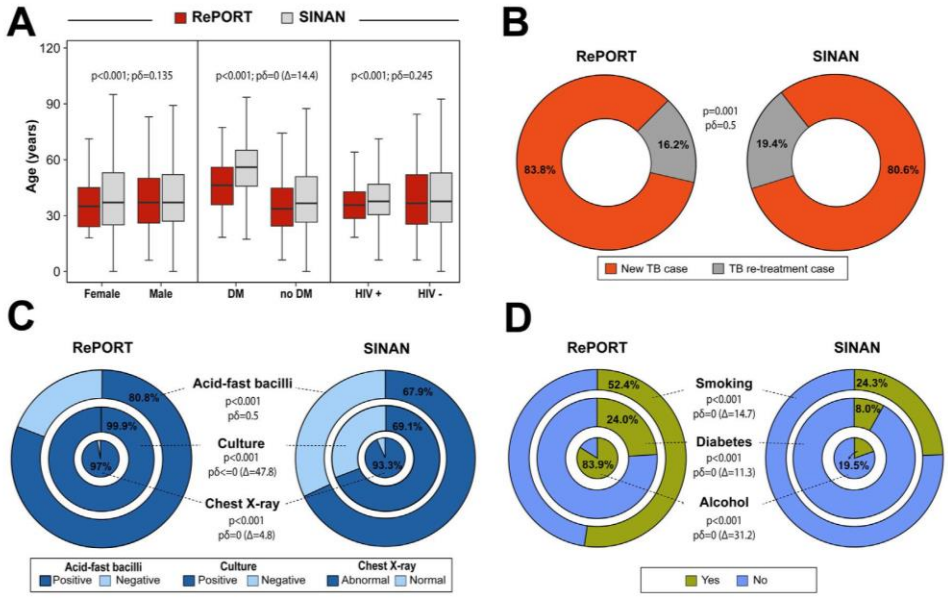

Figure 2. Characteristics of the TB cases in RePORT and SINAN (2015–2019).
(A) Comparison of the age distribution (median and interquartile range values) between sex, diabetes condition, and HIV infection among RePORT participants and TB cases reported by SINAN within the study period. (B) The proportion of new and retreatment cases of tuberculosis. (C) Comparison between RePORT and SINAN TB cases (prior to the initiation of anti-TB treatment) in regard to frequency of individuals stratified by acid-fast bacilli (AFB) and *M. tuberculosis* culture results as well as of abnormal chest radiograph presentation. (D) Comparison between RePORT and SINAN TB cases with regard to smoking habit and alcohol consumption (smoking and alcohol: in the past or at the time of evaluation before anti-TB treatment). The proportion of TB-diabetes comorbidity is also shown. See the Supplemental Fig. 1 for the interpretation of the pδ-value.
Abbreviations: Δ = delta-gap. pδ-value: second-generation p-value, RePORT: Regional Prospective Observational Research for Tuberculosis, SINAN: Sistema de Informação de Agravos de Notificação, and TB: Tuberculosis.

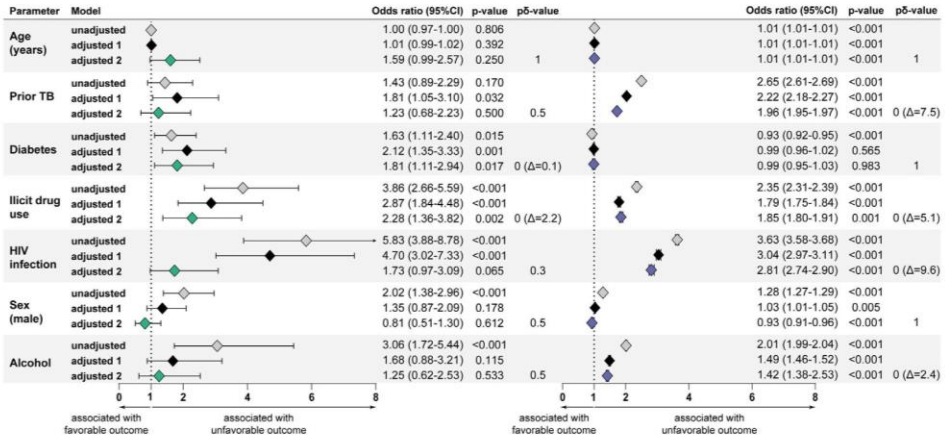

Figure 3. Characteristics associated with unfavorable treatment outcomes in tuberculosis patients.
Two logistic regression models (LASSO regression and mixed effects) were performed to evaluate the independent associations between clinical characteristics of tuberculosis patients and antitubercular treatment unfavorable outcomes (failure, death, and lost to follow-up) in either RePORT (left panel) or SINAN (right panel; where the CI are present, but narrow due to the large sample size). Optimal parameters were found by a cross-validation step, which was repeated 100 times to stabilize the results (Supplementary Table 2 for RePORT and/or Supplementary Table 3 for SINAN) and were included in the adjusted models.
Adjusted model 1: LASSO regression using a cross-validation step.
Adjusted model 2: The mixed effects model, including the variables "Brazilian states" as a random effect.
In addition to the p-value, the second-generation p-value (pδ-value) and the *delta-gap* (Δ) (when applicable) are shown. See the Supplemental Figure 2 for the interpretation of the pδ-value.
Abbreviations: Δ = delta-gap, pδ-value: second-generation p-value, RePORT: Regional Prospective Observational Research for Tuberculosis, SINAN: Sistema de Informação de Agravos de Notificação, and TB: Tuberculosis.

Discussion

In this study, demographic characteristics such as age, sex, and race were similar in both the RePORT-Brazil and SINAN cohorts of TB patients, which support our hypothesis that the RePORT-Brazil cohort is representative of individuals with pulmonary TB in Brazil (Fernandes et al., 2018; Zhang et al., 2011). However, certain characteristics varied in the RePORT-Brazil cohort as compared to the general TB population. Literacy rate was higher among patients in RePORT, possibly because study sites are located in large cities, where access to school and overall literacy are higher than in rural areas (Ministério da Educação, 2008). Alcohol consumption, smoking, and the use of illicit drugs were significantly more commonly reported in RePORT patients. The RePORT study may have a higher detection rate of substance use as it was included in structured questionnaires and validated tools for screening. Conversely, SINAN notification templates include simple yes/no questions to evaluate these characteristics, which may be more prone to reporting or detection bias (Rocha et al., 2020). Moreover, SINAN templates are completed by health care workers who collect this information from the patient or medical charts, which often lack the detailed information needed (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2007). These factors may have led to reduced substance use identification in the national database, as noted previously (Rocha et al., 2020; Silva et al., 2010).

The proportions of patients reporting comorbidities such as cancer, chronic obstructive pulmonary disease, kidney disease, and hypertension were similar in both cohorts. The proportion reporting "other" comorbidities was higher in SINAN, and the proportions reporting diabetes or HIV were higher in RePORT-Brazil. This may be due to differences in the ascertainment of these comorbid conditions in the two cohorts (Althubaiti, 2016). Abnormal chest x-rays were reported more often in RePORT cases, possibly that reflect care provided by trained TB specialists, which is not as common in most health care facilities in Brazil (Shazzadur Rahman et al., 2019). The increased frequency of extrapulmonary manifestations of TB may also reflect treatment by experienced TB specialists and greater availability of diagnostic tests at reference centers from RePORT.

Interestingly, our study identified differences in relevant clinical characteristics such as an increased prevalence of DM, HIV, and multidrug resistance in RePORT as compared to SINAN. These disparities may not necessarily reflect differences in the prevalence of these conditions in the study populations, but rather more frequent diagnosis and notification in RePORT because of uniform HbA1c and HIV testing. These comorbidities are known to be more frequent in patients with TB (Saraceni et al., 2018; Tankeu et al., 2017).

Similarly, all participants in RePORT-Brazil were required to have positive *M. tuberculosis* sputum cultures and drug susceptibility testing, in contrast to SINAN, which resulted in a selection bias. When compared to the national data, we found that in 2019 only 76.1% of patients with TB were tested for HIV, despite the fact that the national guidelines recommend HIV testing in all patients with a TB diagnosis and that low-cost HIV testing is available nationally. Testing for DM is not routinely recommended by national guidelines; patients may have blood glucose testing if they exhibit risk factors or classical symptoms of DM (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2013). In SINAN, the prevalence of DM is likely only self-reported DM and may therefore underrepresent the actual prevalence.

Regarding the detection of drug-resistant TB (DR-TB), the national statistics also indicate possible underdiagnosis. In 2019, nationally, 37.7% of patients with newly diagnosed TB had Xpert-MTB/-RIF performed, and only 24% had sputum culture performed, which suggests that, except for rifampicin, drug sensitivity was unknown for many cases. Among cases of retreatment, 30.4% had sputum culture performed and only 50% of those completed the recommended diagnostic workup, including drug sensitivity tests. This reflects the ongoing limited access to Xpert-MTB-RIF technology nationally (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2020a; Silva et al., 2018) and the lack of routine solicitation from physicians or capacity to perform sputum cultures and drug sensitivity tests in cases of presumed TB. The comparison of these two datasets indicates that the broad testing strategy adopted in the RePORT-Brazil protocol more accurately detected the presence of important comorbidities, exposures, and drug resistance in TB cases.

RePORT-Brazil and SINAN had a similar proportion of cases with cure, death, and loss to follow-up. Reporting on these outcomes is less difficult than other TB outcomes possibly due to the simplicity of their definitions. Nevertheless, RePORT had a higher proportion of treatment failures and lower frequency of individuals who were transferred out, than SINAN. These discrepancies may be because patients enrolled in RePORT-Brazil were actively followed up for 24 months from treatment initiation. In such scenarios, the treatment outcome is likely obtained in a more reliable fashion, particularly in cases of treatment failure, loss to follow-up, and transferred out. In SINAN, information on outcome is usually recorded at the end of treatment. In public health care centers, it is not recommended that patients return after finishing anti-TB treatment. Indeed, other studies (Baldez do Canto and Borges Nedel, 2020; Rocha et al., 2020; Silva et al., 2010) have described limitations related to the underreporting of treatment outcome results and lack of follow-up for patients who were transferred out or discontinued treatment.

This study had some limitations. RePORT-Brazil had more active follow-up than SINAN, and the ability to follow-up prospectively in the latter cohort was mainly because of the large number of patients. In addition, routine follow-up for clinical care usually does not extend beyond the end of TB treatment. Another limitation was that follow-up for study endpoints in RePORT-Brazil is ongoing. However, for this analysis, we truncated follow-up so that it was similar to SINAN. Nonetheless, the present study adds to current knowledge in the field by demonstrating the close similarities of the RePORT-Brazil and SINAN cohorts regarding patient characteristics and treatment outcomes. This is beneficial for both cohorts. For the smaller RePORT-Brazil cohort, this supports the generalizability of findings from current and future translational studies (Jaehn et al., 2020). For the larger SINAN cohort, it means that smaller, less-expensive population-based studies in RePORT-Brazil may provide important data that can inform TB treatment strategies throughout all of Brazil.

In this study, we found similarities between both databases, though significant differences were identified regarding TB diagnosis, due primarily to RePORT-Brazil inclusion criteria. This study highlights critical gaps in comprehensive TB care and identifies data that could be collected in SINAN that would facilitate improvements in the care and outcomes of TB patients in Brazil (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2013).

Summary

We compared a multicenter tuberculosis cohort enrolled from three regions of Brazil with the Brazilian National Tuberculosis Program registry, using innovative statistical approaches. The cohort was representative of TB patients overall, facilitating generalizability of study outcomes.

Ethical approval

All clinical investigations were conducted according to the principles of the Declaration of Helsinki. The RePORT-Brazil

protocol, informed consent, and study documents were approved by the institutional review boards at each study site and at Vanderbilt University Medical Center. Participation in RePORT-Brazil was voluntary, and written informed consent was obtained from all such participants. For the data extracted from SINAN, the anonymity of study subjects was preserved, and all data were de-identified.

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Disclaimer

The funder of the study had no role in the study design, data collection, or data analysis; however, a representative of the Brazilian Ministry of Health (K.A.) was involved in data interpretation and writing the report.

Conflicts of interest

None declared.

CRediT authorship contribution statement

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.11.140.

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SUPPLEMENTARY MATERIAL

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Supplementary Methods

RePORT Brazil

RePORT-Brazil study sites are located in Manaus (Amazonas state, Northern region), Salvador (Bahia state, Northeastern region), and Rio de Janeiro (Rio de Janeiro state, Southeastern region), with a total of five health units: Instituto Nacional de Infectologia Evandro Chagas, Clínica da Familia Rinaldo Delamare, and Secretaria de Saúde de Duque de Caxias (Rio de Janeiro), Instituto Brasileiro para Investigação da Tuberculose (Bahia), and Fundação de Medicina Tropical Doutor Heitor Vieira Dourado (Amazonas), representing both a heterogeneous population and the Brazilian cities with among the highest TB burden (Regional Prospective Observational Research for Tuberculosis, 2020).

SINAN

SINAN is a system for the notification and investigation of transmissible diseases that has been implemented, supported and maintained by the Brazilian Ministry of Health (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2020). Notification of these diseases, including TB, has been mandatory in Brazilian municipalities and states since 1993. For each reported case, epidemiologic and clinical data are collected (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2007). The information is provided without patient identifiers and available on the SINAN website (Ministério da Saúde do Brasil and Secretaria de Vigilância em Saúde, 2020).

Second Generation *p* (pδ)

Second generation p-values (pδ) are used for scientific adjustment when traditional p-values are likely affected by large sample sizes in each analytical group (example: the age distribution between RePORT and SINAN could be the same, but differ statistically (using a traditional p-value) due to the large sample size). The pδ provides more reliable inferential power by a *priori* specifying which hypotheses are more clinically significant. An interval for the null hypothesis, containing effect sizes that are indistinguishable

from the null value hypothesis. In this study, pδ identified differences that were clinically relevant.(Blume et al., 2018) For its interpretation, we considered all cases in which pδ = zero were clinically of interest, and statistically "significant" at 5% value, via classical p-values. On the contrary, when pδ = 1, the data affirmed only the effects that were null or almost null and that had little clinical interest, which would confirm the lack of association. When pδ = 0.5, then the data were inconclusive.(Blume et al., 2018) In case of pδ = zero, the delta-gap (Δ) was used, which is defined as the distance between the intervals in δ units. The delta-gap value was directly associated with the difference in distribution of values between the groups (i.e., the higher the delta value, the greater the effect size), as described in **Supplementary Figure 2**.

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Supplementary Table 1. Definition of tuberculosis treatment outcomes

Type of outcome treatment	Outcome tuberculosis treatment	RePORT	SINAN[a]
Favorable	Cure	Resolution of symptoms consistent with TB by the end of therapy. Patients without symptoms consistent with TB at the beginning of TB treatment cannot have their clinical response evaluated.	Cure is established when pulmonary TB patients, initially sputum smear-positive, present, during treatment, with at least two negative sputum smears: one in the follow-up phase and the other at the end of treatment.
	Completed treatment	When the patient does not have treatment failure or loss to follow-up, and has received at least 90% of the total number of doses of the standard recommended anti-TB therapy by the National TB Program in a period up to one year for drug susceptible cases, and up to two years for MDR cases. For drug-susceptible TB, the drug regimen consists of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampin for 4 months. For drug-resistant TB, treatment is according to the presence of resistance.	Completion of treatment based on clinical criteria and radiological: (i) when the patient has not undergone sputum examination due to absence sputum and are discharged based on clinical data and complementary exams, (ii) in cases of initially negative pulmonary tuberculosis; (iii) in cases of extrapulmonary tuberculosis
Unfavorable	Loss to follow up	A participant who no longer participates in study visit follow-up or when an outcome cannot be assigned due to insufficient information.	A patient who has failed to attend the unit for more than 30 consecutive days after the expected return date. In treatment cases supervised, the period of 30 days is counted from the last date of taking the drug.
	Death	A participant who dies for any reason after consenting to participate and prior to the end of the study.	On the occasion of knowledge of the patient's death during treatment.
	Failure	Sputum smear- or culture-positive at month 5 or later during treatment.	When sputum positivity persists at the end treatment. Also classified as failure are patients who beginning of treatment are strongly positive (++ or +++) and maintain this until the fourth month, or those with initial positivity followed by negativity and new positivity for two consecutive months, from the fourth month of treatment.
	Transferred out	When the patient is transferred to another health service.	When the patient is transferred to another health service.

Table note: [a]Described in the Manual of Recommendations for the Control of TB of Brazil. Abbreviations: RePORT: Regional Prospective Observational Research for Tuberculosis. SINAN: Sistema de Informação de Agravos de Notificação. MDR: Multidrug-Resistant. TB: Tuberculosis.

Supplementary Table 3. Characteristics of RePORT-Brazil TB cases according to anti-TB treatment outcome

Characteristics	Favorable outcome (n=435)	Unfavorable outcome (n=191)	p-value
Sex – no. (%)			<0·001
Male	262 (60·2)	144 (75·4)	
Female	173 (39·8)	47 (24·6)	
Age – median (IQR)	37 (27-50)	37 (26-49)	0·806
Race/Ethnicity – no. (%)			<0·001
White	117 (26·9)	35 (18·3)	
Black	115 (26·4)	37 (19·4)	
Asian	1 (0·2)	0 (0·0)	
Pardo	199 (45·7)	110 (57·6)	
Indigenous	3 (0·7)	9 (4·7)	
Literate– no. (%)	414 (95·2)	182 (95·3)	1·000
Health worker – no. (%)	21 (4·8)	9 (4·7)	1·000
Comorbidities[a] – no. (%)			<0·001
Cancer	7 (1·8)	3 (1·6)	
Chronic Obstructive Pulmonary Disease/Emphysema	2 (0·5)	0 (0·0)	
Kidney disease	1 (0·3)	2 (1·1)	
Hypertension	39 (10·1)	14 (7·7)	
Others	32 (8·2)	13 (7·1)	
No comorbidity	307 (79·1)	151 (82·5)	
Diabetes – no. (%)	93 (21·6)	59 (31·1)	0·015
HIV infection – no. (%)	51 (11·9)	84 (44·0)	<0·001
Antiretroviral therapy (ART)[b] – no. (%)	51(100)	72 (85·7)	0·005
Alcohol consumption – no. (%)	345 (79·3)	176 (92·1)	<0·001
Illicit drug use – no. (%)	83 (19·1)	91 (47·6)	<0·001
Smoking – no. (%)	192 (44·1)	121 (63·4)	<0·001
Prior TB – no. (%)	83 (19·2)	27 (14·3)	0·170
Abnormal chest x-ray – no. (%)	421 (96·8)	183 (95·8)	0·638
Type of TB[c] – no. (%)			0·020
Pulmonary	394 (90·6)	160 (83·8)	
Extrapulmonary	0 (0·0)	0 (0·0)	
Pulmonary and Extrapulmonary	41 (9·4)	31 (16·2)	
Positive acid-fast bacilli (AFB) – no. (%)	347 (80·0)	152 (80·4)	1·000
Positive culture – no. (%)	434 (100·0)	188 (99·5)	0·303
Drug-susceptibility testing (DST) – no. (%)			0·061
Rifampicin resistance	0 (0·0)	2 (1·1)	
Isoniazid resistance	12 (2·8)	13 (7·0)	
Rifampicin-Isoniazid resistance	5 (1·2)	10 (5·4)	
Any drug resistance[d]	47 (11·0)	11 (5·9)	
Sensitive	365 (85·1)	150 (80·6)	
Directly observed treatment (DOT) – no. (%)	242 (56·1)	102 (53·4)	0·541

Table note: Data represent no. (%) or median with Interquartile range (IQR). Favorable outcomes treatment: Bacteriological and clinical cure, Unfavorable outcomes treatment: failure, death and lost to follow-up (see details in **Supplementary Table 2**).

Alcohol consumption: Past or current any consumption of alcohol. Smoking: Past or current cigarette smoker. Illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin or crack)
[a]It did not include DM and HIV. [b]ART frequency was calculated among the persons living with HIV. [c]All individuals from the RePORT cohort had a diagnosis of pulmonary tuberculosis, in some cases with presence in other anatomical sites. [d]Any drug (anti-TB) resistance except rifampicin and isoniazid: Pyrazinamide, ethambutol, streptomycin, kanamycin, ethionamide.
Abbreviations: RePORT: Regional Prospective Observational Research for Tuberculosis. SINAN: Sistema de Informação de Agravos de Notificação. TB: Tuberculosis.

Supplementary Table 4. Characteristics of the SINAN patients according to anti-TB treatment outcome

Characteristics	Favorable outcome (n=258,355)	Unfavorable outcome (n=127,780)	p-value
Sex – no. (%)			<0·001
Male	175583 (68·0)	92379 (72·3)	
Female	82757 (32·0)	35393 (27·7)	
Age – median (IQR)	37 (26-51)	39 (28-53)	<0·001
Race/Ethnicity – no. (%)			<0·001
White	82457 (34·4)	35295 (30·0)	
Black	30777 (12·8)	18083 (15·4)	
Asian	1923 (0·8)	851 (0·7)	
Pardo	121438 (50·7)	62451 (53·0)	
Indigenous	3040 (1·3)	1112 (0·9)	
Literate– no. (%)	152793 (83·8)	63689 (80·4)	<0·001
Health worker – no. (%)	3771 (1·6)	919 (0·8)	<0·001
Comorbidities[a] – no. (%)			<0·001
Cancer	2106 (0·8)	1299 (1·0)	
Chronic Obstructive Pulmonary Disease/Emphysema	261 (0·1)	309 (0·2)	
Kidney disease	112 (0·0)	173 (0·1)	
Hypertension	25517 (9·9)	14573 (11·4)	
Others	39189 (15·2)	17002 (13·3)	
No comorbidity	191165 (74·0)	94422 (73·9)	
Diabetes – no. (%)	19724 (8·1)	9024 (7·8)	0·001
HIV infection – no. (%)	18769 (8·6)	23951 (24·9)	<0·001
Antiretroviral therapy (ART)[b] – no. (%)	7261 (38·7)	7128 (29·8)	<0·001
Alcohol consumption – no. (%)	38796 (15·8)	32216 (27·6)	<0·001
Illicit drug use – no. (%)	28545 (11·8)	26604 (23·3)	<0·001
Smoking – no. (%)	51842 (21·4)	34726 (30·2)	<0·001
Prior TB – no. (%)	36620 (14·2)	38724 (30·5)	<0·001
Abnormal chest x-ray – no. (%)	183227 (93·3)	92648 (93·8)	<0·001
Type of TB[c] – no. (%)			<0·001
Pulmonary	218993 (84·8)	107214 (83·9)	
Extrapulmonary	32970 (12·8)	15163 (11·9)	
Pulmonary and Extrapulmonary	6384 (2·5)	5388 (4·2)	
Positive acid-fast bacilli (AFB) – no. (%)	135107 (69·7)	58448 (64·5)	<0·001
Positive culture – no. (%)	58663 (68·1)	25162 (69·9)	<0·001
Drug-susceptibility testing (DST) – no. (%)			<0·001
Rifampicin resistance	129 (0·4)	498 (3·4)	
Isoniazid resistance	357 (1·0)	1351 (9·3)	
Rifampicin-Isoniazid resistance	106 (0·3)	1119 (7·7)	
Any drug resistance[d]	652 (1·9)	673 (4·7)	
Sensitive	32822 (96·3)	10823 (74·8)	
Directly observed treatment (DOT) – no. (%)	110588 (54·2)	27661 (36·9)	<0·001

Table note: Data represent no. (%) or median with Interquartile range (IQR). Favorable outcomes treatment: Bacteriological and clinical cure, Unfavorable outcomes treatment: failure, death and lost to follow-up (see details in **Supplementary Table 2**).

Alcohol consumption: Past or current any consumption of alcohol. Smoking: Past or current cigarette smoker. Illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin or crack)
[a]It did not include DM and HIV. [b]ART frequency was calculated among the persons living with HIV. [c]All individuals from the RePORT cohort had a diagnosis of pulmonary tuberculosis, in some cases with presence in other anatomical sites. [d]Any drug (anti-TB) resistance except rifampicin and isoniazid: Pyrazinamide, ethambutol, streptomycin, kanamycin, ethionamide.

Abbreviations: RePORT: Regional Prospective Observational Research for Tuberculosis. SINAN: Sistema de Informação de Agravos de Notificação. TB: Tuberculosis.

Supplementary Table 5. Characteristics of TB patients from Duque de Caxias city

Characteristics	RePORT-Brazil (n=196)	SINAN (n=4302)	p-value	pδ-value
Sex – no. (%)			0.107	0.38
Male	124 (63.3)	2957 (68.7)		
Female	72 (36.7)	1345 (31.3)		
Age – median (IQR)	39 (27-53)	37 (25-52)		1
Race/Ethnicity – no. (%)			<0.001	0.14
White	23 (11.7)	997 (27.1)		
Black	66 (33.7)	892(24.2)		
Asian	1 (0.5)	47 (1.3)		
Pardo	103 (52.6)	1739 (47.3)		
Indigenous	3 (1.5)	5 (0.1)		
Literate– no. (%)	187 (95.4)	2115 (82.0)	<0.001	0 (Δ=7.84)
Health worker – no. (%)	8 (4.1)	37 (1.1)	<0.001	0 (Δ=4.60)
Comorbidities[a] – no. (%)			<0.001	1
Cancer	0 (0.0)	17 (0.4)		
Chronic Obstructive Pulmonary Disease/Emphysema	3 (1.7)	4 (0.1)		
Kidney disease	1 (0.6)	4 (0.1)		
Hypertension	21 (12.0)	83 (1.9)		
Others	13 (7.4)	94 (2.2)		
No comorbidity	137 (78.3)	4100 (95.3)		
Diabetes – no. (%)	41 (21.1)	366 (9.8)	<0.001	0 (Δ=4.73)
HIV infection – no. (%)	8 (4.3)	482 (13.3)	<0.001	0 (Δ=4.47)
Antiretroviral therapy (ART)[b] – no. (%)	1 (12.5)	125 (29.9)	0.285	0.5
Alcohol consumption – no. (%)	163 (83.2)	715 (18.6)	<0.001	0 (Δ=27.45)
Illicit drug use – no. (%)	62 (31.8)	645 (17.1)	<0.001	0 (Δ=4.27)
Smoking – no. (%)	123 (62.8)	921 (24.2)	<0.001	0 (Δ=13.30)
Prior TB – no. (%)	32 (16.5)	1019 (23.8)	0.019	0.06
Abnormal chest x-ray – no. (%)	193 (98.5)	4124 (96.8)	0.181	0.5
Type of TB (Pulmonary) [c] – no. (%)	194 (99.0)	4259 (99.0)	0.997	0.5
Positive AFB – no. (%)	166 (85.6)	1262 (66.0)	<0.001	0.5
Positive culture – no. (%)	194 (100.0)	441 (60.2)	<0.001	0.5
Drug-susceptibility testing (DST) – no. (%)			0.002	0.62
Rifampicin resistance	0 (0.0)	9 (1.6)		
Isoniazid resistance	9 (4.7)	24 (4.3)		
Rifampicin-Isoniazid resistance	1 (0.5)	19 (3.4)		
Any drug resistance[d]	20 (10.5)	24 (4.3)		
Sensitive	161 (84.3)	488 (86.5)		
Directly observed treatment (DOT) – no. (%)	123 (64.1)	1478 (45.4)	<0.001	0 (Δ=3.83)
Treatment Outcome[e]– no. (%)			<0.001	0.62
Cure	109 (91.6)	2264 (66.2)		
Failure	2 (1.7)	3 (0.1)		
Relapse	0 (0.0)	63 (1.8)		
Death	7 (5.9)	286 (8.4)		
Lost to follow-up	0 (0.0)	529 (15.5)		
Transferred out	1 (0.8)	236 (6.9)		

Table note: Data represent no. (%) or median with Interquartile range (IQR). pδ-value: second-generation p-value. Δ= delta-gap. See the Supplemental Figure 2 for interpretation of the pδ-value. Details of the total data available in the re Report-Brazil and SINAN bases in the **Supplementary Table 2**.

Alcohol consumption: Past or current any consumption of alcohol. Smoking: Past or current cigarette smoker. Illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin or crack)
[a] It did not include DM and HIV. [b]ART frequency was calculated among the persons living with HIV. [c]All individuals from the RePORT cohort had a diagnosis of pulmonary tuberculosis, in some cases with presence in other anatomical sites. [d]Any drug (anti-TB) resistance except rifampicin and isoniazid: Pyrazinamide, ethambutol, streptomycin, kanamycin, ethionamide. [e]In RePORT-Brazil study, the results of anti-TB treatment are recorded at the last study visit (24 months after the start of treatment).

Abbreviations: TB: Tuberculosis. SINAN - Sistema de Informação de Agravos de Notificação. (Brazilian Notification Information System). AFB: acid fast bacilli. ART: Antiretroviral therapy.

Supplementary Table 6. Characteristics of TB patients from Manaus city

Characteristics	RePORT-Brazil (n=321)	SINAN (n=13561)	p-value	pδ-value
Sex – no. (%)			<0.001	0 (Δ=1.32)
Male	236 (73.5)	8597 (63.4)		
Female	85 (26.5)	4964 (36.6)		
Age – median (IQR)	34 (25-42)	36 (25-51)	0.787	1
Race/Ethnicity – no. (%)			<0.001	0.859
White	34 (10.6)	1528(11.7)		
Black	17 (5.3)	438 (3.3)		
Asian	2 (0.6)	71 (0.5)		
Pardo	256 (80)	10948 (83.5)		
Indigenous	11 (3.4)	125 (1.0)		
Literate– no. (%)	310 (96.9)	9097 (87.4)	<0.001	0 (Δ=8.08)
Health worker – no. (%)	13 (4.1)	186 (1.5)	<0.001	0 (Δ=4.09)
Comorbidities[a] – no. (%)			<0.001	1
Cancer	2 (0.7)	47 (0.3)		
Chronic Obstructive Pulmonary Disease/Emphysema	0 (0.0)	8 (0.1)		
Kidney disease	0 (0.0)	43 (0.3)		
Hypertension	18 (5.9)	235 (1.7)		
Others	13 (4.3)	334 (2.5)		
No comorbidity	272 (89.2)	12892 (95.1)		
Diabetes – no. (%)	107 (33.3)	1428 (11.0)	<0.001	0 (Δ=11.11)
HIV infection – no. (%)	163 (50.8)	2337 (22.8)	<0.001	0 (Δ=9.77)
Antiretroviral therapy (ART)[b] – no. (%)	50 (45.5)	1295 (70.3)	<0.001	0 (Δ=5.90)
Alcohol consumption – no. (%)	294 (91.6)	1893 (14.7)	<0.001	0 (Δ=38.37)
Illicit drug use – no. (%)	165 (51.4)	1297 (10.2)	<0.001	0 (Δ=20.04)
Smoking – no. (%)	195 (60.7)	1885 (14.8)	<0.001	0 (Δ=19.55)
Prior TB – no. (%)	40 (12.5)	2545 (18.8)	0.005	0 (Δ=0.50)
Abnormal chest x-ray – no. (%)	304 (94.7)	12567 (95.3)	0.602	0.5
Type of TB[c] – no. (%)	249 (77.6)	13311 (98.2)	<0.001	0 (Δ=24.63)
Positive AFB – no. (%)	239 (74.9)	3696 (54.5)	<0.001	0.5
Positive culture – no. (%)	318 (99.7)	2942 (56.5)	<0.001	0 (Δ=36.12)
Drug-susceptibility testing (DST) – no. (%)			0.015	0.31
Rifampicin resistance	3 (1.0)	22 (1.4)		
Isoniazid resistance	24 (7.6)	60 (3.8)		
Rifampicin-Isoniazid resistance	6 (1.9)	33 (2.1)		
Any drug resistance[d]	13 (4.1)	41 (2.6)		
Sensitive	268 (85.4)	1439 (90.2)		
Directly observed treatment (DOT) – no. (%)	237 (73.8)	1118 (17.4)	<0.001	0 (Δ=23.50)
Treatment Outcome[e]– no. (%)			<0.001	1
Cure	44 (27.8)	7543 (66.1)		
Failure	12 (7.6)	2 (0.0)		
Relapse	5 (3.2)	296 (2.6)		
Death	33 (20.9)	1064 (9.3)		
Lost to follow-up	56 (35.4)	1880 (16.5)		
Transferred out	8 (5.1)	425 (3.7)		

Table note: Data represent no. (%) or median with Interquartile range (IQR). pδ-value: second-generation p-value. Δ= delta-gap. See the Supplemental Figure 2 for interpretation of the pδ-value. Details of the total data available in the re Report-Brazil and SINAN bases in the **Supplementary Table 2.**
Alcohol consumption: Past or current any consumption of alcohol. Smoking: Past or current cigarette smoker. Illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin or crack)

[a] It did not include DM and HIV. [b]ART frequency was calculated among the persons living with HIV. [c]All individuals from the RePORT cohort had a diagnosis of pulmonary tuberculosis, in some cases with presence in other anatomical sites. [d]Any drug (anti-TB) resistance except rifampicin and isoniazid: Pyrazinamide, ethambutol, streptomycin, kanamycin, ethionamide. [e]In RePORT-Brazil study, the results of anti-TB treatment are recorded at the last study visit (24 months after the start of treatment).

Abbreviations: TB: Tuberculosis. SINAN - Sistema de Informação de Agravos de Notificação. (Brazilian Notification Information System). AFB: acid fast bacilli. ART: Antiretroviral therapy.

Supplementary Table 7. Characteristics of TB patients from Salvador city

Characteristics	RePORT-Brazil (n=252)	SINAN (n=10505)	p-value	pδ-value
Sex – no. (%)			0.515	0.5
Male	165 (65.5)	6668 (63.5)		
Female	87 (34.5)	3836 (36.5)		
Age – median (IQR)	37 (26-50)	39 (28-53)		
Race/Ethnicity – no. (%)			<0.001	0 (Δ=1.39)
White	18 (7.1)	725 (8.1)		
Black	131 (52)	2568 (28.7)		
Asian	3 (1.2)	64 (0.7)		
Pardo	1 (0.4)	5585 (62.3)		
Indigenous	165 (65.5)	18 (0.2)		
Literate– no. (%)	240 (95.2)	5688 (86.4)	<0.001	0 (Δ=5.54)
Health worker – no. (%)	13 (5.2)	139 (1.4)	<0.001	0 (Δ=6.70)
Comorbidities[a] – no. (%)			0.001	1
Cancer	0 (0.0)	70 (0.7)		
Chronic Obstructive Pulmonary Disease/Emphysema	0 (0.0)	26 (0.2)		
Kidney disease	0 (0.0)	22 (0.2)		
Hypertension	18 (7.9)	310 (3.0)		
Others	7 (3.1)	469 (4.5)		
No comorbidity	204 (89.1)	9608 (91.5)		
Diabetes – no. (%)	58 (23.1)	987 (10.6)	<0.001	0 (Δ=5.65)
HIV infection – no. (%)	3 (1.2)	1119 (15.7)	<0.001	0 (Δ=15.77)
Antiretroviral therapy (ART)[b] – no. (%)	1 (50.0)	598 (60.8)	0.754	0.5
Alcohol consumption – no. (%)	225 (89.3)	2088 (22.4)	<0.001	0 (Δ=30.06)
Illicit drug use – no. (%)	57 (22.6)	1104 (12.2)	<0.001	0 (Δ=3.64)
Smoking – no. (%)	104 (41.3)	1862 (20.3)	<0.001	0 (Δ=6.93)
Prior TB – no. (%)	19 (7.6)	2881 (27.6)	<0.001	0 (Δ=10.21)
Abnormal chest x-ray – no. (%)	251 (99.6)	9623 (95.2)	0.001	0 (Δ=5.12)
Type of TB[c] – no. (%)	252 (100.0)	10397 (99.0)	0.106	0.5
Positive AFB – no. (%)	225 (89.3)	2264 (62.0)	<0.001	0.5
Positive culture – no. (%)	250 (100.0)	1599 (67.4)	<0.001	0.5
Drug-susceptibility testing (DST) – no. (%)			<0.001	0.65
Rifampicin resistance	1 (0.4)	11 (1.0)		
Isoniazid resistance	6 (2.5)	44 (3.9)		
Rifampicin-Isoniazid resistance	3 (1.2)	33 (2.9)		
Any drug resistance[d]	19 (7.8)	23 (2.0)		
Sensitive	214 (88.1)	1020 (90.2)		
Directly observed treatment (DOT) – no. (%)	148 (58.7)	343 (6.6)	<0.001	0 (Δ=27.62)
Treatment Outcome[e]– no. (%)			<0.001	1
Cure	109 (75.7)	5395 (61.2)		
Failure	10 (6.9)	4 (0.0)		
Relapse	0 (0.0)	154 (1.7)		
Death	4 (2.8)	604 (6.9)		
Lost to follow-up	19 (13.2)	1240 (14.1)		
Transferred out	2 (1.4)	1248 (14.2)		

Table note: Data represent no. (%) or median with Interquartile range (IQR). pδ-value: second-generation p-value. Δ= delta-gap. See the Supplemental Figure 2 for interpretation of the pδ-value. Details of the total data available in the re Report-Brazil and SINAN bases in the **Supplementary Table 2**.

Alcohol consumption: Past or current any consumption of alcohol. Smoking: Past or current cigarette smoker. Illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin or crack)

[a] It did not include DM and HIV. [b] ART frequency was calculated among the persons living with HIV. [c] All individuals from the RePORT cohort had a diagnosis of pulmonary tuberculosis, in some cases with presence in other anatomical sites. [d] Any drug (anti-TB) resistance except rifampicin and isoniazid: Pyrazinamide, ethambutol, streptomycin, kanamycin, ethionamide. [e] In RePORT-Brazil study, the results of anti-TB treatment are recorded at the last study visit (24 months after the start of treatment).

Abbreviations: TB: Tuberculosis. SINAN - Sistema de Informação de Agravos de Notificação. (Brazilian Notification Information System). AFB: acid fast bacilli. ART: Antiretroviral therapy.

Supplementary Table 8. Characteristics of TB patients from INI/Rocinha city

Characteristics	RePORT-Brazil (n=291)	SINAN (n=38142)	p-value	pδ-value
Sex – no. (%)			0.007	0.01
Male	178 (61.2)	26150 (68.6)		
Female	113 (38.8)	11992 (31.4)		
Age – median (IQR)	34 (25-48)	35 (24-50)		1
Race/Ethnicity – no. (%)			<0.001	0 (Δ=0.80)
White	139 (47.8)	10575 (30.5)		
Black	58 (19.9)	7805 (22.5)		
Asian	0 (0)	339 (45.8)		
Pardo	93 (32)	60 (0.2)		
Indigenous	1 (0.3)	26150 (68.6)		
Literate– no. (%)	272 (93.5)	22508 (83.8)	<0.001	0 (Δ=4.76)
Health worker – no. (%)	11 (3.8)	575 (1.6)	0.003	0 (Δ=1.89)
Comorbidities[a] – no. (%)			<0.001	1
Cancer	8 (2.9)	244 (0.6)		
Chronic Obstructive Pulmonary Disease/Emphysema	3 (1.1)	93 (0.2)		
Kidney disease	4 (1.4)	117 (0.3)		
Hypertension	24 (8.7)	813 (2.1)		
Others	33 (11.9)	1518 (4.0)		
No comorbidity	205 (74.0)	35352 (92.7)		
Diabetes – no. (%)	44 (15.9)	2410 (7.3)	<0.001	0 (Δ=4.74)
HIV infection – no. (%)	46 (16.0)	3979 (13.0)	0.138	0.45
Antiretroviral therapy (ART)[b] – no. (%)	17 (54.8)	2257 (63.1)	0.341	0.5
Alcohol consumption – no. (%)	208 (71.5)	5269 (16.0)	<0.001	0 (Δ=23.34)
Illicit drug use – no. (%)	77 (26.6)	6240 (19.2)	0.002	0 (Δ=0.64)
Smoking – no. (%)	133 (45.7)	7772 (23.8)	<0.001	0 (Δ=6.94)
Prior TB – no. (%)	80 (27.9)	8253 (21.8)	0.013	0.07
Abnormal chest x-ray – no. (%)	279 (95.9)	35862 (95.2)	0.615	0.5
Type of TB[c] – no. (%)	242 (83.2)	37590 (98.6)	<0.001	0 (23.19)
Positive AFB – no. (%)	222 (76.6)	10530 (71.4)	0.080	0.5
Positive culture – no. (%)	291 (100.0)	9730 (77.3)	<0.001	0.5
Drug-susceptibility testing (DST) – no. (%)			<0.001	0.23
Rifampicin resistance	1 (0.3)	83 (1.6)		
Isoniazid resistance	12 (4.1)	207 (4.1)		
Rifampicin-Isoniazid resistance	16 (5.5)	143 (2.8)		
Any drug resistance[d]	46 (15.8)	200 (3.9)		
Sensitive	216 (74.2)	4446 (87.5)		
Directly observed treatment (DOT) – no. (%)	233 (80.9)	20451 (76.5)		0.34
Treatment Outcome[e]– no. (%)			<0.001	0.92
Cure	173 (84.4)	19581 (63.7)		
Failure	2 (1.0)	42 (0.1)		
Relapse	4 (2.0)	624 (2.0)		
Death	8 (3.9)	2388 (7.8)		
Lost to follow-up	17 (8.3)	4974 (16.2)		
Transferred out	1 (0.5)	2106 (6.8)		

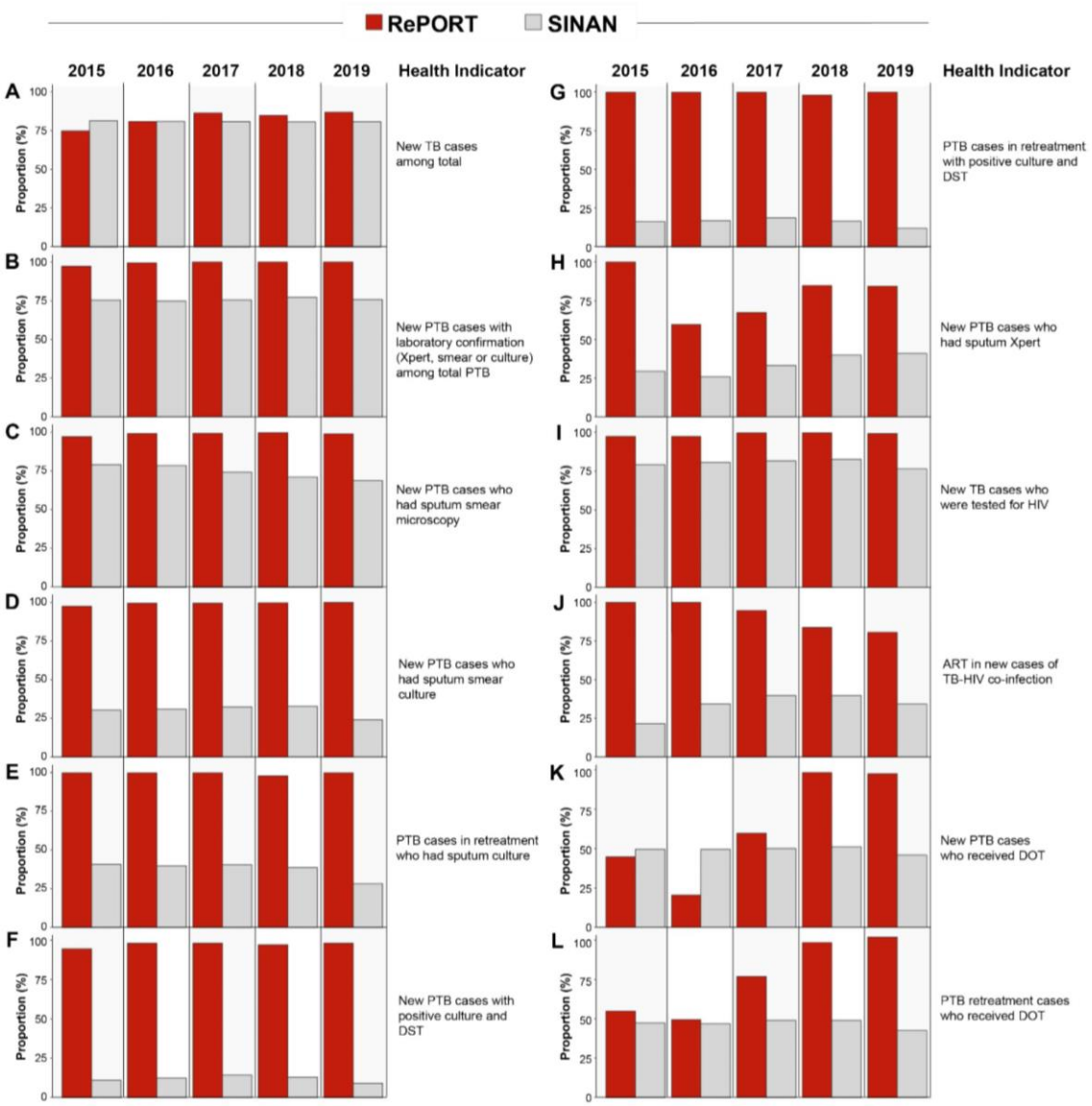
Table note: Data represent no. (%) or median with Interquartile range (IQR). pδ-value: second-generation p-value. Δ= delta-gap. See the Supplemental Figure 2 for interpretation of the pδ-value. Details of the total data available in the re Report-Brazil and SINAN bases in the **Supplementary Table 2**.

Alcohol consumption: Past or current any consumption of alcohol. Smoking: Past or current cigarette smoker. Illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin or crack)

[a] It did not include DM and HIV. [b]ART frequency was calculated among the persons living with HIV. [c]All individuals from the RePORT cohort had a diagnosis of pulmonary tuberculosis, in some cases with presence in other anatomical sites. [d]Any drug (anti-TB) resistance except rifampicin and isoniazid: Pyrazinamide, ethambutol, streptomycin, kanamycin, ethionamide. [e]In RePORT-Brazil study, the results of anti-TB treatment are recorded at the last study visit (24 months after the start of treatment).

Abbreviations: INI: Instituto Nacional de Infectologia Evandro Chagas. TB: Tuberculosis. SINAN - Sistema de Informação de Agravos de Notificação. (Brazilian Notification Information System). AFB: acid fast bacilli. ART: Antiretroviral therapy.

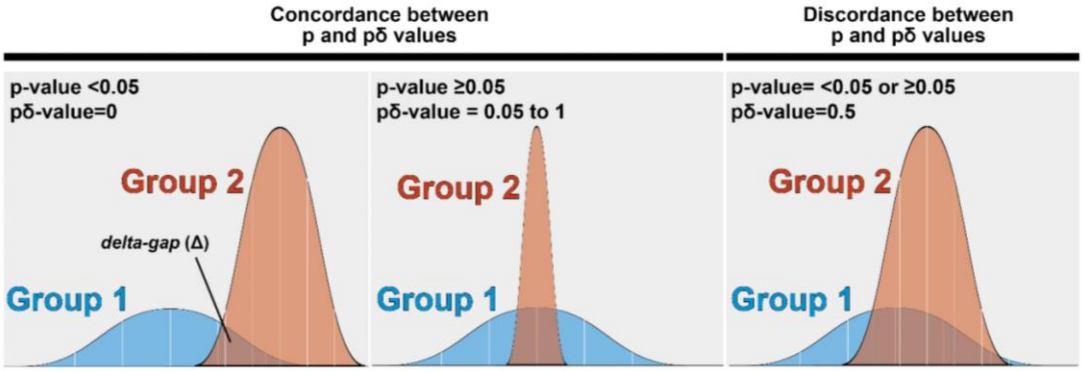
SUPPLEMENTARY FIGURE LEGENDS



Supplementary Figure 1. Epidemiological and operational indicators of tuberculosis cases in RePORT-Brazil) and SINAN during the study period.

Main epidemiological and operational indicators were calculated per year based on data available on the Notifiable Diseases Information System for Tuberculosis (SINAN-TB) and RePORT-Brazil data.

Abbreviations: DOT: directly observed tuberculosis therapy. DST: drug sensitivity test. PTB: pulmonary tuberculosis. TB: Tuberculosis.



Supplementary Figure 2. Interpreting the p-value and the second-generation p-value.

The second-generation p-value (pδ) is the proportion of data-supported hypotheses that are also null hypotheses. As such, second-generation p-values indicate when the data are compatible with null hypotheses pδ = 1, or with alternative hypotheses pδ = 0, or when the data are inconclusive 0< pδ < 1. The graphs illustrate three examples on how to interpret the pδ results. The left panel shows an interval estimate (Group 2) that does not overlap with the null region (Group 1), resulting in a second-generation p-value of 0. The *delta-gap* is the distance between the intervals in δ units and its value is directly associated with the difference in distribution of values between the groups (e.g. the higher the delta value, the more different the groups are). In such setting, both p-value and pδ-value indicate statistically significant differences. The middle panel displays an interval that falls entirely within the null region (with the exact mean values), so the second-generation p-value is 1. In this scenario, both p-value and pδ-value denote absence of differences statistically significant. The right panel shows an interval that includes the null region, but not entirely, resulting in a pδ-value of 0.5. In this last example, one may have a significant p-value and a nonsignificant pδ-value.

6.2 MANUSCRITO II

Determinants of losses in the latent tuberculosis cascade of care in Brazil: A retrospective cohort study

O rastreio de contactantes de pacientes com TB e tratamento profilático daqueles com infecção latente são importantes para o controle da transmissão da doença. Logo, a perda de acompanhamento desses pacientes pode estar associada ao lento combate da TB. Esse trabalho avalia os fatores associados às perdas na cascata de cuidados da ILTB em contatos de pacientes com TB em um centro de referência em uma região altamente endêmica do Brasil: Salvador-Bahia.

Resumo dos resultados: Nesta coorte acompanhada entre os anos 2009 e 2014, as perdas de seguimento ocorreram principalmente nos estágios iniciais do tratamento, que correspondem a realização de exames, retorno para a leitura do teste tuberculínico e primeiros meses de tratamento anti-TB. Além disso, foi demonstrado que o aumento da idade estava associado a perda de acompanhamento, independente dos outros fatores estudados.

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Determinants of losses in the latent tuberculosis cascade of care in Brazil: A retrospective cohort study

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ABSTRACT

Background: The present study evaluated factors associated with losses in the latent tuberculosis infection (LTBI) cascade of care in contacts of tuberculosis (TB) patients, in a referral center from a highly endemic region in Brazil.
Methods: Contacts of 1672 TB patients were retrospectively studied between 2009 and 2014. Data on TB screening by clinical investigation, radiographic examination and tuberculin skin test (TST) were extracted from medical records. Losses in the cascade of care and TB incidence within 2-year follow-up were calculated.
Results: From a total of 1180 TB contacts initially identified, only 495 were examined (58% loss), and 20 were diagnosed with active TB at this stage. Furthermore, 435 persons returned for TST result interpretation and 351 (~81%) were TST positive. Among those with positive TST, 249 (73%) were treated with isoniazid for 6 months whereas 51 abandoned therapy early. Three individuals who did not receive LTBI treatment, one with incomplete treatment and another who completed treatment developed active TB. A logistic regression analysis revealed that increases in age were associated with losses in the LTBI cascade independent of other clinical and epidemiological characteristics.
Conclusions: Major losses occur at initial stages and older patients are at higher risk of not completing the LTBI cascade of care.

Introduction

The majority of new cases of Tuberculosis (TB) occur in 30 countries with high disease burden such as Brazil, India, China, and South Africa (WHO, 2019). Furthermore, approximately 1.5 million deaths attributable to TB globally were reported in 2018 (WHO, 2019). Factors that may underlie the slow improvement of TB control include inaccurate diagnosis and loss to follow up of patients or household contacts undergoing anti-TB treatment (Zelner et al., 2018). In Brazil, despite significant investment from the government, the reported reduction in TB incidence (−1.34% per year) is considered insufficient to meet targets established by the World Health Organization (WHO) to reduce the incidence of TB by 90% by 2035 and eliminate TB (less than 1 incident case per 1,000,000 per year) by 2050 (Houben and Dodd, 2016). To achieve

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the WHO goals, it is critical to develop and implement effective health care policies that improve screening of TB and adherence to treatment of individuals diagnosed with latent TB infection (LTBI) (WHO, 2019).

LTBI is defined by the presence of a specific immune response against *Mycobacterium tuberculosis* (Mtb) in individuals who do not exhibit clinical and radiographic signs of active disease and who had negative microbiologic screening for TB (acid-fast bacilli [AFB] in sputum and Mtb cultures) (Parrish and Carroll, 2011). Approximately one fourth of the world's population is thought to be infected with Mtb, with most individuals developing active disease within the first two years after initial infection (Mendonca et al., 2016). It is imperative to target LTBI treatment in individuals at higher risk of developing active TB, including people with HIV and contacts of patients with pulmonary TB (Secretaria de Vigilância em Saúde, 2011).

Recent studies in Brazil and other high burden countries have described struggles in diagnosis and treatment of LTBI, highlighting the urgent need for new strategies to effectively treat this population (Martinez et al., 2017; Mendonca et al., 2015; Salame et al., 2017). The present study aimed to determine factors associated with losses in the LTBI cascade of care of TB contacts, who were followed up at a reference center for treatment of TB in the city of Salvador, Northeast of Brazil. A secondary aim was to compare the TB incidence between individuals who completed treatment for LTBI and those who did not.

Methods

Clinical study design

The present study was a retrospective cohort of contacts of microbiologically confirmed pulmonary TB patients (positive sputum cultures using solid media), who were followed at the outpatient clinic of the Instituto Brasileiro para Investigação da Tuberculose (IBIT) between 2009 and 2014, with data being extracted during the first quarter of 2018. IBIT is a reference center for the investigation and treatment of LTBI and active TB. At IBIT, TB screening is performed in contacts of every patient diagnosed with pulmonary TB. This referral center uses the WHO definition of TB contact, which is "a person living in the same household or who is in frequent contact (>20 hours per week) with the source case". As part of the routine investigation, all contacts identified during the TB case investigation are invited for a screening visit. During the first visit, the contacts are evaluated by nurse practitioners who perform tuberculin skin testing (TST), chest radiographic examination and bacteriological evaluation of sputum in those with cough in accordance with the Brazilian guidelines (Secretaria de Vigilância em Saúde, 2011). Patients with respiratory symptoms or with abnormal chest radiograph (e.g. infiltration or enlarged nodes) and/or blood laboratory results are then referred to consultation with pulmonologists at IBIT who further exclude TB by microbiological and clinical examination. Of note, for the present study, a positive TST was defined as ≥5 mm in duration (Secretaria de Vigilância em Saúde, 2011). All health care workers in this facility are routinely trained to identify contacts based on Brazilian guideline definitions from 2000 to 2016 (Secretaria de Vigilância em Saúde, 2011). During the study period, 1672 patients with active TB were identified and contacts search was performed by the health care workers from IBIT.

For this study, the data were manually extracted from the electronic medical record system used at IBIT (MV System Software, Brazil). Inclusion criteria were the following: to be a close contact of a pulmonary TB patient with documentation of at least one medical appointment at IBIT. The criterium used for diagnosis of LTBI was TST induration ≥5 mm in the absence of clinical and radiographic signs of the disease. Exclusion criteria included individuals with active TB and/or who had previous TB treatment.

Among the TB contacts who were diagnosed with LTBI, treatment was initiated depending on physician and patient decision to treat. The LTBI treatment was performed with isoniazid, at a dose of 5 mg/kg, a maximum of 300 mg and at least 180 doses. Individuals undergoing LTBI treatment received pills to be taken at

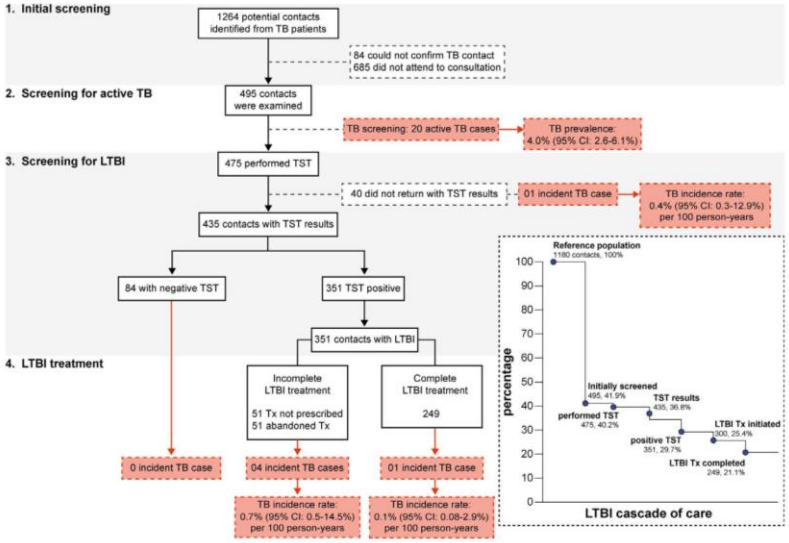

Figure 1. Study flowchart.
The flowchart depicts the retrospective cohort investigation performed at IBIT. Grey dashed lines represent exclusions from the study. Red squares indicate TB occurrence. TST, tuberculin skin test. Tx, treatment. See Methods for details in study design.

Individuals who did not receive any treatment were more commonly older, female, had history of smoking (e.g. an individual who reported smoking habit at least once in his/her life) and more often had comorbidities such as hypertension and type-2 diabetes (Supplementary Table S2). Study participants who received complete or incomplete treatment were more frequently household contacts of TB patients than those who were not treated (Supplementary Table S2). Nonspecific abnormal findings in chest radiographs (e.g. infiltrations and/or enlarged nodes) were more common in those who did not receive therapy (Supplementary Table S2).

A total of 5 individuals developed active TB during follow up, of which 3 did not have treatment for LTBI prescribed (representing 5.9% of this group), whereas 1 abandoned treatment and 1 completed isoniazid therapy (p = 0.003, Supplementary Table S2). Whilst 145 children under 5 years old were recruited, only 95 (65.5%) received treatment for LTBI. The LTBI individuals who developed active TB were all children ≤ 14 years old.

Given the results presented above, we tried to depict in more detail the characteristics of the study population that were associated with losses in the LTBI cascade of care. The majority of our population was under 18 years old (n = 387; Supplementary Table S3 and Figure 2A). The adults were mostly female (n = 38, 79.2%, p = 0.001), with a high frequency of hypertension, smoking and abnormal chest radiographs (p = <0.01). Approximately 98% of the children and adolescents had BCG vaccination (Supplementary Table S3 and Figure 2B). Moreover, children and adolescents more frequently received full LTBI treatment (n = 239; p = <0.01, Supplementary Table S3 and Figure 2B). Moreover, we compared the groups of study participants who were losses at any stage in the LTBI cascade of care with those who fully completed the cascade steps. Individuals who were losses in the cascade were on average older and more frequently female, smokers, and more commonly exhibited abnormal chest radiographs than those who completed the cascade (Table 2). On the converse, the individuals who completed the cascade were more frequently household contacts, had proportionally more TST results recorded and more commonly were BCG vaccinated (Table 2). Finally, we performed a multivariable binary logistic regression analysis to identify the characteristics that were independently associated with losses in the LTBI cascade of care. Among the variables that were statistically different between the study groups in univariate analysis, only age remained significantly associated with losses (Figure 3). Indeed, increases of 1 year of age resulted in augmented odds of loss in the LTBI cascade of care (Figure 3).

Discussion

Understanding losses in the cascade of care for LTBI and clinical outcomes of TB contacts is key for TB control and elimination strategies. Identification of the determinants that lead to losses may expand detection of LTBI cases in high TB-burden settings and reduce incident cases (Alsdurf et al., 2016; Morrison et al., 2008). In this study, we found an incidence of active TB in contacts of 2.2/100,000 inhabitants (95% CI:1.5/100,000–3.2/100,000), highlighting the importance of systematic screening in of such a population. Herein, we found significant losses in the LTBI cascade in a cohort of TB contacts from a primary care center that is a reference for TB care in the state of Bahia, Brazil. While increasing age was a factor independently associated with losses, all incident TB cases occurred in younger individuals (all ≤ 14years old). These findings highlight that the LTBI care cascade is ineffective even in a center renowned for high quality of TB care. Additional studies that evaluate losses in the LTBI cascade of care in other centers from

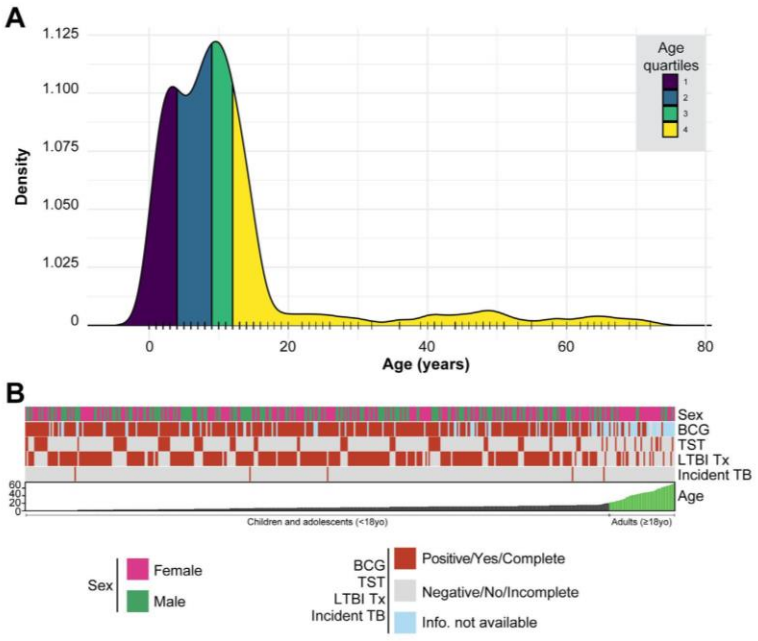

Figure 2. Characteristics of study participants.
(A) Density Plot visualizes age distribution of contacts. (B) Heatmap based on age distribution of the contacts shows the characteristics of sex, BCG vaccine, TST, LTBI treatment, and incidence TB of the participants.

Type 2 diabetes mellitus	8 (1.8)	0 (0.0)	1.00
Asthma	64 (14.7)	5 (12.5)	0.82
Hypertension	8 (1.8)	2 (5.0)	0.2
TB symptoms	3 (1.2)	0 (0.0)	1.00
Active TB diagnosis during follow up	5 (1.1)	1 (2.5)	0.41

Data represent no. and %, except for age which is reported as median and interquartile range.
[a] TST without result: performed TST but patients did not return to read the result. TB: Tuberculosis; TST: Tuberculosis skin test. Data were compared using the U Mann Whitney and Fisher's exact test.

Table 2
Characteristics of individuals according to losses in the LTBI cascade of care.

Characteristic	Total losses in the LTBI cascade of care (n = 142)	Complete LTBI cascade of care[a] (n = 300)	p-value
Age-median (IQR)	13 (6–29)	8 (4–11)	<0.01
Female	90 (63.4)	176 (52.9)	0.043
Smoking	16 (25.8)	4 (3.1)	<0.01
TST performed			<0.01
Yes	102 (71.8)	333 (100)	
No	40 (28.2)	0 (0)	
Contact type			<0.005
Household contact	118 (83.1)	307 (92.2)	
Other close contact	24 (16.9)	26 (7.8)	
BCG vaccination	84 (91.3)	261 (97)	0.035
Abnormal radiography	19 (15.6)	17 (5.2)	0.001
DM2	5 (3.5)	3 (0.9)	0.06
Asthma	16 (11.3)	53 (15.9)	0.2
LTBI treatment	53 (37.3)	249 (83)	<0.01

Data represent no. and %, except for age which is reported as median and interquartile range. LTBI: Latent Tuberculosis Infection; TST: Tuberculosis skin test.
[a] TST negative: 84 patients.

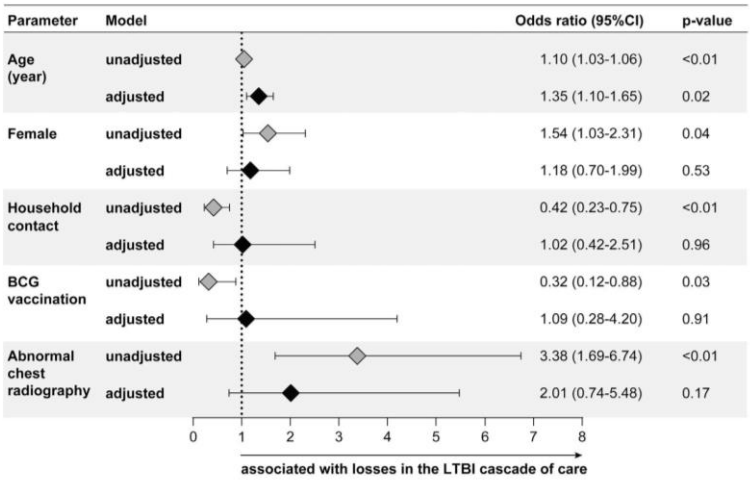

Figure 3. Multivariable logistic regression analysis to evaluate association between epidemiological and clinical characteristics and losses in the LTBI cascade of care. Using the study population stratified according to occurrence of losses in the LTBI cascade (total losses in the LTBI cascade vs. complete LTBI cascade, see Table 2 for detailed univariate comparisons). A binary logistic regression analysis was then employed with each variable individually (unadjusted) and then all variables shown in Table 2 were included in a multivariable model (adjusted). For age, calculations were performed per increase of 1 year.

high-burden cities in Brazil are warranted to determine the extent of this problem.

Our results identified that losses in the LTBI care cascade occurred primarily during the initial screening, implementation and completion of treatment for LTBI. These results are similar to those reported by other studies in Brazil (Salame et al., 2017), Uganda (Armstrong-Hough et al., 2017) and Vietnam (Fox et al., 2013). Moreover, a systematic review performed in middle to low-income countries from the Americas, European, African and Asian continents also confirmed this critical breakdown in LTBI screening and treatment (Morrison et al., 2008). Notably, in our study, 4 of the 5 individuals who developed active TB were initially seen by the health care service but failed to be adequately followed up.

While our study may appear to have a low number of screened TB contacts (41.9% of all the potential contacts identified), it is higher than the reported average for the State of Bahia (31.6%) (Secretaria de Vigilância em Saúde, 2017). Of note, a recent study carried out in São José do Rio Preto, São Paulo (Southeast Brazil) found that active case detection is not systematically performed despite the existence of a program specifically dedicated to providing assistance to TB contacts (Wysocki et al., 2016). Another study reported that only 43% of the contacts were screened with TST, very similar to our findings (Salame et al., 2017).

Most of the study subjects in our cohort were children and adolescents. Interestingly, only 88 (47%) of the 189 countries reporting TB cases described data on the number of contacts under 5 years of age who started treatment for LTBI (WHO, 2019). The present study recruited 145 children under the age of 5 years old (30.5% of the entire study population), although successfully implemented LTBI treatment was observed in only 94 individuals (65%). It is possible that the inability to effectively treat LTBI has led to the fact that all the TB incident cases occurred in persons $\leq$14 years old. In Brazil, one of the difficulties that may impair treatment of LTBI in children is a lack of trained clinical staff in

primary and secondary health units (Mendonca et al., 2015). This is unlikely to explain the screening and treatment implementation within the cohort at IBIT, given the high percentage of patients who initiated and completed LTBI treatment. A study in Malawi identified that LTBI treatment in children was hampered by a lack of materials to perform TST and equipment to perform diagnostic x-ray examination, although a shortage of trained personnel to interpret TST results and high workload of health care professionals appeared to be the most important barriers (Hector et al., 2017). These observations strongly support the idea that optimization of TB screening and implementation of treatment for LTBI in children is crucial, particularly in those who are household contacts of those with active TB.

Although the primary approach to diagnose LTBI traditionally consists of TST, interferon gamma release assays (IGRA) have emerged as an alternative to address the high rate of failure to return for TST interpretation (Albanese et al., 2015; Salame et al., 2017), which compromises LTBI diagnosis. In contrast, our study found that only 40 individuals (8% of those tested with TST) failed to return for interpretation. These differences made us hypothesize that there may be specific actions taken by health-care providers to increase return for TST interpretation, including explanation of the importance of TB screening particularly in non-household contacts.

A recent study demonstrated that contacts of pulmonary TB patients not receiving antitubercular treatment are at increased risk of withdrawing from the isoniazid treatment of LTBI (OR: 7.30; 95% CI: 1.00–53.3) in the city of Rio de Janeiro, Brazil (Mendonca et al., 2016). Sociodemographic factors should be considered as they may also impact LTBI treatment adherence. Currently supported treatment of LTBI in Brazil is the 6 months isoniazid regimen, while an alternative three-month approach with once weekly directly observed isoniazid-rifapentine is highly efficient (Sterling et al., 2011). Shorter treatment duration could increase adherence, offering an alternative to that implemented by the Brazilian government. Furthermore, a report indicates that 6-month treatment of LTBI with isoniazid may be inferior (International Union Against Tuberculosis Committee on Prophylaxis, 1982) and is contraindicated by the American Thoracic Society (ATS) / Centers of Disease Control and Prevention (CDC) for children.

Whilst our study has several strengths including a well characterized cohort with thorough follow up data and including a younger population, there are limitations that warrant discussion. There are limitations similar to other retrospective studies based on analysis of secondary data, such as loss to follow up information. Regardless, the results presented here illuminate a serious situation in the follow up of a population with high risk of developing active TB disease, even in a TB treatment referral center with a high cure rate of active TB cases.

Conclusions

This study demonstrates significant losses in the LTBI cascade in an important TB referral center from large city in Brazil. Most of the losses occurred in the first step of the cascade, which was the initial screening. Older age was the most important factor associated with the losses, although incident active TB cases preferably occurred in children and adolescents.

Contributions

Conceived and designed the study: NCNA, CMSC, EMN, BBA. Performed the experiments: MBA, JMC-A, MSR, PSS-M, GMM, IMBM, ICPES, LLA, CMA, LAS. Analyzed the data: NCNA, MBA, JMC-A, EMN, BBA. Wrote the paper: NCNA, MBA, KMC-A, BBA

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Potential conflicts of interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.02.015.

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Supplementary Table 2. Characteristics of LTBI patients according to treatment of LTBI

Characteristic	Treatment of LTBI			P-value
	Complete n=249	Incomplete n=51	Not prescribed n=51	
Age -median (IQR)	8 (4-12)	9 (2-15)	16 (8-58)	<0.01
Female	129 (51.8)	28 (54.9)	39 (76.5)	0.003
Smoking	2 (2.5)	1 (6.7)	6 (24)	0.001
Had results for HIV serology	10 (4)	2 (3.9)	1 (2)	0.521
Household contact of TB patient	233 (93.6)	48 (94.1)	39 (76.5)	0.001
BCG vaccination	196 (98)	41 (93.2)	30 (96.8)	0.313
Performed chest radiography	246 (98.8)	50 (98)	46 (90.2)	0.001
Abnormal chest radiography	10 (4.1)	1 (2)	11 (23.9)	<0.01
Active TB diagnosis during follow up	1 (0.4)	1 (2)	3 (5.9)	0.003
Asthma	40 (16.1)	6 (11.8)	5 (9.8)	0.198
Hypertension	2 (0.8)	0	3 (5.9)	0.019
Type 2 diabetes mellitus	2 (0.8)	1 (2)	4 (7.8)	0.002

Data represent no. and %, except for age which is reported as median and interquartile range. TB: Tuberculosis; TST: Tuberculosis skin test. Data were compared using the Kruskal Wallis test.

Supplementary Table 3. Characteristics of contacts of patients with pulmonary tuberculosis stratified by age

	Children and adolescents (<18yo) n=387	Adults (≥18yo) n=48	P-value
Female	205 (53)	38 (79.2)	0.001
Asthma	60 (15.5)	4 (8.3)	0.278
Hypertension	0 (0)	8 (16.7)	<0.01
Smoking	0 (0)	11 (36.7)	<0.01
BCG vaccination	320 (98.2)	12 (66.7)	<0.01
Abnormal chest radiography	18 (4.7)	11 (25)	<0.01
TST result			0.85
Positive	313 (80.9)	38 (79.2)	
Negative	74 (19.1)	10 (20.8)	
Treatment LTBI			<0.01
Complete	239 (76.4)	10 (26.3)	
Incomplete	47 (15)	4 (10.5)	
Not prescribed	27 (8.6)	24 (63.2)	
TB incidence	4 (1)	1 (2.1)	0.44

Data represent no. and %.BCG: Bacillus Calmette-Guérin, LTBI: Latent Tuberculosis infection, TB: tuberculosis, TST: Tuberculosis skin test; compared using chi-squared test

6.3 MANUSCRITO III

Determinants of losses in the latent tuberculosis infection cascade of care in Brazil.

Após identificar os determinantes na perda de acompanhamento de ILTB em um centro de referência entre os anos de 2009 e 2014, nós decidimos expandir a avaliação para outros quatro centros, utilizando a coorte retrospectiva do RePORT-Brasil com dados do período de 2015 a 2019. Assim como o trabalho anterior, este estudo também avalia os fatores associados às perdas na cascata de cuidados da ILTB em contatos de pacientes com TB, agora em cinco centros distribuídos em quatro cidades brasileiras altamente endêmicas para TB: Salvador-BA, Manaus-AM, Duque de Caxias-RJ e Rio de Janeiro-RJ (2 centros).

Resumo dos resultados: Nesta coorte composta por 4145 contatos acompanhados entre 20015 e 2016, as perdas de seguimento ocorreram em todos os estágios do tratamento, mas novamente se concentraram nas etapas iniciais. Ao expandir as análises nesse estudo, conseguimos também identificar que o baixo status socioeconômico e a coinfecção por HIV aumentaram o risco de não completar a cascata de acompanhamento de ILTB de forma independente dos outros fatores.

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Original research

BMJ Global Health

Determinants of losses in the latent tuberculosis infection cascade of care in Brazil

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ABSTRACT

Introduction Factors associated with losses in the latent tuberculosis infection (LTBI) cascade of care in contacts of patients with tuberculosis (TB) were investigated in a multicentre prospective cohort from highly endemic regions in Brazil.

Methods Close contacts of 1187 patients with culture-confirmed pulmonary TB were prospectively studied between 2015 and 2019, with follow-up of 6–24 months. Data on TB screening by clinical investigation, radiographic examination and interferon-gamma release assay (IGRA) were collected. Multivariable regressions were used to identify determinants of losses in the LTBI cascade.

Results Among 4145 TB contacts initially identified, 1901 were examined (54% loss). Among those examined, 933 were people living with HIV, ≤5 years old and/or had positive IGRA results, and therefore had a recommendation to start TB preventive treatment (TPT). Of those, 454 (23%) initiated treatment, and 247 (54% of those initiating; 26% of those in whom treatment was recommended) completed TPT. Multivariable regression analysis revealed that living with HIV, illiteracy and black/*pardo* (brown) race were independently associated with losses in the cascade.

Conclusion There were losses at all LTBI cascade stages, but particularly at the initial screening and examination steps. Close contacts of low socioeconomic status and living with HIV were at heightened risk of not completing the LTBI cascade of care in Brazil.

Key questions

What is already known?
- The treatment of latent tuberculosis infection (LTBI) is a cornerstone for tuberculosis (TB) control and elimination.
- Recent studies indicate that important losses occur at all stages of the LTBI cascade of care. However, the reasons for these losses are not well known.

What are the new findings?
- In a large prospective cohort of contacts of persons with TB in Brazil, we identified losses in all LTBI cascade of care stages, mostly at the initial screening and examination steps.
- Low socioeconomic status and HIV infection were significant determinants of losses in the LTBI cascade of care, independent of other confounding factors.

What do the new findings imply?
- The greatest losses in the LTBI cascade occurred in people at the highest risk of developing active TB.
- Interventions to improve retention of these groups in the LTBI cascade are urgently needed.

INTRODUCTION

The United Nations (UN) and the WHO have set ambitious targets for reducing the global burden of tuberculosis (TB) by 2030, and recognise the essential role of treatment of latent TB infection (LTBI) as a strategy for TB control and elimination.[1 2] Management of LTBI involves multiple stages in the care process, from the identification of at-risk populations for testing until completion of TB preventive therapy (TPT).[1 2]

Brazil is one of the 30 high TB-burden nations. Despite strategies implemented by the National TB Control Program, TB rates have changed little in recent years.[3] Among the most recent recommendations of the Brazilian Ministry of Health was TPT for all TB contacts with a positive interferon-gamma release assay (IGRA) or tuberculin skin testing (TST), as well as all close contacts who are children≤5 years old or people living with HIV (PLWH), regardless of the test result.[4]

Recent studies conducted in high-income and low-income and middle-income countries indicate that important losses occur at all stages of the LTBI cascade of care.[5] A study conducted in 12 health facilities in three Brazilian cities with high TB incidence rates found that most losses in the cascade occurred in the first two steps, which were contact identification and TST.[6] Another study found that few people who had a positive TST were started on TPT, and the completion rate was also low.[7] In a study carried out in a paediatric hospital from Rio de Janeiro, Brazil, there was an association between low human development index and loss to follow-up during TPT in children and adolescents.[8]

Modelling studies suggest that diagnosing and treating LTBI in persons at high risk of developing active disease will accelerate TB elimination.[9 10] However, there can be many challenges in implementing this policy programmatically. Thus, evaluating the cascade of care of LTBI and the factors associated with failures at each step can provide important insights for TB control.

To date, most of the studies evaluating the LTBI care cascade have been retrospective or cross sectional. Therefore, the established literature does not currently provide robust identification of reliable factors that directly lead to losses in the LTBI care cascade. The current study was performed to fill this important gap in knowledge, and to help design decision-making strategies to improve TB control. We evaluated the LTBI care cascade in a prospective Brazilian cohort of contacts of patients with culture-confirmed pulmonary TB (PTB), and identified factors associated with losses at each phase of the cascade.

METHODS

Study design

In this study, we included data from close TB contacts identified in the Regional Prospective Observational Research in Tuberculosis (RePORT)-Brazil cohort[11] between 27 August 2015, and 18 July 2019, with follow-up of up to 24 months, for initiation of TPT, and completion of TPT after initiation.

The RePORT-Brazil consortium is an ongoing, multicentre, cohort study, which follows culture-confirmed PTB cases and their close contacts. Enrolment sites are in three Brazilian states, recruiting participants from five health units: Instituto Nacional de Infectologia Evandro Chagas, Clínica da Familia Rinaldo Delamare and Secretaria de Saúde de Duque de Caxias (all from Rio de Janeiro state), Instituto Brasileiro para Investigação da Tuberculose (Salvador, Bahia), and Fundação Medicina Tropical Dr. Heitor Vieira Dourado (Manaus, Amazonas). The representativeness and operational indicators of the RePORT-Brazil cohort compared with all patients with TB in Brazil have been described previously.[11] Site details are presented in the online supplemental material 1.

For the present study, contacts were eligible to participate if exposed to an index case of culture-confirmed PTB who enrolled into RePORT-Brazil and had no evidence of active TB. Exposure to the index TB case was defined as at least 4 hours in 1 week in the 6 months prior to TB diagnosis.

Procedures

After enrolment of the index case, close contacts were invited to be interviewed and examined at the RePORT-Brazil healthcare units by phone call, text message or in person. Eligible contacts who attended the study sites were approached by study personnel to enrol into the RePORT-Brazil cohort and to be investigated for LTBI. Contacts were evaluated in-person at baseline and 6 months after enrolment; subsequent evaluations every 6 months were by telephone. At baseline, we performed a clinical evaluation, chest X-ray, and collected blood for IGRA and HIV testing. Clinical and demographic data were collected via standardised case report forms. All procedures were performed according to the Brazilian National TB Guideline.[4] Per the RePORT-Brazil protocol, all contacts returned after 6 months/complete TPT for a new clinical evaluation. Contacts with a negative or indeterminate baseline IGRA test underwent repeat testing at month 6. IGRA collection, processing and interpretation were performed according to the manufacturer's recommendations for QuantiFERON assay (Qiagen).

We considered eligible for TPT all TB contacts with a positive IGRA, as well as all close contacts who were children≤5 years old or PLWH, regardless of the test result.[2 4] Isoniazid (6–9 months) were used for TPT,[2 4] according to the routine practice of the health units and medical provider decision.

All contacts identified by patients with TB and with whom the study team was able to communicate were encouraged to be evaluated clinically and to initiate and complete TPT (if recommended and initiated), regardless of their follow-up in the study.

LTBI cascade: definitions of each stage of care

We used the cascade of care model published previously[5 7 12]; this model was first used for people with HIV.[13] The accumulated quantification allowed us to observe the impact of the losses at each stage of care. For this model, the following stages of the LTBI cascade of care were considered: (1) identified by patients with TB as close contacts (reference population); (2) initially screened for LTBI presented to clinic; (3) agreed to participate, signed consent, completed the medical examination, had IGRA performed and radiographic evaluations; (4) recommended to receive TPT; (5) accepted and initiated TPT; (6) completed TPT (defined as:>6 months of isoniazid).

Definition of losses in the LTBI cascade

For this study, we considered losses in the LTBI cascade among the participants who provided informed consent, were examined and performed the first IGRA, and in addition: (1) contacts who did not perform the second

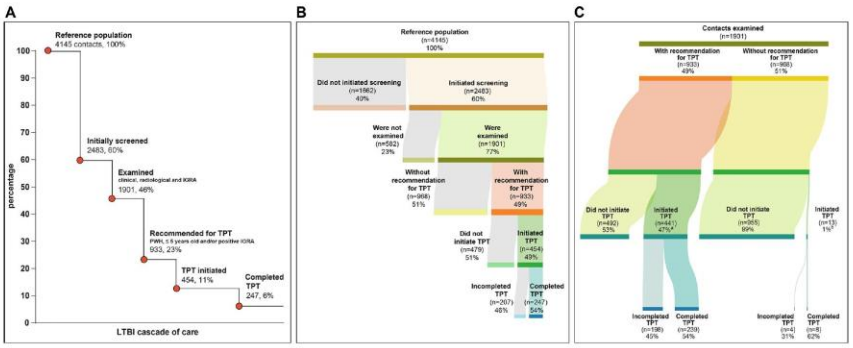

Figure 1 Cascade of care of latent tuberculosis infection (LTBI) in contacts from tuberculosis (TB) cases. (A) Losses and drop-outs at each stage of the LTBI cascade of care. Percentages were calculated among the number of contacts initially identified (n=4145). (B) Reference population and distribution among losses in the LTBI cascade of care and those who completed the LTBI cascade. (C) This figure shows the number of contacts who started treatment and those who completed treatment according to the category of TB preventive therapy (TPT) recommendation. (A) Four contacts were still undergoing TPT at the time of analysis (not considered losses). (B) One contact was still undergoing TPT at the time of analysis (not considered loss). IGRA, interferon-gamma release assay; PWH, people with HIV.

IGRA (when applicable) or (2) did not initiate recommended TPT or (3) did not complete TPT.

Data analysis

Categorical variables were presented as frequencies and compared using Fisher's exact test (2×2) or Pearson's χ^2 test. Continuous variables were described using median and IQRs and compared using the Mann-Whitney U test (2 groups) or the Kruskal Wallis test (>2 groups).

A multivariable generalised estimating equation[14] with a logit-link and an independent working correlation matrix was used to identify factors associated with losses in the LTBI cascade of care. Close contacts from the same TB index case and study site were treated as a cluster because participants from the same site could be correlated, as well as close contacts of the same TB index case. Variables included (age, alcohol consumption, comorbidities, illicit drug use, education, HIV infection, income, sex, smoking, secondary smoking, race and time between the baseline visit of the TB case and baseline visit of the contact) in all multivariable regressions were selected a priori, based on clinical factors and the literature.[5 15]

Because a proportion of the data were missing (maximum of 3.3% for income), multiple imputation by chained equations[16] was used to generate 20 imputed datasets and final estimates were obtained via Rubin's rule.[17] The imputation procedure was based on logistic models for categorical variables (race, income and education level), adjusting for baseline variables and outcome. Hierarchical cluster analysis (Ward's method) was employed to depict the overall profile of the study subgroups stratified according to the final IGRA status.

Data analysis was performed using SPSS V.25.0 (IBM) GraphPad Prism V.8.0 (GraphPad Software, La Jolla, California), JMP Pro V.14.0 (SAS), and R V.3.5.0 (R Foundation). All analyses were prespecified and two tailed. Differences with p value<0.05 were considered statistically significant.

Patient and public involvement

Neither patients nor the public were involved in the design, conduct or reporting of the research.

RESULTS

Characteristics of the study participants

There were 4145 close contacts referred from 1187 PTB cases (average of 3.5 contacts per TB case), but only 2483 contacts of 641 culture confirmed PTB cases could be reached for invitation to present at the healthcare units and showed up for LTBI screening (figure 1A). Of the 2483 contacts who presented to clinic and were invited to participate in the study, 1901 (77%) agreed to participate in the study, provided informed consent and were investigated for LTBI (figure 1A).

The characteristics of TB contacts are presented in table 1. Median age was 32 years (IQR 16.2–46.8), 1130 (59%) were female, 1507 (79%) were black/*pardo* (brown), 192 (10%) were illiterate and 46 (2%) were PLWH. A positive IGRA result was detected in 43% of the study participants, including results from both baseline and month 6. Participants with a positive IGRA were more likely to report smoking (30% vs 24%; p=0.002), and secondary smoking (35% vs 30%; p=0.04) than persons with a negative IGRA result.

Losses of LTBI cascade of care

The losses in the LTBI cascade are presented in figure 1. We observed losses at all steps of the cascade. Most losses occurred early in the cascade, where 40% of the identified contacts were not evaluated for screening, and

Table 1 Characteristics of the tuberculosis (TB) contacts by interferon-gamma release assay (IGRA) result

Characteristics	Negative (n=1059, 57%)	Positive (n=813, 43%)	P value
Female—no. (%)	606 (57)	509 (63)	0.002
Age—median (IQR)	30 (15–44)	36 (18–50)	0.004
Race/ethnicity—no. (%)*			0.003
Black/Pardo	813 (77)	671 (83)	
Others	245 (23)	142 (17)	
Income—no. (%)†			0.954
More than a minimum wage	409 (40)	276 (35)	
Equal or less than a minimum wage	388 (38)	357 (45)	
Without income	225 (22)	155 (20)	
BCG scar—no. (%)	950 (90)	721 (89)	0.498
HIV infection—no. (%)	32 (3)	14 (2)	0.097
Antiretroviral therapy—no. (%)	26 (8)	10 (7)	0.465
Education—no. (%)‡			0.137
Literate	943 (89)	743 (91)	
Illiterate	114 (11)	70 (9)	
Smoking—no. (%)§	253 (24)	246 (30)	0.002
Secondary smoking—no. (%)¶	319 (30)	281 (35)	0.04
Alcohol consumption—no. (%)**	565 (53)	442 (54)	0.674
Alcohol consumption (years)—median (IQR)	10 (3–18)	14 (5–25)	0.002
CAGE score of 2 and above—no. (%)††	110 (30)	67 (24)	0.075
Illicit drug use—no. (%)	102 (10)	84 (10)	0.640
Comorbidities—no. (%)‡‡	242 (23)	199 (245)	0.411
Diabetes	58 (6)	34 (4)	0.235
Hypertension	120 (11)	111 (14)	0.137

Data represent no. (%). or median with IQR.
29 (1.5%) individuals had an indeterminate result in the first or second IGRA.
*Race ethnicity was self-reported. Others ethnicities: white, Asian and Indian.
†Income: monthly money received in the household, categorised in wage on this study. One Brazilian minimum wage was US$266/month (The World Bank), the average value in the period (2015–2019).
‡Education: categorised in: literate: defined as patients who reported ability to read and write. Illiterate: defined as patients who reported unable to read or write.
§Smoking: defined as patients who reported currently smoking or before being diagnosed with tuberculosis.
¶Secondary smoking: patients who reported being exposed to cigarette smoke from other smokers (passive smoker).
**Alcohol consumption: defined as patients who reported consuming currently alcohol or before being diagnosed with tuberculosis.
††Alcohol abuse was defined as a CAGE score ≥2 points as described in Methods. Continuous variables were compared using the Mann-Whitney U test and categorical variables were using the Fisher's exact test (2×2) or Pearson's χ^2 test. Missing information was identified in three variables: race (1 (0.05%)), income (62 (3.3%)) and education (2 (0.1%)). These three variables were imputed based on baseline variables and outcome.
‡‡Comorbidities: at least one comorbidity (diabetes, hypertension, cancer, chronic obstructive pulmonary/emphysema, kidney disease, heart disease, liver disease and depression).

another 14% were not examined (figure 1A). Of the 933 contacts who met criteria for receiving TPT, 441 (47%) initiated TPT (figure 1B). Of the 441 who initiated treatment, 239 (54% of those initiating; 26% of those eligible; 6% of all contacts) completed it (figure 1A–C). Of those who completed the recommended treatment, all received isoniazid: 24 contacts for 6 months and 215 contacts for 9 months.

Analyses of the time from detection of the PTB index cases to screening of contacts are presented in figure 2. Contacts were evaluated on average approximately 1 month after the diagnosis of the TB index case (median=36 days) (figure 2A–B). Of note, contacts with different outcomes in the LTBI cascade could not be distinguished based on time from identification of the TB index case and the first screening for LTBI (figure 2B–C).

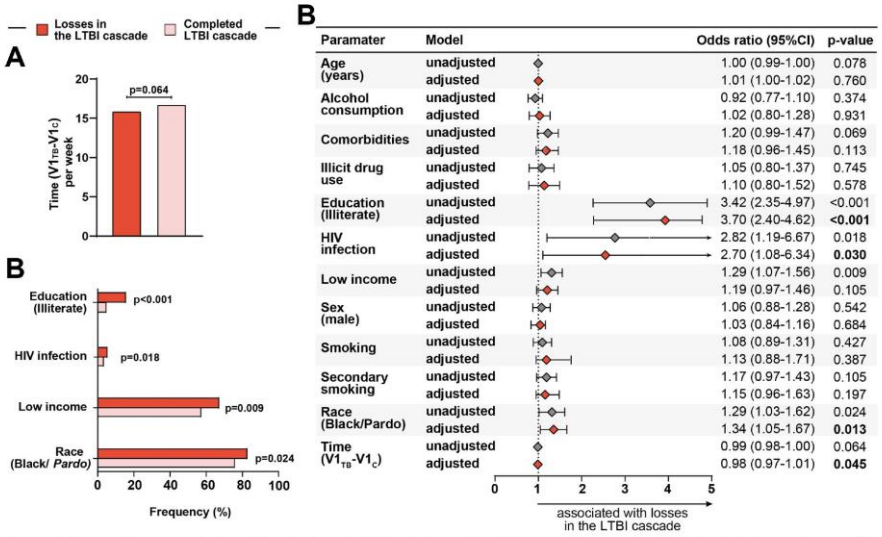

Figure 3 Association between epidemiological and clinical characteristics and losses in the latent tuberculosis infection (LTBI) cascade of care. (A) Time (per week) distribution among losses in the LTBI cascade of care and those who completed the LTBI cascade. Data were compared using the Mann-Whitney U test. (B) Frequency of race/ethnicity (black and *pardo*), income (see definition below), secondary smoking, comorbidities (see definition below) and education (illiterate) between TB contacts stratified based on losses in the LTBI cascade. Data were compared using Fisher's exact test. (C) Generalised estimating equations analysis to evaluate association between epidemiological and clinical characteristics and losses in the LTBI cascade of care. The study population was stratified according to complete TB preventive therapy (TPT) in the LTBI cascade (complete LTBI cascade of care vs losses in the LTBI cascade of care, see online supplemental table 1 for detailed univariate comparisons). A multivariable analysis (see the Methods section for details) was employed with each variable individually (unadjusted) and variables (panels A and C) were included in a multivariable model (adjusted). In all the comparisons, significant p values are shown in bold-type font. Comorbidities: at least one comorbidity (diabetes, hypertension, cancer, chronic obstructive pulmonary/emphysema, kidney disease, heart disease, liver disease and depression). Low income: without income/ equal or less than a minimum wage (reference: more than a minimum wage) ace (Black/*Pardo*) reference: white, Asian, Indian. Ethnicity was self-reported. Time ($V1_{TB}$-$V1_{C}$), time (in weeks) difference between the visit 1 of the tuberculosis case and the visit 1 of the contact.

of health, with people from a lower SES having a lower life expectancy. Several serious conditions are associated with low SES, such as hypertension, diabetes and depression.[18] In addition, low SES is associated with a higher burden of prevalent HIV infection and poorer HIV treatment outcomes.[19 20] Our findings highlight the relevance of social factors in TB care, previously noted in different studies.[21] These results reinforce the need to consider social determinants when developing healthcare public policies.

We found losses in all steps of the cascade, but the most substantial loss occurred before the visit to the clinic, when individuals identified by the TB index cases as contacts did not come for evaluation. This is consistent with findings from previous studies, where with greater losses included completion of testing in between of people intended for screening.[5] Two main reasons for this finding have been identified previously: (1) not having interest in being tested and (2) self-perceived low risk of TB infection.[5] In a study conducted in Myanmar, of 1908 MDR-TB contacts, some participants refused the contact investigation because they strongly believed that they did not have TB disease given that they did not have any signs or symptoms.[22]

Interestingly, the factors associated with loss in the LTBI care cascade are also factors associated with increased TB risk (factors that impair the host's defence against TB infection and disease, such as HIV infection and low SES).[21]

LTBI was significantly more common in black/*pardo* individuals. There is still not enough evidence on the relationship between ethnicity and race associated with complete treatment for ILTB. However, Viana *et al*[23] have showed racial inequalities in incomplete anti-TB treatment, with the black race presenting with the highest frequency of non-compliance (10.5%). This could be explained by the more precarious living conditions, with lower incomes and with limitations in healthcare, more commonly observed in the black and *pardo* population.[24] These findings of race differences in LTBI merit additional investigation; they could reflect social dynamics in Brazil.

A recently published meta-analysis[25] and literature review analysing evidence on interventions to reduce loss in LTBI cascade found that completion of the initial assessment (eg, return for medical visits) is significantly improved by financial and non-financial incentives. To a lesser extent, home visits, reminders and healthcare worker education were also shown to be helpful. Incentives and education of individuals who are indicated for LTBI improved treatment acceptance rates.

Another point worth noting in our study was that less than half of TB contacts who had an indication for TPT attended the medical visit and started it. This was lower than what was found in a meta-analysis (72.2%, 95% CI: 48% to 96%) of 6 cohorts from countries at the low-income or middle-income level.[5] However, our study included patients who came to the medical visit and refused treatment, as well as patients who never came to get the test results and were not seen by the physician to have the issue approached.

In our study, 54% of TB contacts who initiated TPT completed it. We found that lower income was associated with non-complete TPT. A similar proportion (56%) was observed in a cohort of 336 TB contacts in a primary healthcare service in São Paulo state, Brazil and in studies in low or middle-income countries (about 50%).[5 7] Barriers to treatment completion demonstrated before are diverse and vary according to location. Common barriers include side-effects to drugs, long treatment duration, issues related to the health system and individual concerns, such as substance use.[5] Financial barriers and low level of knowledge about the cost–benefit of treatment have also been associated with poor treatment adherence in LTBI patients.[26]

Our study had several limitations. Because the contacts were enrolled in a study conducted in referral centres, and under research conditions, the results may not be generalisable to all close contacts of TB index cases. Second, the contacts were of culture-confirmed TB cases who also enrolled into the RePORT-Brazil observational cohort. This raises the question of representativeness of the study cohort, and generalisability of the findings. Although the RePORT-Brazil cohort of TB cases is representative of all patients with TB in Brazil,[11] it is unclear if the close contacts are representative of all close contacts in Brazil. Third, the low percentage of contacts with HIV and illiteracy in the study population could have led to possibly less precise estimates. Fourth, participants lost to follow-up could have completed TPT elsewhere.

With our limitations noted as above, the results presented here illuminate substantial losses to follow-up among a population at high risk of developing active TB disease. Mitigating losses in the LTBI care cascade and the factors associated is an important step for the control and eradication of TB.

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Contributors ABS, MBA and MCS established the initial conception and wrote this manuscript. ABS, AB, ASRM, MSR, JGO, and MCF collected, analysed and reviewed the data. ABS, MBA, GA, BBA, MC-S, MA-P, BMFN and ATLQ analysed data and designed the illustrations and tables. MC-S, BBA, TS, MCF, BD, SC, ALK, VR and JRLeS supervised the project development, interpreted the data, and reviewed this manuscript. All authors read, discussed the general outline of the article together and approved the final manuscript.

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Patient consent for publication Not required.

Ethics approval The protocol, informed consent, and study documents were approved by the institutional review boards at all study sites. Participation was voluntary and written informed consent was obtained from all participants or their legally responsible guardians, and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki.

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Supplementary Material

Content:

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6. **Supplementary Figure 2**
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Supplementary Tables

Supplementary Table 1. Characteristics of contacts according to losses and completeness of LTBI cascade of care

Characteristics	Lost in the cascade (n=895)*	Completed the cascade (n=1001)	p-value
Female– no. (%)	538 (60)	589 (59)	0.542
Age – median (IQR)	31 (16-47)	33 (17-47)	0.078
Race/Ethnicity – no. (%)			0.024
Black/ Pardo	741 (83)	761 (76)	
Others	153 (17)	240 (24)	
Income – no. (%)			0.009
More than a minimum wage	285 (33)	412 (43)	
Equal or less than a minimum wage	386 (44)	365 (38)	
Without income	197 (23)	189 (19)	
BCG scar – no. (%)	802 (90)	893 (89)	0.820
Time ($V1_{TB}$-$V1_{C}$)	33 (8-82)	41 (14-102)	0.055
HIV infection – no. (%)	31 (4)	15 (2)	0.018
Antiretroviral therapy – no. (%)	23 (74)	13 (87)	0.460
Education– no. (%)			<0.001
Literate	753 (84)	950 (95)	
Illiterate	141 (16)	50 (5)	
Smoking – no. (%)	247 (28)	254 (25)	0.427

Secondary smoking – no. (%)	319 (36)	284 (28)	0.105
Alcohol consumption – no. (%)	471 (53)	545 (54)	0.433
Alcohol consumption (years)-median (IQR)	12 (4-22)	11 (3-20)	0.337
CAGE score of 2 and above [a] – no. (%)	82 (26)	96 (29)	0.333
Illicit drug use – no. (%)	91 (10)	97 (10)	0.758
Comorbidities[b]– no. (%)	241 (27)	204 (20)	0.069
Diabetes	43 (5)	52 (5)	0.752
Hypertension	132 (15)	101 (10)	0.003

Table note: Data represent no. (%), except for age time, which is presented as median and interquartile range (IQR) Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were using the Fisher's exact test (2x2) or Pearson's chi-square test. Time ($V1_{TB}$-$V1_C$): time (in weeks) difference between the visit 1 of the TB case and the visit 1 of the contact.

*Five contacts are ongoing in the TPT

[a]Alcohol abuse was defined as a CAGE score ≥ 2 points *(Ewing, J.A. 1984. Detecting alcoholism: The CAGE questionnaire. JAMA)*.

[b] Comorbidities: At least one comorbidity (diabetes, hypertension, cancer, chronic obstructive pulmonary /emphysema, kidney disease, heart disease, liver disease and depression)

Abbreviations: TB: tuberculosis. LTBI: latent tuberculosis infection. TPT: TB preventive therapy

Supplementary Table 2. Characteristics of contacts according to Initiation of recommended TPT

Characteristics	No initiation of recommended TPT (n=492)	Initiation of recommended TPT (n=454*)	p-value
Female– no. (%)	299 (61)	272 (60)	
Age – median (IQR)	32.5 (11-48)	32.6 (15-48)	0.902
Race/Ethnicity – no. (%)			0.247
Black/ Pardo	408 (83)	362 (80)	
Others	83 (17)	92 (20)	
Income – no. (%)			0.005
More than a minimum wage	150 (31)	171 (39)	
Equal or less than a minimum wage	236 (49)	175 (40)	
Without income	94 (20)	92 (21)	
BCG scar – no. (%)	444 (90)	400 (88)	0.296
Time ($V1_{TB}$-$V1_{C}$)	24 (7-71)	45 (15-102)	0.027
HIV infection – no. (%)	19 (4)	26 (6)	0.555
Antiretroviral therapy – no. (%)	12 (63)	23 (89)	0.070
Education– no. (%)			<0.001
Literate	379 (77)	404 (89)	
Illiterate	113 (23)	50 (11)	
Smoking – no. (%)	131 (27)	134 (30)	0.911

Secondary smoking – no. (%)	190 (39)	134 (30)	0.001
Alcohol consumption – no. (%)	233 (47)	233 (51)	0.241
Alcohol consumption (years)-median (IQR)	14 (5-21)	13 (4-23)	0.918
CAGE score of 2 and above [a] – no. (%)	31 (20)	40 (29)	0.133
Illicit drug use – no. (%)	37 (8)	54 (12)	0.128
Comorbidities [b]– no. (%)	128 (26)	102 (23)	0.295
Diabetes	23 (5)	20 (4)	0.880
Hypertension	65 (13)	64 (14)	0.705

Table note: Data represent no. (%), except for age and time, which is presented as median and interquartile range (IQR) Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were using the Fisher's exact test (2x2) or Pearson's chi-square test. Time ($V1_{TB}$-$V1_C$): time (in weeks) difference between the visit 1 of the TB case and the visit 1 of the contact.

* Among those to whom TPT was recommended (n=933)

[a] Alcohol abuse was defined as a CAGE score ≥ 2 points as described in Methods.

[b] Comorbidities: At least one comorbidity (diabetes, hypertension, cancer, chronic obstructive pulmonary /emphysema, kidney disease, heart disease, liver disease and depression)

Abbreviations: TB: tuberculosis. TPT: TB preventive therapy

(%)			
Alcohol consumption (years)-median (IQR)	12 (3-24)	14 (4-23)	0.581
CAGE score of 2 and above [a] – no. (%)	26 (34)	12 (19)	0.058
Illicit drug use – no. (%)	27 (13)	25 (10)	0.876
Comorbidities[b]– no. (%)	55 (27)	47 (19)	0.119
Diabetes	6 (3)	14 (6)	0.250
Hypertension	35 (17)	29 (12)	0.104

Table note: Data represent no. (%), except for age and time, which is presented as median and interquartile range (IQR) Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were using the Fisher's exact test (2x2) or Pearson's chi-square test. Time ($V1_{TB}$-$V1_{C}$): time (in weeks) difference between the visit 1 of the TB case and the visit 1 of the contact.

*4 no recommended

[a] Alcohol abuse was defined as a CAGE score ≥ 2 points as described in Methods

[b] Comorbidities: At least one comorbidity (diabetes, hypertension, cancer, chronic obstructive pulmonary /emphysema, kidney disease, heart disease, liver disease and depression)

Abbreviations: TB: tuberculosis. LTBI: latent tuberculosis infection. TPT: TB preventive therapy

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Supplementary Table 4. Characteristics of contacts according to 2nd IGRA performed

Characteristics	2nd IGRA not performed (n=242)	2nd IGRA performed (n= 967)	p-value
Female– no. (%)	142 (59)	548 (57)	0.836
Age – median (IQR)	27.1 (16-44.)	30.3 (15-45)	0.412
Race/Ethnicity – no. (%)			0.883
Black/ Pardo	193 (80)	749 (78)	
Others	48 (20)	218 (23)	
Income – no. (%)			0.048
More than a minimum wage	81 (35)	392 (42)	
Equal or less than a minimum wage	83 (36)	362 (39)	
Without income	69 (29)	182 (19)	
BCG scar – no. (%)	221 (91)	865 (90)	0.475
Time ($V1_{TB}$-$V1_C$)	36 (15-96)	40 (13-99)	0.955
HIV infection – no. (%)	7 (3)	28 (3)	0.883
Antiretroviral therapy – no. (%)	5 (71)	24 (86)	0.576
Education– no. (%)			0.632
Literate	211 (88)	860 (89)	
Illiterate	30 (12)	106 (11)	
Smoking – no. (%)	66 (27)	227 (24)	0.301
Secondary smoking – no. (%)	76 (32)	284 (30)	0.872

Alcohol consumption – no. (%)	133 (55	510 (53)	0.565
Alcohol consumption (years)-median (IQR)	10 (2-18)	10 (3-18)	0.644
CAGE score of 2 and above [a] – no. (%)	26 (27)	101 (32)	0.448
Illicit drug use – no. (%)	29 (12)	91 (9)	0.231
Comorbidities[b]– no. (%)	73 (30)	196 (20)	0.023
Diabetes	19 (8)	43 (4)	0.049
Hypertension	40 (17)	93 (10)	0.004

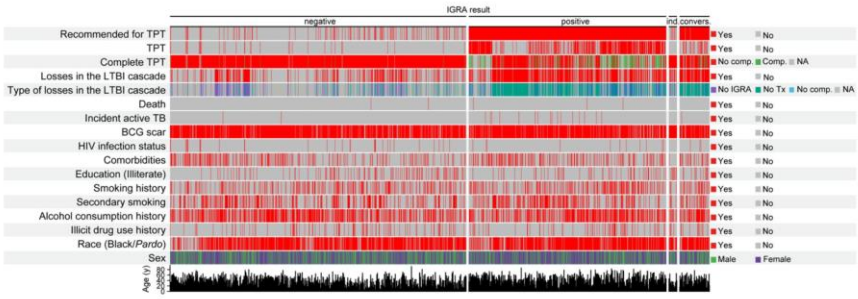
Table note: Data represent no. (%), except for age and time, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were using the Fisher's exact test (2x2) or Pearson's chi-square test. Time ($V1_{TB}$-$V1_C$): time (in weeks) difference between the visit 1 of the TB case and the visit 1 of the contact.

[a] Alcohol abuse was defined as a CAGE score ≥ 2 points as described in Methods.

[b] Comorbidities: At least one comorbidity (diabetes, hypertension, cancer, chronic obstructive pulmonary /emphysema, kidney disease, heart disease, liver disease and depression)

Abbreviations: TB: tuberculosis; IGRA: interferon-gamma release assay.

Supplementary Figures

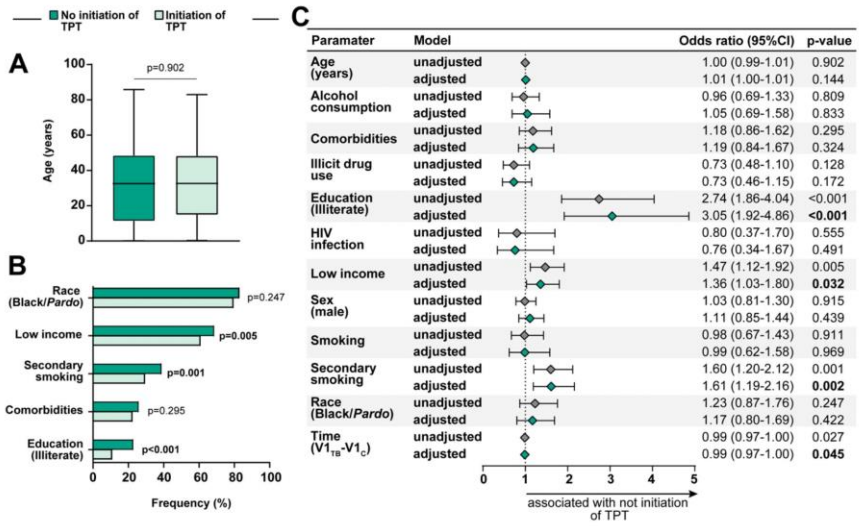


Supplementary Figure 1. Characteristics of study participants

Color map based on TB contacts grouped according to final IGRA results shows the overall characteristics of the study participants. A hierarchical clustering analysis (Ward's method) was employed to group individuals based on the overall profile of each study participant which each IGRA subgroup.

Alcohol abuse was defined as a CAGE score ≥ 2 points. Comorbidities: At least one comorbidity (diabetes, hypertension, cancer, chronic obstructive pulmonary /emphysema, kidney disease, heart disease, liver disease and depression

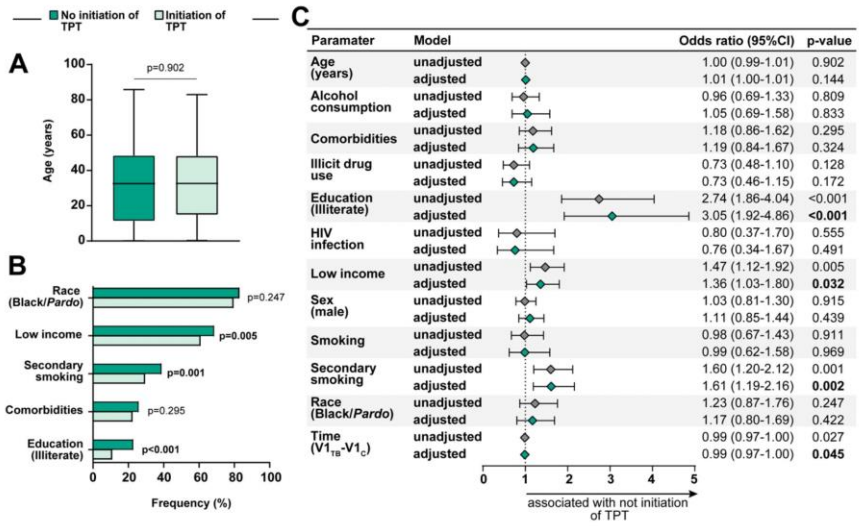
Abbreviations: IGRA: interferon-gamma release assay, Ind: Indeterminate, Convers: conversion, No IGRA 2: Did not perform 2nd IGRA, LTBI: latent tuberculosis infection, TB: tuberculosis. TPT: TB preventive therapy.



Supplementary Figure 2. Association between epidemiological and clinical characteristics and initiation of TPT

(A) Age distribution among TB contacts who did not initiate TPT and those who initiated the TPT. Data were compared using the Mann-Whitney *U* test. **(B)** Frequency of Race/Ethnicity (black and *pardo*), income (see definition below), secondary smoking, comorbidities (see definition below) and education (illiterate) between TB contacts stratified based on initiation of TPT**.** Data were compared using Fisher's exact test. **(C)** Generalized estimating equations analysis to evaluate association between epidemiological and clinical characteristics and not initiation of TPT**.** The study population was stratified according to initiation of TPT (not initiation of TPT and initiation of the TPT, see Supplementary Table 2 for detailed univariate comparisons). A multivariable analysis (see Methods for details) was employed with each variable individually (unadjusted) and variables (Panels A and **C)** were included in a multivariable model (adjusted). In all the comparisons, significant p-values are shown in bold-type font.

133 Comorbidities: At least one comorbidity (diabetes, hypertension, cancer, chronic
134 obstructive pulmonary /emphysema, kidney disease, heart disease, liver disease
135 and depression).
136 Low income: without income/equal or less than a minimum wage (reference: more
137 than a minimum wage)
138 Race (Black/*Pardo*) reference: White, Asian, Indian.
139 Abbreviations: 95%CI: 95% confidence interval. Time (V1TB-V1C): time (in weeks)
140 difference between the visit 1 of the TB case and the visit 1 of the contact. TPT: TB
141 preventive therapy.
142



Supplementary Figure 3. Association between epidemiological and clinical characteristics and completeness of the TB preventive therapy

(A) Age distribution among those who did not complete the TPT and who complete the TPT. Data were compared using the Mann-Whitney *U* test. **(B)** Frequency of Race/Ethnicity (black and *pardo*), income (see definition below), secondary smoking, comorbidities (see definition below) and education (illiterate) between TB contacts stratified based completeness of the TPT (complete vs. incomplete)**.** Data were compared using Fisher's exact test. **(C)** Generalized estimating equations analysis to evaluate association between epidemiological and clinical characteristics and who did not complete the TPT and who complete the TPT. The study population was stratified according to complete TPT in the LTBI cascade (incomplete TPT vs. complete cascade of care, see Supplementary Table 3 for detailed univariate comparisons). A multivariable analysis (see Methods for details) was employed with each variable individually (unadjusted) and variables (panels A

158 and **C)** were included in a multivariable model (adjusted). In all the comparisons,
159 significant p-values are shown in bold-type font.
160 Comorbidities: At least one comorbidity (diabetes, hypertension, cancer, chronic
161 obstructive pulmonary /emphysema, kidney disease, heart disease, liver disease
162 and depression).
163 Low income: without income/equal or less than a minimum wage (reference: more
164 than a minimum wage)
165 Race (Black/*Pardo*) reference: White, Asian, Indian.
166 Abbreviations: 95%CI: 95% confidence interval. Time ($V1_{TB}$-$V1_{C}$): time (in weeks)
167 difference between the visit 1 of the TB case and the visit 1 of the contact. TPT: TB
168 preventive therapy.
169

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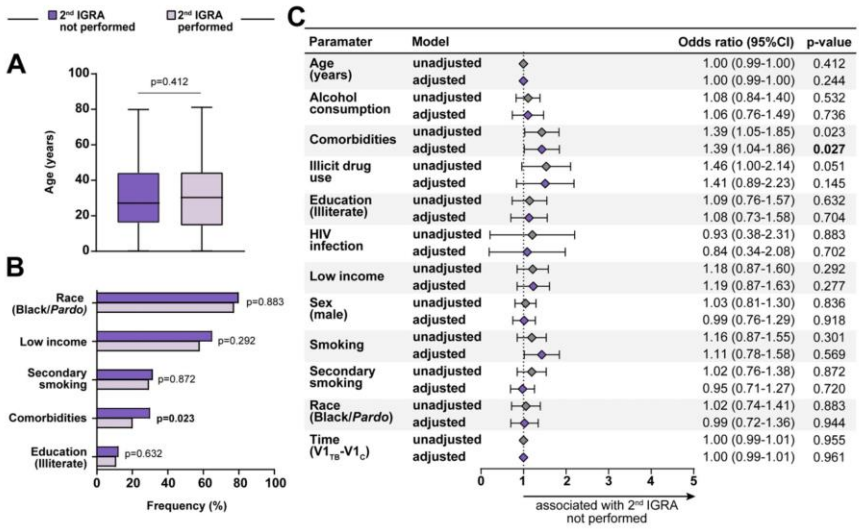

Supplementary Figure 4. Association between epidemiological and clinical characteristics and performing the 2nd IGRA test at month 6 when indicated. **(A)** Age distribution among those who performed the 2nd IGRA and those not performed the 2nd IGRA. Data were compared using the Mann-Whitney *U* test. **(B)** Frequency of Race/Ethnicity (black and *pardo*), income (see definition below), secondary smoking, comorbidities (see definition below) and education (illiterate) between TB contacts stratified based on performing the 2nd IGRA**.** Data were compared using the Fisher's exact test. **(C)** Generalized estimating equations analysis to evaluate association between epidemiological and clinical characteristics and losses in the LTBI cascade of care**.** The study population was stratified according to perform 2nd IGRA (2nd IGRA not performed and 2nd IGRA performed, see Supplementary Table 3 for detailed univariate comparisons). A multivariable analysis (see Methods for details) was employed with each variable individually (unadjusted) and variables (panels A and C) were included in a

multivariable model (adjusted). In all the comparisons, significant p-values are shown in bold-type font.

Comorbidities: At least one comorbidity (diabetes, hypertension, cancer, chronic obstructive pulmonary /emphysema, kidney disease, heart disease, liver disease and depression).

Low income: without income/equal or less than a minimum wage (reference: more than a minimum wage)

Race (Black/*Pardo*) reference: White, Asian, Indian.

Abbreviations: 95%CI: 95% confidence interval. Time (V1TB-V1C): time (in weeks) difference between the visit 1 of the TB case and the visit 1 of the contact.

6.4 MANUSCRITO IV

The Effect of Diabetes and Prediabetes on Anti-tuberculosis Treatment Outcomes: A Multicentric Prospective Cohort Study

Apesar de já estar descrito na literatura que DM é um fator de risco para o desenvolvimento de TB ativa, pouco havia sido estudado sobre o impacto da DM ou pré-DM no tratamento anti-TB. Esse estudo foi realizado com a coorte retrospectiva do RePORT-Brasil e validado com dados disponíveis no SINAN-TB a fim de identificar o efeito da diabetes e pré-DM no desfecho do tratamento anti-TB.

Resumo dos resultados: A DM foi associada a um risco aumentado de desfechos desfavoráveis de tratamento (falha, recorrência e morte), assim como de mortalidade avaliada individualmente, em pacientes com tuberculose pulmonar. Além disso, os desfechos desfavoráveis foram mais frequentemente associados à resistência aos medicamentos e à coinfecção por HIV. Essas observações foram validadas no Sistema Nacional de Notificação de Doenças no mesmo período.

O resumo deste manuscrito foi aceito no *52nd Union World Conference on Lung Health* como e-poster (19-23 de outubro 2021)

Este trabalho foi publicado no periódico *Journal of Infectious Diseases*, cujo Fator de Impacto (JCR 2021) foi igual a 5,23. **DOI**: https://doi.org/10.1101/2021.03.15.21253595

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MAJOR ARTICLE

The Effect of Diabetes and Prediabetes on Antituberculosis Treatment Outcomes: A Multicenter Prospective Cohort Study

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Background. It is unclear whether diabetes or prediabetes affects unfavorable treatment outcomes and death in people with tuberculosis (PWTB).

Methods. Culture-confirmed, drug-susceptible PWTB, enrolled in the Regional Prospective Observational Research in Tuberculosis (RePORT)–Brazil cohort between 2015 and 2019 (N = 643) were stratified based on glycemic status according to baseline glycated hemoglobin. Unfavorable tuberculosis (TB) outcome was defined as treatment failure or modification, recurrence, or death; favorable outcome was cure or treatment completion. We corroborated the findings using data from PWTB reported to the Brazilian National System of Diseases Notification (SINAN) during 2015–2019 (N = 20 989). Logistic regression models evaluated associations between glycemic status and outcomes.

Results. In both cohorts, in univariate analysis, unfavorable outcomes were more frequently associated with smoking, illicit drug use, and human immunodeficiency virus infection. Diabetes, but not prediabetes, was associated with unfavorable outcomes in the RePORT-Brazil (adjusted relative risk [aRR], 2.45; $P < .001$) and SINAN (aRR, 1.76; $P < .001$) cohorts. Furthermore, diabetes was associated with high risk of death (during TB treatment) in both RePORT-Brazil (aRR, 2.16; $P = .040$) and SINAN (aRR, 1.93; $P = .001$).

Conclusions. Diabetes was associated with an increased risk of unfavorable outcomes and mortality in Brazilian PWTB. Interventions to improve TB treatment outcomes in persons with diabetes are needed.

Keywords. diabetes; prediabetes; treatment outcome; SINAN; *Mycobacterium tuberculosis*.

Diabetes mellitus (DM) is recognized by the World Health Organization (WHO) as a global epidemic [1]. This metabolic disease triples the risk of active tuberculosis (TB) in patients with latent *Mycobacterium tuberculosis* (*Mtb*) infection [2]. In 2019, approximately 400 000 people with TB (PWTB) worldwide were also diagnosed with DM [3]. Importantly, DM prevalence is increasing globally, including settings with a high TB burden, such as China and India [4].

The high prevalence of DM among TB patients (10%–30%) in high-TB-burden countries and the negative impact of TB-DM comorbidity has been previously described by many groups [5–8], including higher mycobacterial loads and prevalence of sputum acid-fast bacilli positive, treatment failure, and death outcomes during TB treatment, among others.

We have reported an association between DM and more severe TB clinical presentation (higher frequency of cough, night sweats, hemoptysis, and malaise) [9], increased lung pathology reflected by severe radiographic manifestations (higher number of pulmonary lesions, including cavitation) [10], increased bacterial load in sputum [11], and delayed sputum conversion after anti-TB treatment initiation [12]. Furthermore, activation of tissue remodeling responses [12] and increased and persistent

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systemic inflammation [13] have been reported during treatment in TB-DM patients. Thus, the increase in the number of people with DM may further complicate care and control of TB, especially in areas with a high burden of both diseases [14].

There is also evidence that patients with concomitant TB and DM have an increased risk of unfavorable anti-TB treatment outcome such as failure, recurrence, and death compared to normoglycemic patients [15–17]. However, the findings have not been consistent [18, 19]. In the present study we evaluated the effect of dysglycemia (DM or prediabetes [pre-DM]) on anti-TB treatment outcomes in a prospective Brazilian cohort of patients with pulmonary TB (Regional Prospective Observational Research in Tuberculosis [RePORT]–Brazil), and also among PWTB reported to the Brazilian National TB Registry through the National System of Diseases Notification (SINAN).

METHODS

Ethics Statement

The study was conducted according to the principles in the Declaration of Helsinki. The RePORT-Brazil protocol was approved by the institutional review boards at each study site and at Vanderbilt University Medical Center. Participation in RePORT-Brazil was voluntary, and written informed consent was obtained from all participants. All data extracted from SINAN were public and freely accessible. All data were de-identified to preserve the anonymity of study participants.

Overall Study Design

RePORT-Brazil includes 5 study sites, located in 3 cities with high TB burden: 1 site each in Salvador and Manaus, and 3 sites in Rio de Janeiro [20]. One main objective of the consortium is to describe the clinical outcomes of TB treatment and latent *Mtb* infection in Brazil. The details of the sites and representativeness of the RePORT-Brazil cohort to all TB patients in Brazil have been described previously [20].

For the current analysis, we selected RePORT-Brazil participants meeting the following inclusion criteria: pulmonary TB, age ≥18 years, and enrolled between June 2015 and June 2019 (Figure 1A), with new or previously diagnosed culture-positive sputum (Lowenstein–Jensen medium or BD BACTEC MGIT), who received anti-TB treatment and had a treatment outcome recorded in the study database. For this study we only used information from patients with confirmed anti-TB drug susceptibility to the first-line scheme drugs, in RePORT-Brazil and from the SINAN database. Clinical and epidemiological information was collected at 3 in-person visits: (*i*) at TB diagnosis and anti-TB treatment initiation (baseline); (*ii*) 2 months after initiating treatment; and (*iii*) at the completion of anti-TB treatment. In addition, telephone follow-up was performed for all participants every 6 months until up to month 24. All data collected were stored in REDCap [21].

To establish the glycemic status of PWTB, baseline glycated hemoglobin (HbA1c) (prior to TB treatment) in blood was measured. DM was defined according to American Diabetes Association guidelines [22]. Patients were classified as having DM (HbA1c ≥6.5%), pre-DM (HbA1c = 5.7%–6.4%), or normoglycemia (HbA1c <5.7%). HbA1c ≥5.7% was classified as dysglycemia.

SINAN [23] includes diseases that require notification in all states and municipalities of Brazil; TB is a notifiable disease. The details of SINAN have been previously described

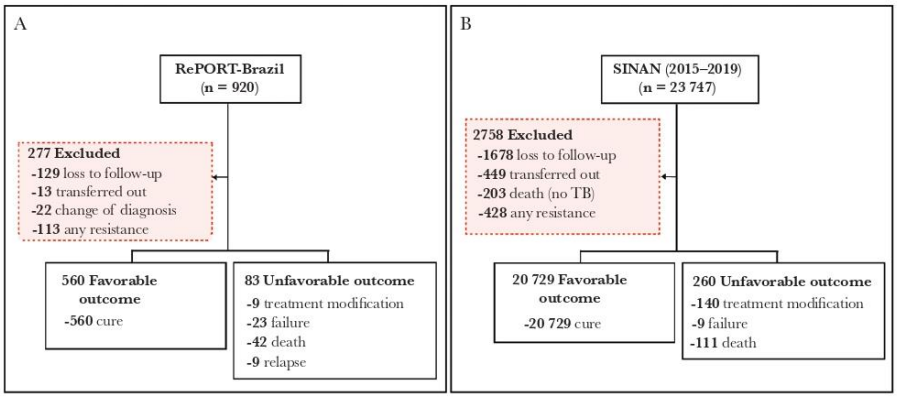

Figure 1. Study flowchart presenting the people with tuberculosis (TB) included and excluded from Regional Prospective Observational Research in Tuberculosis (RePORT)–Brazil (*A*) and reported to the Brazilian National System of Diseases Notification (SINAN, *B*) between 2015 and 2019.

[20]. PWTB reported to SINAN are diagnosed following the criteria in the Brazilian Manual of Recommendations for Tuberculosis Control [24]. Diagnostic criteria include (*i*) clinical and epidemiologic factors (presumptive diagnosis); (*ii*) bacteriology (sputum smear positive) or positive culture for *Mtb* (solid or liquid media); (*iii*) positive Xpert MTB/RIF; (*iv*) chest radiography; or (*v*) in the case of extrapulmonary TB, histopathology [24]. For each TB case reported, characteristics such as sex, age, race, education, alcohol consumption, illicit drug use, smoking habits, comorbidities, presence of human immunodeficiency virus (HIV) infection, and test results, among others, were also reported. Glycemic status was reported to SINAN as a diagnosis of DM (yes/ no), not exclusively based on HbA1c level.

We used the SINAN information from the years 2015–2019 to match the enrollment period of RePORT-Brazil [20] (Figure 1B). Of note, in 2014 the "strategies for care of people with chronic diseases," addressing comprehensive basic care for patients with TB and DM among others [25], was implemented in Brazil. In addition, we used data reported from Salvador, Manaus, and Rio de Janeiro, the cities with RePORT-Brazil study sites.

Outcome Definition

The primary outcome in this study was an unfavorable treatment outcome, defined as treatment modification, treatment failure, recurrence, or death (during TB treatment). The secondary outcome was mortality (TB patient who dies for any reason before starting or during the course of treatment) [26]. All definitions of outcome treatments were established in accordance with the Manual of Recommendations for the Control of TB of Brazil [24]. The treatment outcome definitions used in RePORT-Brazil and SINAN are depicted in Supplementary Table 1. A favorable outcome was defined as cure or treatment completion (defined as at least 90% of the total number of doses over 1 year for drug-susceptible TB). Patients who were lost to follow-up or transferred out or had a change in diagnosis (not a TB case) as the treatment outcome were excluded. The numbers of participants per outcome in this study are shown in more detail in Figure 1.

Data Analysis

All analyses were prespecified. Medians and interquartile ranges (IQRs) were used as measures of central tendency. Categorical variables were represented as percentages and compared using a 2-sided Pearson χ^2 test with Yates correction or the Fisher 2-tailed test in 2 × 3 or 2 × 2 tables, respectively. Quantitative variables were compared using the Mann–Whitney *U* test. We performed a logistic regression in both the RePORT-Brazil and SINAN cohorts, using variables with univariate *P* value ≤ .2 to assess the risk factors among characteristics of TB patients (1 model for each stratification strategy of the glycemic status: dysglycemia, DM, pre-DM, and HbA1c value) with the composite unfavorable treatment outcome or with mortality alone. Results from both regression approaches were presented in terms of relative risk (RR) and 95% confidence intervals (CIs). *P* values < .05 were considered statistically significant. Statistical analyses were performed using SPSS 25.0 (IBM Corporation, Armonk, New York), Graph Pad Prism 9.0 (GraphPad Software, San Diego, California), and JMP 13.0 (SAS Institute, Cary, North Carolina) software.

RESULTS

Factors Associated With TB Treatment Outcomes in RePORT-Brazil

The RePORT cohort included 643 participants with culture-confirmed pulmonary TB who were treated with anti-TB drugs for at least 6 months. Patients were grouped according to treatment outcomes: favorable (n = 560 [87.1%]) and unfavorable (n = 83 [12.9%]) (Figure 1A). The median age in the RePORT cohort was 38 years (IQR, 27–52 years), and most study participants were male. Patients with unfavorable outcomes more frequently reported current smoking (*P* = .025) and illicit drug use (*P* = .006) (Table 1). These patients also had a higher frequency of DM (*P* = .003) and HIV infection (*P* < .001) (Table 1). The proportion of individuals with dysglycemia (ie, with DM or pre-DM) did not differ significantly between those with unfavorable vs favorable outcomes. In contrast, persons with unfavorable outcomes had lower hemoglobin levels (10.6 g/dL [IQR, 8.98–12.4 g/dL] vs 12.2 g/dL [IQR, 10.9–13.4 g/dL]) among those with favorable outcomes (*P* < .001; Table 1).

Regarding TB clinical presentation at study enrollment, patients who developed unfavorable outcomes were more likely to be living with HIV (*P* < .001) and to present with fatigue (*P* < .001), whereas those who experienced a favorable treatment outcome more frequently presented with cough (*P* < .001) and hemoptysis (*P* = .043) (Supplementary Figure 1*A* and 1*B*).

We next evaluated the impact of baseline glycemic status on each type of treatment outcome (cure, treatment modification, failure, death, recurrence). Dysglycemia was more frequent in TB patients with treatment failure (*P* = .02) or who died (*P* = .045) during TB treatment (Figure 2). Baseline HbA1c values were distinguishable between the subgroups of participants who further developed favorable and unfavorable outcome when the outcomes were examined individually (treatment modification, failure, death, recurrence, and cure). Individuals with favorable treatment outcomes had lower HbA1c levels than those who experienced treatment modification (*P* = .016), treatment failure (*P* = .002), or death (*P* = .047) during treatment follow-up. Among individuals with unfavorable outcomes, those who experienced treatment modification had lower HbA1c values than patients who had treatment failure (*P* < .001) or died (*P* = .012) (Figure 2). Furthermore, TB patients who experienced treatment failure, recurrence, or death exhibited a median HbA1c of 6.6 g/dL (IQR, 5.9–9.6 g/dL).

Table 1. Characteristics of People With Tuberculosis in the Regional Prospective Observational Research in Tuberculosis (RePORT)–Brazil Cohort, by Outcome

Characteristics	Unfavorable (n = 83)	Favorable (n = 560)	P Value
Male sex	57 (68.67)	359 (64.11)	.462
Age, y, median (IQR)	38 (27–52)	35 (25–49)	.399
Race			**.039**
White	13 (15.66)	123 (22)	
Black	18 (21.69)	146 (26.12)	
Asian	0 (0)	2 (0.36)	
Pardo[a]	48 (57.83)	279 (49.91)	
Indigenous	4 (4.82)	9 (1.61)	
Illiterate	80 (96.39)	538 (96.07)	1
Smoking[b]	52 (62.65)	275 (49.11)	**.025**
Alcohol consumption[c]	76 (91.57)	470 (83.93)	.072
Illicit drug use[d]	35 (42.17)	152 (27.14)	**.006**
BMI, kg/m^2, median (IQR)	20.4 (17.1–22.9)	20.3 (18.4–22.5)	.384
Prior TB	10 (12.05)	89 (16.01)	.418
Type of TB[e]			.61
PTB	68 (81.93)	502 (89.64)	
PTB + EPTB	15 (18.07)	58 (10.36)	
Abnormal radiograph	77 (92.77)	547 (97.68)	**.026**
Positive smear	64 (77.11)	456 (81.43)	.37
Glycemic status[f]			
Diabetes mellitus	31 (37.35)	108 (19.29)	**.003**
Prediabetes	19 (22.89)	186 (33.21)	.554
Normoglycemia	33 (39.76)	266 (47.5)	Ref.
Dysglycemia	50 (60.24)	294 (52.5)	.197
Metformin use[g]	0 (0)	8 (2.73)	.609
Hemoglobin, g/dL, median (IQR)	10.6 (8.98–12.4)	12.2 (10.9–13.4)	**<.001**
HbA1c, %, median (IQR)	6 (5.4–6.8)	5.7 (5.3–6.2)	.082
HIV status	33 (40.24)	84 (15.16)	**<.001**
ART[h]	9 (27.27)	30 (35.29)	.514
Hypertension	7 (8.43)	46 (8.21)	1
Other comorbidities[i]	7 (8.43)	32 (5.71)	.325

Data are presented as No. (%) unless otherwise indicated. Favorable: cure/complete treatment. Unfavorable: failure, recurrence, treatment modification, or death. In the Regional Prospective Observational Research in Tuberculosis (RePORT)–Brazil cohort, all patients had a positive culture at baseline. Bold values denote statistical significance at the $P < .05$ level.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; EPTB, extrapulmonary tuberculosis; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; IQR, interquartile range; PTB, pulmonary tuberculosis; TB, tuberculosis.

[a]Definition of Pardo race: Mixture of European, black, and Amerindian.

[b]Past or current cigarette smoker.

[c]Past or current consumption of alcohol (any).

[d]Past or current illicit drug use (marijuana, cocaine, heroin, or crack).

[e]All individuals from the RePORT cohort had a diagnosis of PTB; some also had involvement at extrapulmonary sites.

[f]Of participants with diabetes mellitus (DM), 12 with an unfavorable outcome and 67 with a favorable outcome had a diagnosis of DM prior to TB diagnosis.

[g]Frequency of use of metformin was calculated only in patients with DM.

[h]ART frequency was calculated among the persons living with HIV.

[i]Cancer, kidney disease, chronic obstructive pulmonary disease, emphysema, and asthma.

Determinants of TB Treatment Outcomes in SINAN

In the SINAN cohort, 23 747 PWTB were notified in the 3 cities where RePORT study sites are located. A total of 2758 were excluded for reasons listed in Figure 1, resulting in a cohort of 20 989 PWTB. Males represented >60% of patients in both groups, and patients with unfavorable outcomes were older (39 years [IQR, 33–47 years]; $P < .001$) and more likely to report smoking ($P = .003$), alcohol consumption ($P = .019$), and illicit drug use ($P = .014$) than those with favorable outcomes. Among patients with HIV coinfection, those with unfavorable outcome were less likely to report antiretroviral therapy ($P < .001$) than patients with favorable outcome. Unfavorable outcome was associated with previous TB ($P < .001$), DM ($P = .022$), HIV coinfection ($P < .001$), and other comorbidities ($P = .004$) (Table 2, Supplementary Figure 1*C*).

We likewise evaluated the impact of glycemic status on the TB clinical presentation by the study participants in both cohorts (Supplementary Figure 2). In RePORT patients, weight loss was more commonly observed in people with DM than in those with pre-DM or normoglycemia ($P < .001$). In patients from SINAN, there was a higher proportion of PWTB with dysglycemia presenting with a positive smear at baseline than in those with normoglycemia ($P < .001$). In addition, frequency of HIV infection was higher in the normoglycemic patients from the SINAN dataset ($P < .001$). Additional details of other clinical factors are displayed in Supplementary Figure 2.

Multivariable Logistic Regression to Assess Association Between Glycemic Status and TB Treatment Outcomes

A logistic regression analysis was performed to determine the RR according to glycemic status (dysglycemia, DM, pre-DM, or HbA1c values) and treatment outcome in the RePORT cohort. DM was associated with unfavorable treatment outcomes independent of the other factors (adjusted RR [aRR], 2.45 [95% CI, 1.54–3.90]; $P < .001$) (Figure 3, model 2). HbA1c values were also independently associated with unfavorable treatment outcomes (aRR, 1.13 [95% CI, 1.02–126]; $P = .02$) (Figure 3, model 4). Pre-DM and the overall category of dysglycemia were not significantly associated with unfavorable treatment outcome (Figure 3). This analysis also was performed in the SINAN cohort, and DM was independently associated with unfavorable TB treatment outcomes (aRR, 1.76 [95% CI, 1.104–2.81]; $P < .001$) (Figure 3). Details of the logistic regression models are shown in Supplementary Table 2.

Mortality During TB Treatment

We next compared patients with cure outcome vs those who died during TB treatment (n = 42) in the RePORT cohort. Mortality was associated with male sex ($P = .029$), increasing age ($P = .035$), illicit drug use ($P = .034$), HIV infection ($P = .001$), DM ($P = .028$), and lower concentrations of hemoglobin (death: 9.45 g/dL [IQR, 8.00–10.7 g/dL]; cure: 12.2 g/dL [IQR, 10.9–13.4 g/dL]; $P < .001$) and higher values of HbA1c (death: 6% [IQR, 5.2%–6.9%]; cure: 5.7% [IQR, 5.3%–6.2%]; $P < .001$) (Supplementary Table 3).

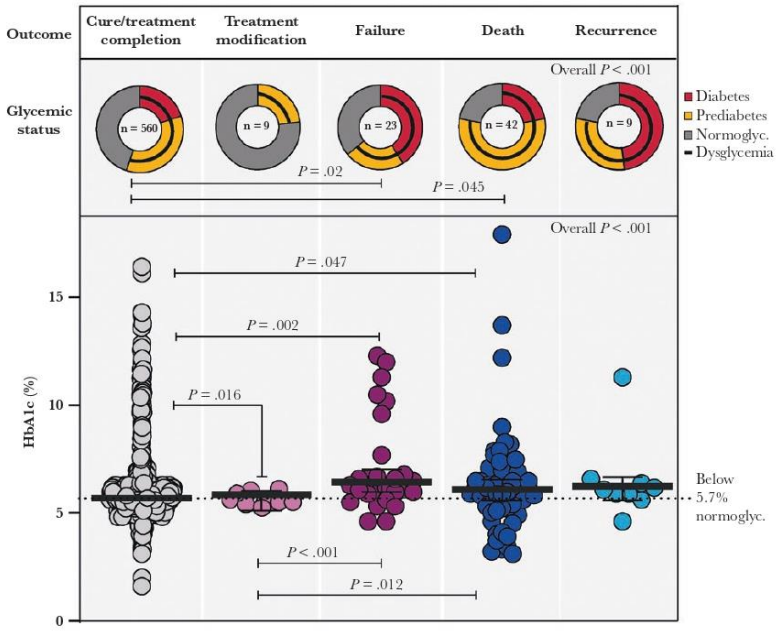

Figure 2. Distribution of glycemic status and glycated hemoglobin (HbA1c) levels according to treatment outcomes in patients with tuberculosis (TB) in the Regional Prospective Observational Research in Tuberculosis–Brazil cohort. Frequency of TB patients with diabetes, prediabetes, normoglycemia, and dysglycemia (diabetes + prediabetes) diagnosed using HbA1c levels is shown according to TB treatment outcome (cure, treatment modification, failure, death, and recurrence). Only comparisons (frequency dysglycemia status between TB treatment outcomes) with significant *P* values are displayed. Scatterplots depict the frequency of HbA1c values in TB patients according to TB treatment outcome. Lines represent median and interquartile range. The differences in median values of HbA1c between groups were compared using the Kruskal–Wallis test with Dunn multiple comparisons posttest. Only comparisons with significant *P* values are displayed. Abbreviations: HbA1c, glycated hemoglobin, normoglyc., normoglycemia.

In the SINAN cohort, death was associated with the same statistically significant variables as those that predicted the composite unfavorable outcome vs cure (Supplementary Table 4). Mortality was associated with smoking ($P = .003$), alcohol consumption ($P = .003$), illicit drug use ($P = .009$), HIV infection ($P < .001$), and other comorbidities ($P = .006$). In SINAN, patients who died had a higher frequency of DM ($P = .024$) and a lower frequency of antiretroviral therapy use in individuals with HIV infection ($P = .004$).

A logistic regression analysis was performed comparing cure and death and presented similar results to the first model exploring the composite unfavorable outcome. In the RePORT cohort, DM was once again strongly associated with mortality (aRR, 2.16 [95% CI, 1.01–2.40]; $P = .040$) (Figure 4, model 2). Pre-DM and dysglycemia were not significantly associated with death (Figure 4). In the SINAN cohort, DM was also significantly associated with death (aRR, 1.93 [95% CI, 1.30–2.85]; $P = .001$) (Figure 4). Details of the logistic regression models are shown in Supplementary Table 2.

DISCUSSION

There has recently been increased recognition of DM as an important risk factor for developing active TB and experiencing unfavorable TB treatment outcomes [14–16, 27]. As the prevalence of DM increases [28], particularly in developing countries, it is necessary to determine the public health impact of this syndemic in large populations. Our study analyzed data from PWTB from 2 data sources (a longitudinal cohort and the nationwide disease notification system) in the same period and the same 3 cities to determine the impact of DM on TB treatment outcomes in a Brazilian population.

Our results show that the frequency of unfavorable outcomes of anti-TB treatment in the RePORT-Brazil cohort was similar to those reported by other studies [19] We have also

Table 2. Characteristics of People With Tuberculosis in the Brazilian National System of Diseases Notification (SINAN) Cohort (2015–2019), by Outcome

Characteristic	Unfavorable (n = 260)	Favorable (n = 20 729)	PValue
Male sex	137 (69.9)	12 827 (62.8)	**.046**
Age, y, median (IQR)	39 (33–47)	38 (28–52)	
Race			.234
White	49 (27.5)	5029 (26.4)	
Black	38 (21.3)	3421 (17.9)	
Asian	4 (2.2)	166 (0.9)	
Pardo[a]	87 (48.9)	10 381 (54.5)	
Indigenous	0 (0.0)	62 (0.3)	
Illiterate	28 (20.4)	2382 (15.3)	.092
Smoking[b]	46 (26.9)	3465 (17.9)	**.003**
Alcohol consumption[c]	33 (19.4)	2556 (13.1)	**.019**
Illicit drug use[d]	26 (15.3)	1828 (9.5)	**.014**
Prior TB	81 (41.3)	3155 (15.4)	**<.001**
Type of TB[e]			**<.001**
PTB	184 (93.9)	19 780 (96.8)	
EPTB	3 (1.5)	117 (0.6)	
PTB + EPTB	9 (4.6)	536 (2.6)	
Abnormal radiograph	170 (97.1)	17 662 (97.3)	.811
Positive smear	108 (75.0)	10 512 (76.1)	.775
Diabetes mellitus	28 (15.8)	2047 (10.5)	**.022**
HIV status	21 (70.0)	1880 (10.7)	**<.001**
ART[f]	38 (23.8)	1154 (76.2)	**<.001**
Hypertension	5 (2.6)	559 (2.7)	1.000
Other comorbidities[g]	16 (8.5)	782 (4.0)	**.004**

Data are presented as No. (%) unless otherwise indicated. Favorable: cure/complete treatment. Unfavorable: failure, recurrence, treatment modification, or death. Bold values denote statistical significance at the P < .05 level.

Abbreviations: ART, antiretroviral therapy; EPTB, extrapulmonary tuberculosis; HIV, human immunodeficiency virus; PTB, pulmonary tuberculosis; TB, tuberculosis.

[a]Definition of Pardo race: mixture of European, black, and Amerindian.

[b]Past or current cigarette smoker.

[c]Past or current consumption of alcohol (any).

[d]Past or current illicit drug use (marijuana, cocaine, heroin, or crack).

[e]Only individuals from the SINAN 2015–2019 cohort who had a diagnosis of PTB, in some cases with presence in other anatomical sites, were included.

[f]ART frequency was calculated among the persons living with HIV.

[g]Cancer, kidney disease, chronic obstructive pulmonary disease, emphysema, and asthma.

demonstrated that TB patients in RePORT-Brazil are comparable to/representative of all PWTB reported in Brazil. [20].

It is interesting to note that the factors consistently associated with poor outcomes in the 2 datasets analyzed—namely, substance use (alcohol, tobacco, and illicit drug) and HIV infection—were all in accordance with previous literature [19, 29] but different from other studies [30]. The analyses from RePORT also identified other drug resistance, anemia, and normal chest radiograph as factors associated with worse outcomes. This latter observation may be because RePORT performs systematic collection of these variables, which coincides with findings from other studies [19, 31].

In addition to the above factors, we found an association between higher HbA1c levels and treatment modification, treatment failure, and death, when compared with the HbA1c levels among TB patients who were successfully treated, and this was reflected in the significantly higher proportion of people with DM among those with unfavorable anti-TB treatment outcomes. In the RePORT cohort, the risk of having an unfavorable outcome was 2.45 times higher in DM patients compared with normoglycemic individuals. A risk of 1.76 was found in the SINAN dataset. Additionally, patients with higher HbA1c values were also at a higher risk of experiencing unfavorable outcomes. The relatively lower detection of DM cases in the SINAN dataset probably led to an underestimation of the effect of DM in TB outcomes. Our results are similar to those from previous studies [13, 16]. The risk of death in the DM groups was 2.16 times higher than in normoglycemic patients in the RePORT dataset and 1.93 in the SINAN dataset. The risk of death in the RePORT cohort was more compatible with what has been described in literature [16]. Previous studies showed how TB-DM comorbidity is associated with a higher burden of immune pathology and systemic inflammation compared to normoglycemic PWTB [13, 32]. Furthermore, a defective regulation of the innate immune response in TB-DM patients could maintain inflammatory foci despite anti-TB treatment, resulting in worse treatment results [13].

Moreover, all participants from RePORT had HbA1c measured at the baseline visit, whereas in SINAN the diagnosis of DM was self-reported in most cases, possibly missing many diagnoses. Of note, a longitudinal cohort study done in Brazil found that 50% of individuals diagnosed with DM did not know of their diagnosis [33]. Thus, in the SINAN cohort, with increasing clinical evidence that DM is a risk factor for developing active TB [2] and a more severe clinical TB presentation [9], screening for DM has increased in recent years. But the problem of underdiagnosis and subnotification still exists.

The findings presented here suggest that the impact of DM on TB in Brazil is underestimated. While the results reiterate the value of cohorts like RePORT in better delineating the local epidemiology, they highlight the importance of guidelines recommending laboratory investigation of DM in all TB incident cases and to establish specific treatment recommendations for this population. This implies that long-term glycemic control may improve the outcome of TB treatment in patients with TB-DM comorbidity [34]. The integrated care of individuals with both diseases has specific challenges, such as the interaction between oral antidiabetic and anti-TB drugs [35] and the greater risk for adverse events [36].

We did not find an association between unfavorable outcome and death with either pre-DM or dysglycemia in the RePORT cohort; these associations were observed only with DM. Previous studies reported the normalization of glycemic levels during TB treatment among persons who were dysglycemic prior to anti-TB treatment [37, 38]. Therefore, the deleterious effects on the immune response and treatment outcome caused by chronic DM and associated hyperglycemia may be less likely with pre-DM, which could explain the lack of association with

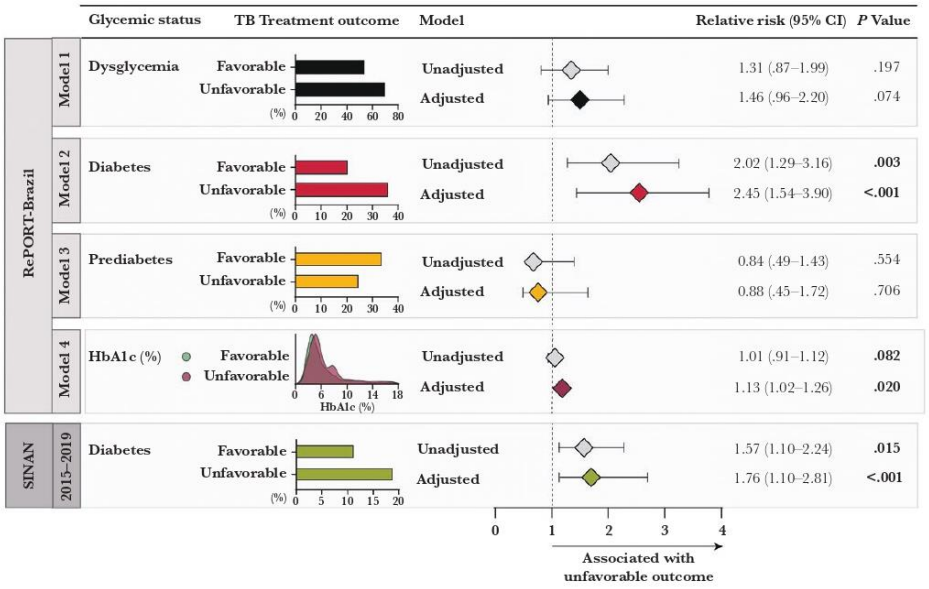

Figure 3. Association between glycemic status and tuberculosis (TB) treatment outcomes among TB patients from the Regional Prospective Observational Research in Tuberculosis (RePORT)–Brazil and the Brazilian National System of Diseases Notification (SINAN) cohorts. In the RePORT cohort (upper panel), logistic regression was performed to evaluate the independent associations between glycemic status of TB patients (model 1: dysglycemia; model 2: diabetes; model 3: prediabetes; model 4: increases of 1 unit in glycated hemoglobin level) and variables with P value < .2 in the univariate analyses (Table 1) and unfavorable treatment outcome (treatment modification, failure, recurrence, and death). Comparisons of diabetes, prediabetes, and dysglycemia were performed using normoglycemia as the reference. In the SINAN cohort (lower panel), logistic regression was performed to evaluate the independent associations between diabetes and unfavorable TB treatment outcome (treatment modification, treatment failure, and death). Variables with P < .2 in the univariate analyses (Table 2) were included. Details of the bivariate binomial logistic regression models are shown in Supplementary Table 2. Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; RePORT, Regional Prospective Observational Research for Tuberculosis; SINAN, National System of Diseases Notification; TB, tuberculosis.

unfavorable and death outcomes in the latter group [37, 38]. The dysglycemia group included pre-DM, and this likely influenced the results.

This study had several limitations. First, RePORT and SINAN are both observational cohorts; unmeasured or residual confounding could have explained the findings. However, the consistent results across both cohorts support their reproducibility. Second, SINAN is a disease notification system that is not part of a study protocol. While SINAN represents TB cases from all of Brazil, there could be incomplete data collection or endpoint ascertainment, as well as different sources of information (ie, self-reported vs information from medical records) for different patients. Third, we did not have information on serum drug levels; low drug levels have been associated with unfavorable TB treatment outcomes, including in PWTB with advanced HIV and DM [39]. Fourth, HbA1c levels could be affected by hemoglobin levels and, in RePORT, HbA1c was the only method used to define DM; the rationale for this was that obtaining fasting glucose levels on all study participants was not feasible. Fifth, the number of patients with a follow-up outcome who were excluded from the study may affect the interpretation of outcomes. Finally, we did not have glycemic status in the following months or at the end of treatment, so we did not have data to identify transient hyperglycemia. Nevertheless, we believe our study provides valuable information on the impact of TB-DM on a population level.

Diabetes is a disease with increasing prevalence and a major risk factor for unfavorable outcomes, including death during treatment, in individuals with TB, along with HIV infection and substance use. Actions prioritizing these groups are essential for the control of TB in Brazil.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors.

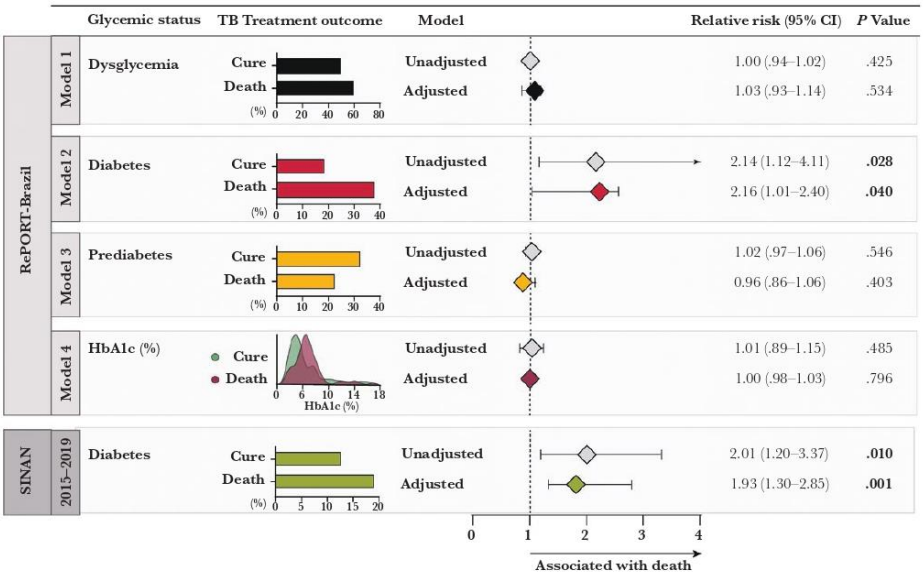

Figure 4. Association between glycemic status and death during antituberculosis treatment among tuberculosis (TB) patients from the Regional Prospective Observational Research for Tuberculosis (RePORT)–Brazil and the Brazilian National System of Diseases Notification (SINAN) cohorts. In the RePORT cohort (upper panel), logistic regression was performed to evaluate the independent associations between glycemic status of TB patients (model 1: dysglycemia; model 2: diabetes; model 3: prediabetes; model 4: increases of 1 unit in glycated hemoglobin level) and variables with $P < .2$ in the univariate analyses (Supplementary Table 3) and death. Comparisons of diabetes, prediabetes, and dysglycemia were performed using normoglycemia as reference. In the SINAN cohort (lower panel), logistic regression was performed to evaluate the independent associations between diabetes in TB patients in the period 2015–2019 and variables with $P < .2$ in the univariate analyses (Supplementary Table 4) and death. Details of the bivariate binomial logistic regression models are shown in Supplementary Table 5. Abbreviations: CI, confidence interval; HbA1c, glycated hemoglobin; RePORT, Regional Prospective Observational Research for Tuberculosis; SINAN, National System of Diseases Notification; TB, tuberculosis.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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6.5 MANUSCRITO V

Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru

A comorbidade está relacionada com a apresentação clínica e manifestações radiográficas da doença. Essa relação tem sido explorada nos recentes anos. Porém, não achamos estudos longitudinais que avaliem a dysglycemia (diabetes o pré-diabetes) persistente durante o tratamento antituberculose. Este estudo tem como objetivo avaliar se a dysglycemia (classificada com a glicose em jejum e HbA1c) persistente em casos TB, está associada com desfechos desfavoráveis no tratamento antituberculose em uma coorte peruana.

Resumo dos resultados: A disglicemia nos indivíduos com TB pulmonar foi associada a piores perfis bioquímicos e lesões mais extensas na radiografia de tórax. Nossa análise de agrupamento hierárquico demonstrou ainda que o perfil celular e bioquímico associado à disglicemia persistente também estava relacionado a lesões pulmonares, contagem elevada de leucócitos e aumento dos níveis de transaminases hepáticas, colesterol total e hemoglobina baixa, o que nosso grupo tinha achado em outras pesquisas.

Nesta coorte de indivíduos com diagnostico de TB, a disglicemia persistente, incluindo pacientes diabéticos e pré-diabéticos durante o tratamento anti-TB, foi independentemente associada desfechos desfavoráveis do tratamento da TB.

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Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru

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Highlights (for review) of Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru

- Patients with TB are still unaware of their glycemic status.
- Persistent dysglycemia is common condition in patients with TB during TB treatment.
- Persistent dysglycemia is independently associated with unfavorable TB outcomes.
- Control of persistent dysglycemia must be ensured in the TB management.

Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru

Short title: Dysglycemia persists in unfavorable TB outcomes.

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ABSTRACT

Background

Dysglycemia (i.e., prediabetes or diabetes) on patients with tuberculosis (PWTB) was associated with increased odds of mortality and treatment failure. Whether such association holds when dysglycemia is transient or persistent is unknown. Here we tested the association between persistent dysglycemia (PD) during anti-TB treatment and unfavorable treatment outcomes in PWTB from Lima, Peru.

Methods

PWTB enrolled between February and November 2017 were followed for 24-months. Dysglycemia was measured by fasting glucose and HbA1c at baseline, 2nd-and 6th-month of TB treatment. PD was defined as dysglycemia detected in two different visits. The association between PD and unfavorable TB treatment outcome was evaluated by logistic regression.

Results

Among 125 PWTB, PD prevalence was 29.6%. PD was associated with more lung lesion types, higher bacillary loads, low hemoglobin and high body mass index (BMI). Unfavorable TB treatment outcome was associated with older age, higher BMI, more lung lesion types and PD. After adjusting for age, hemoglobin levels, smoking and smear grade, PD was independently associated with unfavorable treatment (aOR: 6.1; 95%CI: 1.9–19.6).

Conclusion

Persistent dysglycemia is significantly associated with higher odds of unfavorable TB treatment outcomes. Dysglycemia control trough anti-TB treatment gives the opportunity to introduce appropriate interventions to TB management.

Keywords: Persistent dysglycemia, pulmonary tuberculosis, antituberculosis treatment, unfavorable outcome, Peru.

INTRODUCTION

Tuberculosis (TB) is the cause of death of 1.5 million people a year, especially in low and middle income countries and, as a consequence of recent efforts to improve National Tuberculosis Control Programs (NTPs), its incidence is decreasing, but at slow pace (World Health Organization, 2021). It is widely documented that high-risk conditions, such as malnutrition, smoking, AIDS and dysglycemia (Almeida-Junior et al., 2016, Calderon et al., 2019, Huang et al., 2014, Odone et al., 2014, World Health Organization, 2015) compromise the NTPs performance in its task of reducing TB burden, despite specific interventions (World Health Organization, 2015) despite specific interventions, such as comprehensive health care as a complementary strategy to active case and contact tracing, as well as the universalization of first-line drug susceptibility testing and screening for comorbidities such as HIV and diabetes mellitus (DM). (Cole et al., 2020)

Dysglycemia, which in the present study includes DM and prediabetes (PDM), influences TB risk, clinical and radiographic presentation, as well as TB treatment outcome and has been extensively studied in recent years. Indeed, DM is described to be associated with increased risk of progression from latent to active TB (Jeon and Murray, 2008), with the persistence of acid-fast bacilli (AFB) in sputum (Gil-Santana et al., 2016), and with unfavorable TB treatment outcomes and death (Arriaga et al., 2021, Baker et al., 2011). Importantly, DM in people with pulmonary TB (PWTB) has also been shown to increase the risk of *Mycobacterium tuberculosis* (MTB) transmission to close contacts (Arriaga et al., 2021). Moreover, PDM has been frequently reported in PWTB (Almeida-Junior et al., 2016) and is thought to increase the chance of TB among household contacts (Shivakumar et al., 2018). However, is still unanswered if the presence of PDM has any effect on antituberculosis therapy. The World Health Organization (WHO) and the NTPs recommend the detection and management of DM in patients with TB (Lin et al., 2019, Ministerio de Salud Peru, 2013), but despite these indications, most PWTB are still unaware of their glycemic status and remains uncertain the impact of dysglycemia on TB treatment outcomes. A previous study conducted in Lima-Peru reported a high prevalence of dysglycemia in PWTB (14%) and

highlighted the programmatic limitations for the identification and treatment of non-diabetic dysglycemia (Calderon et al., 2019). Since TB increases insulin resistance and stress-induced hyperglycemia, an overdiagnosis can be observed during the acute phase of TB (Dungan et al., 2009), but dysglycemic states may persist throughout treatment (Calderon et al., 2019) for epigenetic changes that cause persistent increases in proatherogenic gene expression (El-Osta et al., 2008). So, patients with higher glycemic levels show clinical, radiological, and biochemical manifestations (Barreda et al., 2020) that in turn could be associated with unfavorable anti-TB outcomes.

Our objective of the present study was to assess whether persistent dysglycemia is associated with unfavorable TB treatment outcome in a cohort of PWTB from 14 health centers and one public reference hospital in Lima-Peru.

PATIENTS AND METHODS

Settings and study design

We analyzed a prospective cohort of PWTB (Calderon et al., 2019) recruited between February and November 2017 and followed up for 24 months after TB treatment initiation. The study was performed in two districts of North Lima - Peru, with high TB burden, recruiting patients from 14 health centers and from the Public Hospital Sergio Bernales.

Study TB patients

Adult patients (age ≥ 18 years) with pulmonary TB diagnosed by the study units were screened for inclusion. TB diagnosis and follow up monitoring were based on AFB smear microscopy, culture for MTB in Lowenstein Jensen medium, chest radiograph aspects (assessed by an experienced radiologist) and clinical findings as described elsewhere (Calderon et al., 2019, Ministerio de Salud Peru, 2013). Additionally, drug susceptibility testing was performed using the BD BACTEC™ MGIT™ 960 at the study laboratory to bring support for a properly treatment following the national and international recommendations (Ministerio de Salud Peru, 2013).

Clinical data and definition of dysglycemia and persistent dysglycemia

Data on clinical characteristics, chest radiographic findings, comorbidities and TB treatment outcomes were obtained by medical records reviewing as authorized by local IRB and recorded in the Socios En Salud Informatic System (SEIS) software [5, 16].

DM or PDM conditions were categorized as dysglycemia and were assessed by an endocrinologist as described previously (Barreda et al., 2020, Calderon et al., 2019). DM and PDM were defined in agreement with the American Diabetes Association (ADA) guidelines (International Diabetes Federation, 2017), respectively as HbA1c ≥ 6.5% or fasting glucose ≥ 126 mg/dL; and HbA1c 5.7 – 6.4% or fasting glucose 100 – 125 mg/dL. Persistent dysglycemia was defined when the patient has dysglycemia (i) in each (all) study visit or (ii) at baseline and 2nd-month visit or (iii) at baseline and the 6th-month visit or (iv) at the 2nd-month visit and 6th-month. Patients with dysglycemia at only one study visit were classified as normoglycemic.

Data on white blood cells count (WBC) as well as hemoglobin (Hb) levels, serum cholesterol (Chol), serum triglycerides (TG), serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST) and serum albumin were retrieved and analyzed from the electronic medical records.

TB Treatment outcome

Information on TB treatment outcome was obtained through follow-up visits carried out on 2nd, 6th and 24th months after treatment initiation. TB treatment outcome was defined in agree with WHO guidelines as favorable or unfavorable (World Health Organization, 2010) and these categories are showed in **Supplementary Table 1**. A favorable outcome was defined as cure or TB treatment completion. Death, relapse or failure to the scheme received were considered as unfavorable outcomes. "Lost to follow-up" and "not evaluated" were not included in the unfavorable outcomes as by other authors (Arriaga et al., 2021, Carvalho et al., 2021).

Data analysis

Kolmogorov Smirnov test was used to test the normality of study population distribution. Characteristics of PWTB are presented as median and interquartile ranges (IQR) as measures of central tendency and dispersion for continuous variables and frequency or percentages for categorical variables. Continuous variables were compared using the Mann-Whitney *U* test (between two groups) or the Kruskal-Wallis test with Dunn's multiple comparisons (between > 2 groups). Categorical variables were compared using a two-sided Pearson's chi square test with Yates's correction or the Fisher's two-tailed test in 2 x 3 or 2 x 2 tables, respectively.

Hierarchical cluster analysis (Ward's method, with bootstrap 100×) was performed to describe associations with persistent dysglycemia and unfavorable outcomes. Values of each biochemical and hematologic parameter were $\log_{10}$ transformed. Mean values for each indicated clinical group were z-score normalized.

We performed two multivariate logistic regressions: the first regression to assess the association between unfavorable TB treatment outcome and persistent dysglycemia and the second regression

to assess the association between unfavorable TB treatment outcome and persistent non-diabetic dysglycemia. For both regressions we used variables with a univariate p-value < 0.2 and we adjusted the following potential confounding variables: age, body mass index (BMI), hemoglobin and lung lesion types. Additionally, we included smoking and AFB smear grade as these variables may have an impact on the degree of lung inflammation or indirectly indicate the extension of pulmonary TB disease (Almeida-Junior et al., 2016, Gil-Santana et al., 2016), as showed in **Supplementary Table 2**.

All analyzes were prespecified. Two-sided p-value ≤ 0.05 after adjustment for multiple comparisons (Bonferroni method) was considered statistically significant. Analyzes were performed with SPSS version 24 (Armonk, NY: IBM Corp.) and GraphPad Prism version 8 (Software Inc., San Diego, CA, USA).

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Ethical issues

Written informed consent was obtained from all participants and investigations were conducted according with the Declaration of Helsinki and Peruvian regulations. The study was approved by the Institutional Committee of Ethics for Humans (CIEI, approval number: 458–22–16 of November 30, 2016), an autonomous committee established at the Universidad Peruana Cayetano Heredia, authorized by National Institute of Health in Peru.

RESULTS

From February to November 2017, 143 microbiologically confirmed PWTB attending the primary health care centers were screened in this cohort and 125 patients with active TB were included in the study, in which 4 PWTB requested voluntary withdrawal for several reasons. On the other hand, and in accordance with our analysis plan, we excluded 3 patients with a diagnosis of HIV infection and 11 patients lost to follow-up or patients not evaluated (**Supplementary Figure 1A**).

All diagnostic tests for dysglycemia were performed by the study staff at each scheduled visit up to 6th month. Evenly, TB treatment outcomes were evaluated on scheduled visits up to 24th month. More detailed information of study procedures is showed in **Supplementary Figure 1B**.

Persistent dysglycemia and normoglycemia were detected respectively in 29.6 % (95% CI: 22.3 – 38.1) and in 52% of PWTB (95% CI: 43.24% – 60.76%) of PWTB. Non-persistent dysglycemia was found in 18.4% (95% CI: 11.6% – 25.2%) of PWTB.

The sociodemographic, clinical, radiographic and laboratory characteristics of PWTB who presented persistent dysglycemia compared to patients with non-persistent dysglycemia and normoglycemia are described in **Table 1**. Patients with persistent dysglycemia presented more lung lesion types ($p< 0.001$), a higher bacillary load ($p= 0.013$), higher BMI ($p= 0.039$), low hemoglobin levels ($p< 0.001$) and were older than normoglycemic or non-persistent dysglycemic patients (**Table 1**). The characteristics of PWTB stratified by TB treatment outcomes are described in **Table 2**. Twenty-nine PWTB (23%; 95% CI: 16.7% – 31.3%) presented an unfavorable TB treatment outcome and they were more frequently older (median age: 51.3 vs. 27.9 years $p < 0.001$), had higher BMI ($p=0.01$), more lung lesion types ($p= 0.01$) and persistent dysglycemia ($p<0.001$) than PWTB with favorable outcome. Both study groups were similar with regard to a number of other characteristics, including sex, history of prior TB, asthma, renal disease, alcohol use, smoking and illicit drugs use, and TB and DM -related symptoms. Hemoglobin levels and acid-fast bacilli or culture positivity at baseline were also not significantly associated with unfavorable TB treatment

outcomes. The characteristics of PWTB stratified by TB treatment outcomes are displaying in the Supplementary Table 2 .

The dynamicity of the dysglycemia status in the TB patients included in the study, until reaching the category of persistent dysglycemic, are described in the Sankey diagram as shown in **Figure 1A**. The prevalence of persistent dysglycemia (62.1%; 95% CI 44.4% – 79.7%) was significantly higher in PWTB with unfavorable TB treatment outcomes compared to those with favorable outcomes ($p < 0.001$; **Figure 1B**). In addition, the median distribution of fasting glucose and HbA1c levels in persistent dysglycemic PWTB showed significant differences between patients with favorable (p=0.001; **Figure 1C** left panel) and unfavorable TB outcomes (p=0.037; **Figure 1C** right panel). We display the glycemic status (DM, PDM) through the study visits (**Supplementary Figure 2A and 2B)** and the comparison the TB treatment outcomes by persistent between persistent dysglycemia subgroups in **Supplementary Figure 2C**.

We performed a hierarchical cluster analysis using different laboratory baseline parameters measured in peripheral blood to assess whether it was possible to identify specific signatures that could characterize patients with TB presenting persistent dysglycemia and unfavorable outcomes (**Figure 2A**). This approach revealed that patients who mostly had both persistent dysglycemia and unfavorable outcomes presented a different profile marked by significantly lower values of HDL (p=0.09), albumin (p=0.048) and hemoglobin (p=0.036). This same subpopulation of patients also exhibited a distinctive profile hallmarked by significantly higher levels of WBC counts (p=0.036), cholesterol ($p< 0.01$), ALT ($p= 0.01$) and AST ($p= 0.024$) (**Figure 2B**) with exception of total serum proteins and LDL, which were not statistically differentiated.

To further investigate whether the characteristics of TB patients were directly associated with persistent dysglycemia and TB treatment outcomes, we performed a multivariate logistic regression analysis and it is showed in the **Figure 3**. We found that smoking, hemoglobin levels and AFB smear were not independently associated with unfavorable treatment outcomes in PWTB ($p> 0.05$).

Older PWTB (aOR = 1.04, 95% CI %: 1.01 - 1.08) and those with persistent dysglycemia were more likely of having an unfavorable TB treatment outcome (aOR: 6.1, 95% CI: 1.9 – 19.6).

Additionally, the same variables were assessed in a multivariate logistic regression model to evaluate the association of them with TB treatment outcomes in non-diabetic PWTB with persistent dysglycemia (**Supplementary Table 3**). Smoking, hemoglobin levels and the AFB grade were not independently associated with unfavorable treatment outcomes in PWTB. However, non-diabetic PWTB with persistent dysglycemia were at least 7-fold more likely of having an unfavorable TB treatment outcome (aOR: 6.9; 95% CI: 1.7 – 26.9) with age in years (aOR = 1.05, 95% CI %: 1.01 - 1.09).

DISCUSSION

In this cohort of newly diagnosed TB patients in North Lima, persistent dysglycemia, which includes diabetic and prediabetic patients throughout the course of antituberculosis treatment, was independently associated with unfavorable TB treatment outcomes. This finding supports the results of our previous studies, where patients affected with diabetes or prediabetes were associated with poor clinical profiles, such as low hemoglobin, high liver enzymes levels and abnormal lipid values, among others (Barreda et al., 2020).

Our data is part of a larger cohort in which prevalence of TB-DM (14.4%) was not different from that previously reported (14%) (Calderon et al., 2019). In a recently published manuscript, with data from the Tuberculosis Management Information System of the Peruvian NTP, the prevalence of DM in patients with TB was 9,7%, similar to the prevalence reported in our study (Ugarte-Gil et al., 2021). However, the authors poorly demonstrated an association between DM and unfavorable TB treatment outcomes because of several limitations of the reporting system. Our study shows discrepancies in the prevalence of unfavorable TB treatment results from the Peruvian NTP report; so, we consider that our observations may be more reliable, especially in cases of unfavorable outcomes (treatment failure, loss of follow-up, patients not evaluated, and transfers), due to the extended 24-month follow-up. In the NTP reporting system (Ugarte-Gil et al., 2021), TB treatment outcome is generally recorded only once, at the end of treatment.

As far as we know, this is the first description about the frequency of persistent dysglycemia among patients being treated for TB and its potential impact on TB treatment outcome. Our work is also newfangled in showing the increased risk of unfavorable TB treatment outcomes in patients with diabetes or prediabetes during anti-TB treatment, reflected in our definition of persistent dysglycemia. Non-diabetic dysglycemia often did not represent any alarm among general physicians and even among endocrinologists, so no specific care or recommendation has ever been proposed in TB treatment guidelines worldwide. Assuming that TB can induce acute stress-related hyperglycemia, which may lead to epigenetic changes that increases the risk for TB progression and

complications even after blood glucose levels have returned to normal (Magee et al., 2018a), further research should be done to establish the need for specific treatment for dysglycemia in these cases. Therefore, non-diabetic dysglycemia in PWTB must not be overlooked, since it has been shown to be a risk factor for progression to diabetes (Tabák et al., 2012), leading to a higher risk of unfavorable TB treatment outcome, as has been previously described by other authors as well (Arriaga et al., 2021, Baker et al., 2011, Jeon and Murray, 2008).

We have tried to capture that phenomenon of persistent transient high levels of glycemia (El-Osta et al., 2008, Magee et al., 2013) might affects TB treatment outcome, evaluating changes in the fasting glucose or HbA1c levels periodically, similar as reported elsewhere (Kornfeld et al., 2016, Magee et al., 2018a). In our study the glycated hemoglobin levels changed slightly during TB treatment, while fasting glucose was more sensitive to reveal some effect on tuberculosis treatment outcomes. This could be explained because high blood glucose levels would cause persistent effects, despite subsequent normoglycemia, by inducing long-lasting activating epigenetic changes, which leads to some of the variations in the risk of complications that could not be explained by the HbA1c (El-Osta et al., 2008).

Our findings indicate that dysglycemia should not be screened only at the TB diagnosis, but rather throughout the course of antituberculosis therapy and should be properly treated to achieve an effective control of glycemic status (Boillat-Blanco et al., 2016) and avoid unfavorable treatment outcomes. Testing and monitoring for dysglycemia at the time of diagnosis and during TB treatment can be clinically useful in improving the outcome of TB treatment.

High blood levels of glucose were transient in a PWTB group, coincidentally as occurs in patients with other diseases (Dungan et al., 2009). Several metabolic indicators that are altered by inflammation have been observed; but we observed in our study that, despite effective antituberculosis chemotherapy, the hyperinflammatory profile could persists during the intensive phase of treatment, as previously reported (Kumar et al., 2019). As our study as other authors shown that not only dysglycemia is related with a different inflammatory pattern, but also anemia

(Gil-Santana et al., 2019) and with neutrophilia (Carvalho et al., 2021) has reported with persistent hyperinflammatory response despite having started TB treatment.

Dysglycemia in PWTB was associated with worse biochemical profiles and more extensive lesions on chest radiograph, as we described previously (Barreda et al., 2020). Our hierarchical cluster analysis further demonstrated that the cellular and biochemical profile associated with persistent dysglycemia was also linked to lung damage, elevation of WBC count and increased levels of liver transaminases, total cholesterol and low hemoglobin, as previously described (Chiang et al., 2014, Tabák et al., 2012). It is possible that the harmful effect of persistent dysglycemia in the response to TB treatment is linked to the induction of chronic inflammation (Magee et al., 2018b).

Glycemic control has been recommended to decrease the risk of TB transmission (Almeida-Junior et al., 2016), has been associated with better outcomes (Dungan et al., 2009) and may influence the treatment outcome (Boillat-Blanco et al., 2016). TB-DM patients who used metformin had better TB treatment results (Singhal et al., 2014). Unfortunately, in our study we did not have access to information about the treatment for dysglycemia in these patients, therefore we could not evaluate the positive effect of glycemic control in reducing the risk of unfavorable TB treatment outcome.

Our study has several limitations. information on oral glucose tolerance test, the gold standard of dysglycemia screening, was not available because we conducted this study under programmatic conditions of TB services. However, considering our persistent dysglycemia detection model, the follow-up of 2 years was able to consolidate the effect on antituberculosis treatment outcome. Another study limitation was the missing information regarding the treatment of dysglycemic patients detected in the study, data such as severity or duration of organ damage from diabetes was not collected. As previously mentioned, endocrinologists in general are very conservative in diagnosing patients with non-diabetic dysglycemia. For that reason, many patients did not have assured access to metformin or other hypoglycemic medication for the treatment of dysglycemia and that situation may not be different from what has routinely occurred in the management of PWTB. Therefore, this study highlights the necessity to reassess persistent dysglycemia control

among PWTB to mitigate the risk of unfavorable TB treatment outcome. Finally, many of the variables identified as associated with persistent dysglycemia and unfavorable treatment outcome did not enter in the final multivariate model, as they could be affected by sample size, requiring further future research. Likewise, it is important to note that although our data represent a limited sample of patients, it is representative of the population of PWTB in Lima, since our prevalence of diabetic dysglycemia and proportions of unfavorable outcomes were very similar to those reported in previous studies and reports (Arriaga et al., 2021, Baker et al., 2011, Ugarte-Gil et al., 2021).

In conclusion, our study showed that persistent diabetic and non-diabetic dysglycemia were common in PWTB and both conditions were also significantly associated with an unfavorable TB treatment outcome. In addition to TB-DM management, our findings suggest that optimal control of whole dysglycemic condition (including PDM) should be part of TB management in Peru. Currently, few published studies have examined the clinical and care characteristics associated with dysglycemia, the outcome of TB treatment, or the time to MTB culture conversion. A strength of this study was the clinical evaluation of a prospective cohort of PWTB with dysglycemia. Our findings highlight the importance of linking services for the control of TB and dysglycemia and, although more research is needed, in our view this work brings useful data for a better management of dysglycemia in PWTB.

Potential conflicts of interest.

Authors declared any conflicts potential conflicts of interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

NOTES

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Author's contributions: RIC and MBA conceived and designed the study, interpreted the data, and wrote the manuscript. RIC, MBA, NNB, OSS, and LL implemented the lab study and collected the data. RIC, BB-D, JPDF and MBA performed the analysis. LL, BBA, ACC and AK reviewed the manuscript. All authors should have made the final approval of the submitted version of this

manuscript All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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FIGURES

Figure 1. Glycemic status of the TB patients stratified by treatment outcome. (A) Sankey diagram of dysglycemic status identification and categorization of persistent dysglycemia. **(B)** Frequency of persistent dysglycemia by TB treatment outcome. Data were compared using the chi-square (χ^2) test. **(C)** Scatter plots depicting the persistent dysglycemia and no persistent dysglycemia stratified by treatment outcome in the baseline were plotted. Lines represent median values and interquartile ranges (IQR). The differences in

median values (and IQR) between groups were compared using the Mann-Whitney *U* test. Abbreviatures: TB: tuberculosis; IQR: Interquartile range

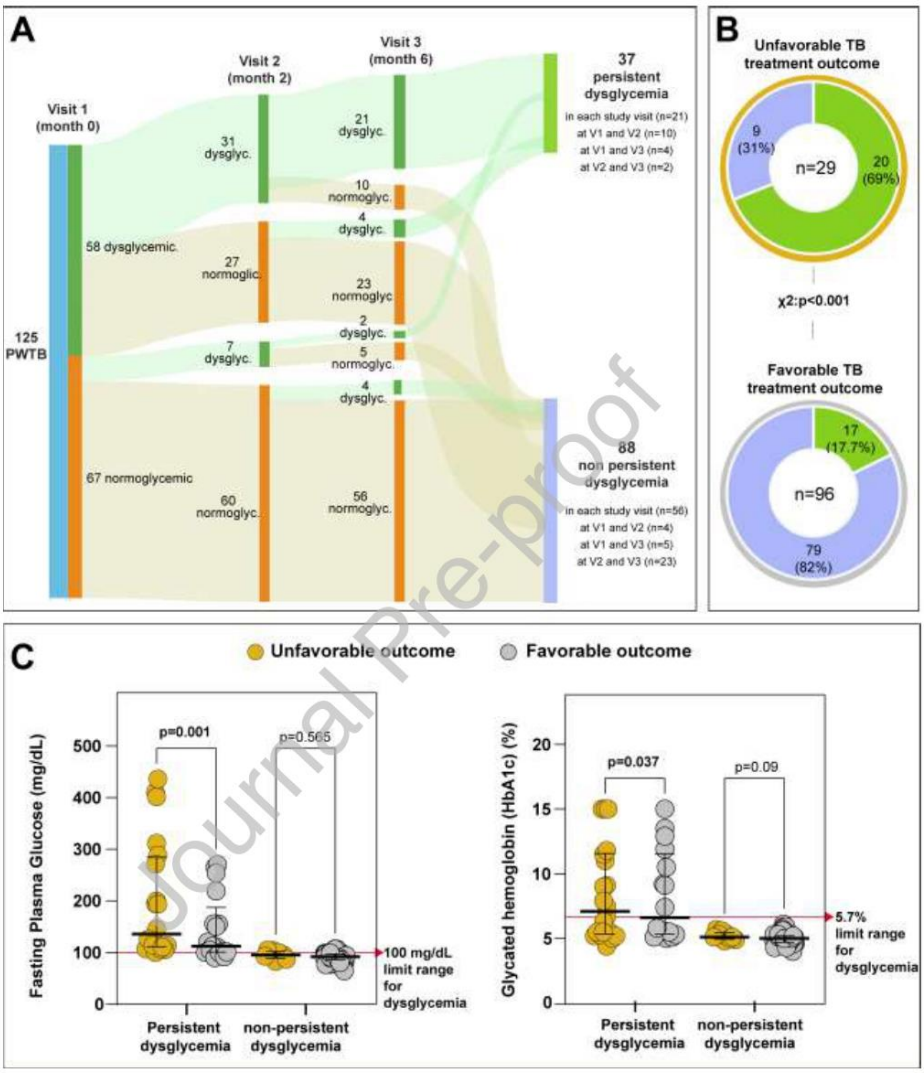


Figure 2. Laboratorial profiles of TB patients by persistent dysglycemia condition. (A) Value of each parameter was $\log_{10}$ transformed. Mean values for each indicated clinical group were z-score normalized and a hierarchical cluster analysis (Ward's method with 100X bootstrap) was performed to illustrate the overall laboratorial profiles. **(B)** Data represent median and interquartile ranges. The Mann-Whitney *U* test was employed to compare the values detected between the study subgroups. The red lines shown the range limit and gray lines indicate the normality values range. Abbreviatures: PD: Persistent dysglycemia; Unf.: Unfavorable; Fav.: Favorable; HbA1c: Glycated hemoglobin; HDL: High Density Lipoprotein; LDL: Low Density Lipoproteins; AST: Aspartate transaminase; ALT: alanine aminotransferase.

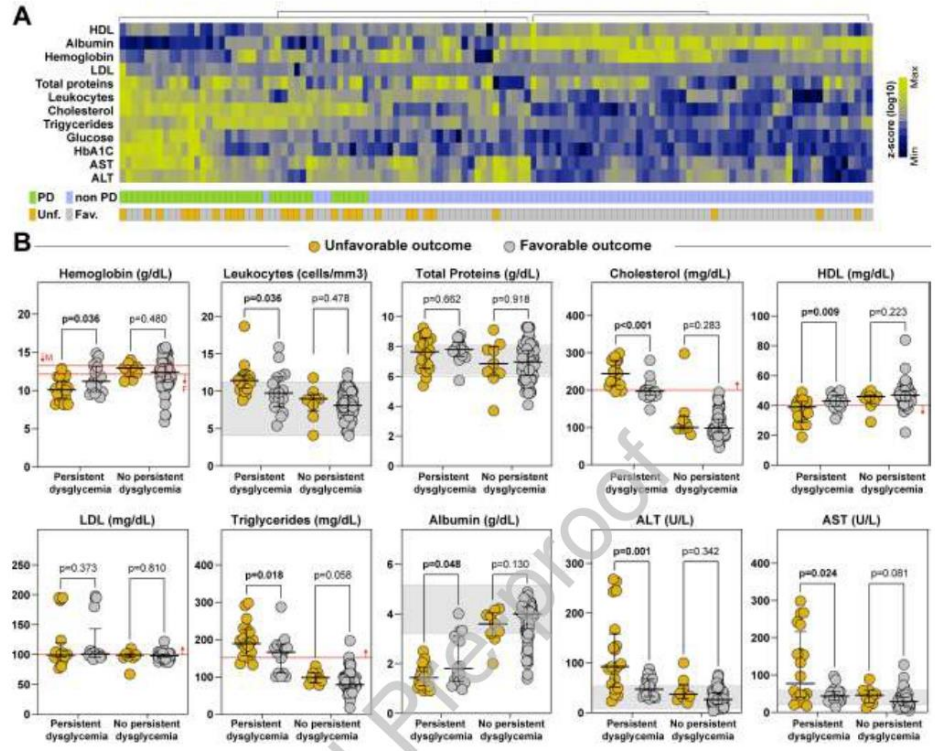
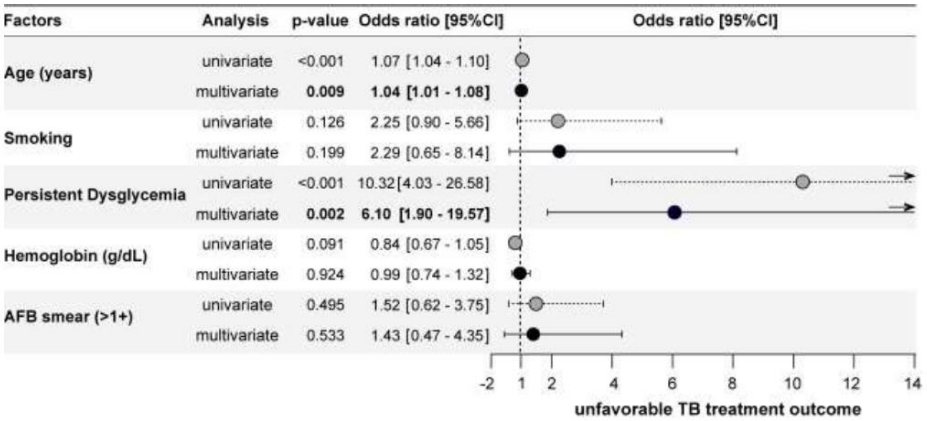


Figure 3. Logistic regression analysis of persistent dysglycemia on TB treatment outcomes. Logistic regression model was performed to evaluate the independent associations between the variables with p-value < 0.2 results in the univariate analyses (**Table 1**) and unfavorable treatment outcome (treatment modification, failure, recurrence, and death). Adjustment was performed for each parameter: smoking (reference: no smoking), persistent dysglycemia (reference: no persistent dysglycemia), AFB smear >+1 (reference: AFB ≤+1). This model had an index of predictive power of 80%. Abbreviatures: AFB: Acid-fast bacilli. Unfavorable TB outcome was defined as treatment failure or modification, recurrence or death, whereas favorable outcome was cure or treatment completion. 95% CI: Confidence Interval.



TABLES

Table 1. Characteristics of patients with pulmonary TB stratified by persistent dysglycemia.

Characteristics	Persistent Dysglycemia (n= 37)	No Persistent Dysglycemia* (n= 88)	p-value
Age (years)-median (IQR)	47.3 (34.9 - 58.3)	27.5 (22.3 - 36.2)	**< 0.001**
Male sex-n (%)	21 (56.8)	58 (65.9)	0.417
BCG vaccination-n (%)	33 (89.2)	82 (94.3)	0.449
Prior TB -n (%)	9 (24.3)	13 (14.8)	0.209
BMI-median (IQR)	23.7 (22.1-26.4)	22.3 (20.3-24.9)	**0.039**
BMI categories -n (%)			0.399
Obesity	1 (2.8)	2 (2.4)	0.567
Overweight	13 (36.1)	19 (22.4)	0.103
Underweight	4 (11.1)	6 (7.1)	0.270
Normal	18 (50.0)	58 (68.2)	Ref.
Lung lesion types-n (%)			**< 0.001**
1 type	3 (8.3)	6 (27.3)	
2 types	13 (36.1)	2 (9.1)	
3 types	20 (55.6)	14 (63.6)	
AFB smear -n (%)			0.060
1+	6 (16.2)	20 (23.0)	
2+	6 (16.2)	8 (9.2)	
3+	11 (29.7)	12 (13.8)	
Scanty	1 (2.7)	4 (4.6)	
Negative	13 (35.1)	43 (49.4)	
L-J Culture -n (%)			0.747
1+	16 (44.4)	12 (57.1)	
2+	5 (13.9)	4 (4.7)	
3+	2 (5.6)	4 (4.7)	
<1+	3 (8.3)	10 (11.6)	
Negative	10 (27.8)	26 (30.2)	
MDR-n (%)	7 (35.0)	11 (22.0)	0.364
Smoking-n (%)	7 (18.9)	21 (24.1)	0.641
Cannabis use-n (%)	4 (10.8)	13 (14.9)	0.776
Other illicit drugs use-n (%)	5 (13.5)	9 (10.3)	0.757
Alcohol use-n (%)	16 (43.2)	47 (54.0)	0.328
Hemoglobin (g/dL) -median (IQR)	11.1 (10.0-12.2)	12.4 (11.2-13.4)	**0.001**
Fasting glucose-median (IQR)	110.1 (100.4 -218.9)	91.9 (86.1-97.7)	**< 0.001**
HbA1c-median (IQR)	6.0 (5.3 -10.8)	5.0 (4.8-5.3)	**< 0.001**
Glycemic status at baseline – n (%)			**< 0.001**
Diabetes	18 (48.6)	0 (0.0)	
Prediabetes	17 (45.9)	23 (26.1)	

Normoglycemia*	2 (5.4)	65 (73.9)	
Use of metformin – n (%)**	14 (37.8)	2 (2.3)	**<0.001**
Hypertension – n (%)	6 (16.2)	0 (0.0)	NA
Asthma – n (%)	1 (2.7)	7 (8.0)	0.268
Renal disease – n (%)	1 (2.7)	2 (2.3)	0.893
TB and DM symptoms – n (%)			
Cough	34 (91.9)	81 (92.0)	0.977
Fever	14 (37.8)	42 (47.7)	0.310
Dyspnea	23 (62.2)	60 (68.2)	0.515
Night sweats	23 (62.2)	48 (54.5)	0.433
Non appetite	21 (56.8)	52 (59.1)	0.809
Weight loss	27 (73.0)	63 (71.6)	0.875
Polyuria	17 (45.9)	33 (37.5)	0.379
Polydipsia	16 (43.2)	43 (48.9)	0.566
Malaise	29 (78.4)	68 (77.3)	0.892
Slow scarring	7 (18.9)	11 (12.6)	0.364

Data represent no. (%). *Sixty-five patients, categorized in no persistent dysglycemia group were normoglycemic in each visit. ** Use of metformin was indicated in patients with diabetes diagnosis. Hypertension, asthma, renal disease as defined by the World Health Organization and described in Methods. Prior TB: diagnosis of active tuberculosis before of this study. Abbreviatures: IQR: Interquartile range. BCG: Bacillus Calmette–Guérin, BMI: Body Mass Index, Hb: Hemoglobin, HbA1c: Glycated Hemoglobin, AFB: Acid-Fast Bacilli, L-J: Löwenstein-Jensen, MDR: Multi Drug Resistant. Ref.: Reference value, NA: not applicable.

Table 2. Characteristics of patients with pulmonary TB stratified by TB treatment outcome.

Characteristics	Unfavorable treatment outcome (n=29)	Favorable treatment outcome (n=96)	p–value
Age (years) – median (IQR)	51.3 (33.6–58.8)	27.9 (22.6–39.8)	**< 0.001**
Sex – n (%)			1.000
Male	18 (62.1)	61 (63.5)	
Female	11 (37.9)	35 (36.5)	
BCG vaccination– n (%)	28 (96.6)	87 (91.6)	0.700
Prior TB – n (%)	5 (17.2)	17 (17.7)	1.000
BMI (kg/m^2) –median (IQR)	23.9 (21.8–26.5)	22.3 (20.4–24.7)	**0.010**
BMI categories – n (%)			0.100
Obesity	2 (7.1)	1 (1.1)	0.100
Overweight	11 (39.3)	21 (22.6)	0.010
Underweight	4 (14.3)	6 (6.5)	0.100
Normal	11 (39.3)	65 (69.9)	Ref.
Lung lesion types– n (%) *			**0.010**
1 type	4 (14.3)	32 (34.0)	
2 types	9 (32.1)	27 (28.7)	
3 types	15 (53.6)	35 (37.2)	
AFB smear – n (%)			0.115
1+	4 (13.8)	22 (23.2)	
2+	4 (13.8)	10 (10.5)	
3+	9 (31.0)	14 (14.7)	
Scanty	1 (3.4)	4 (4.2)	
Negative	11 (37.9)	45 (47.4)	
L-J Culture – n (%)			0.309
1+	14 (50.0)	42 (45.7)	
2+	1 (3.6)	8 (8.7)	
3+	1 (3.6)	5 (5.4)	
<1+	2 (7.1)	11 (12.0)	
Negative	10 (35.7)	26 (28.3)	
MDR– n (%)	2 (16.7)	7 (12.1)	0.646
Smoking– n (%)	10 (34.5)	18 (18.9)	0.126
Cannabis consumption – n (%)	3 (10.3)	14 (14.7)	0.759
Other illicit drug consumption– n (%)	3 (10.3)	11 (11.6)	1.000
Alcohol use– n (%)	16 (55.2)	47 (49.5)	0.673
Hemoglobin (g/dL) – median (IQR)	11.4 (10.3–12.8)	12.25 (10.9–13.3)	0.091
Fasting Glucose (g/dL) –median (IQR)	103.4 (95.3–135.6)	92.9 (87.3–99.8)	**<0.001**
HbA1c (%) – median (IQR)	5.3 (5.1–6.5)	5.1 (4.8–5.3)	**0.001**
Dysglycemia at baseline – n (%)	28 (96.6)	30 (31.3)	**< 0.001**
Glycemic status at baseline – n (%)			**< 0.001**
Diabetes	9 (31.0)	9 (9.4)	**< 0.001**
Prediabetes	19 (65.5)	21 (21.9)	**< 0.001**

Normoglycemia	1 (3.4)	66 (68.8)	Ref.
Use of metformin – n (%)**	6 (20.7)	10 (10.4)	0.147
Persistent Dysglycemia (%)	**20 (69.0)**	**17 (17.7)**	**< 0.001**
Hypertension – n (%)	2 (6.9)	4 (4.2)	0.624
Asthma – n (%)	1 (3.4)	7 (7.4)	0.679
Renal disease – n (%)	1 (3.4)	2 (2.1)	0.554
TB and DM symptoms – n (%)			
Cough	26 (89.7)	89 (92.7)	0.696
Fever	10 (34.5)	46 (47.9)	0.144
Dyspnea	19 (65.5)	64 (66.7)	1.000
Night sweats	15 (51.7)	56 (58.3)	0.531
No appetite	18 (62.1)	55 (57.3)	0.674
weight loss	22 (75.9)	68 (70.8)	0.646
Polyuria	12 (41.4)	38 (39.6)	1.000
Polydipsia	11 (37.9)	48 (50.0)	0.293
Malaise	23 (79.3)	74 (77.1)	1.000
Slow scarring	4 (13.8)	14 (14.7)	1.000

Data represent no. (%). Hypertension, asthma, renal disease as defined by the World Health Organization and described in Methods. The variable "Lung lesion types" refers to the presence of the 3 different types of lung lesions as cavities, infiltrates and fibrous tracts in the radiographic lung profile. ** Use of metformin was indicated in patients with diabetes diagnosis. Prior TB: diagnosis of active tuberculosis before of this study. Abbreviatures: IQR: Interquartile range. BCG: Bacillus Calmette–Guérin, BMI: Body Mass Index, Hb: Hemoglobin, HbA1c: Glycated Hemoglobin, AFB: Acid-Fast Bacilli, L-J: Löwenstein-Jensen, MDR: Multi Drug Resistant. Ref.: Reference value.

6.6 MANUSCRITO VI

Prevalence and Clinical Profiling of Dysglycemia and HIV infection in Persons with Pulmonary Tuberculosis in Brazil

A TB é muito frequente nas pessoas com infecção pelo HIV e tem impacto na qualidade de vida e na mortalidade dessa população. Uma pessoa vivendo com HIV tem 28 vezes mais chances de adquirir TB do que uma pessoa que não tem HIV.

No Brasil há um aumento na prevalência das comorbidades TB-DM e TB-HIV, por isso este estudo identificou e caracterizou a prevalência de HIV e associação com estado glicêmico entre pessoas com TB pulmonar ativa no RePORT-Brasil e no SINAN-TB

Resumo dos resultados: Na coorte RePORT-Brasil, a prevalência de DM e de PDM foi de 23,7% e 37,8%, respectivamente. Além disso, a prevalência de HIV foi de 21,4% no grupo de pessoas com TB-disglicemia e 20,5% no de pacientes com TBDM. Na coorte do SINAN, a prevalência de DM foi de 9,2%, e no grupo TBDM a prevalência de HIV foi de 4,1%.

Há uma alta prevalência de disglicemia em pacientes com TB pulmonar no Brasil, independentemente do status de HIV. Isso reforça a ideia de que o DM deve ser sistematicamente rastreado em pessoas com TB.

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Prevalence and Clinical Profiling of Dysglycemia and HIV Infection in Persons With Pulmonary Tuberculosis in Brazil

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Background: There are scarce data on the prevalence and disease presentation of HIV in patients with tuberculosis (TB) and dysglycemia (diabetes [DM] and prediabetes [PDM]), especially in TB-endemic countries.

Methods: We assessed the baseline epidemiological and clinical characteristics of patients with culture-confirmed pulmonary TB, enrolled in a multicenter prospective cohort in Brazil (RePORT-Brazil) during 2015–2019. Dysglycemia was defined by elevated glycated hemoglobin and stratified as PDM or DM. Additionally, we used data from TB cases obtained through the Brazilian National Notifiable Diseases Information System (SINAN), during 2015–2019. In SINAN, diagnosis of diabetes was based on self-report. Logistic regression models were performed to test independent associations between HIV, dysglycemia status, and other baseline characteristics in both cohorts.

Results: In the RePORT-Brazil cohort, the prevalence of DM and of PDM was 23.7 and 37.8%, respectively. Furthermore, the prevalence of HIV was 21.4% in the group of persons with TB-dysglycemia and 20.5% in that of patients with TBDM. In the SINAN cohort, the prevalence of DM was 9.2%, and among the TBDM group the prevalence of HIV was 4.1%. Logistic regressions demonstrated that aging was independently

associated with PDM or DM in both the RePORT-Brazil and SINAN cohorts. In RePORT-Brazil, illicit drug use was associated with PDM, whereas a higher body mass index (BMI) was associated with DM occurrence. Of note, HIV was not associated with an increased risk of PDM or DM in patients with pulmonary TB in both cohorts. Moreover, in both cohorts, the TBDM-HIV group presented with a lower proportion of positive sputum smear and a higher frequency of tobacco and alcohol users.

Conclusion: There is a high prevalence of dysglycemia in patients with pulmonary TB in Brazil, regardless of the HIV status. This reinforces the idea that DM should be systematically screened in persons with TB. Presence of HIV does not substantially impact clinical presentation in persons with TBDM, although it is associated with more frequent use of recreational drugs and smear negative sputum samples during TB screening.

Keywords: dysglycemia, HIV infection, pulmonary tuberculosis, *Mycobacterium tuberculosis*, diabetes

INTRODUCTION

Approximately one-quarter of the world population is thought to be infected with *Mycobacterium tuberculosis* (Mtb) and about 5–10% of those will develop active disease at some point in their lives, which represents a substantial public health problem (1). Several factors are related to the development of active tuberculosis (TB), such as immunological, genetic, and metabolic factors. Importantly, metabolic disorders associated with glycemic status are considered important risk factors for the development active TB and also for unfavorable anti-TB treatment outcomes (2). In addition, the immune deterioration caused by human immunodeficiency virus (HIV) favors the multiplication of Mtb and the progression to active TB (3).

Dysglycemia is a spectrum of metabolic dysfunctions related to glucose metabolism in the body, which includes several diseases, especially prediabetes (PDM) and diabetes (DM) (4). Approximately 422 million people worldwide live with DM, most of whom are in low-and middle-income countries. Likewise, a significant part of the world's population suffers from PDM, an intermediate state of insulin resistance that partially affects the entry of glucose into cells (5, 6). Interestingly, TB is similarly focused on low-and middle-income countries, which is a problem as DM triples the risk of developing active TB (7). Furthermore, 15.3% of people with TB worldwide have DM as a comorbidity (8). Persons with TB-DM usually exhibit a different clinical presentation, which includes higher frequency of extensive or cavitary pulmonary TB, a higher bacillary load in sputum and delayed mycobacterial clearance compared to normoglycemic TB patients (9, 10). Although much has been described on the interaction between TB and DM in different settings, most of the studies investigated a limited number of participants, and larger studies are warranted to better define such interactions. In addition, the clinical outcomes as well as the pathophysiological mechanisms of patients with TB-DM are still poorly understood (7, 11).

In addition to the importance of metabolic disorders, conditions that directly affect the immune response against TB are also a relevant problem as they contribute to more severe manifestations (12). Importantly, people living with HIV (PLWH) are approximately 50 times more likely to develop active TB than those without HIV exposure (12). Moreover, in 2019, PLWH accounted for 1.2 million (8.2%) of the approximately 10 million people with TB worldwide and of those, 208,000 deaths were related to HIV comorbidity (12). On the other hand, persons living with both TB and HIV often experience accelerated HIV disease progression and TB is placed as the most common opportunistic infection inducing high morbidity (12). HIV has been shown to modify the course of TB by causing severe immunosuppression and Mtb dissemination to multiple organs and increased mortality (13, 14).

Brazil has a high burden of TB-DM (8) and TB-HIV (1). Despite of the high of these comorbidities, to our knowledge there is no information that explores in detail the association between HIV and TB-DM and its impact on clinical presentation of affected persons in the country. The scarce information that exists come from studies performed in African populations and with results that are not consistent with each other (15, 16). Because of the abovementioned reasons, studies that examine the overlap of metabolic and immunological diseases associated with TB are needed to better understand the spectrum of disease presentation of patients with multiple comorbidities such as TB-DM-HIV. In the present study, we aimed at contributing to fill this gap in knowledge in the context of TB, dysglycemia, and HIV-infection, through the identification and characterization of HIV prevalence and its association with glycemic status among persons with active pulmonary TB, in the Regional Prospective Observational Research in Tuberculosis (RePORT-Brazil) study, which is a large multicenter prospective cohort of culture-confirmed pulmonary TB persons which has been shown to be representative of the TB cases reported in the Brazilian national TB registry (17, 18). We also investigated such associations in TB cases reported to the Brazilian National TB Registry through the National System of Diseases Notification (SINAN).

METHODS

Ethics Statement

All clinical investigations were conducted according to the principles of the Declaration of Helsinki. The RePORT-Brazil protocol, informed consent, and study documents were approved by the institutional review boards at each study site and at Vanderbilt University Medical Center (CAAE: 25102414.3.2009.5543). Participation in RePORT-Brazil was voluntary, and written informed consent was obtained from all such participants.

Study Design – RePORT-Brazil

This was a multicenter prospective observational cohort study of individuals ≥ 18 years old with culture-confirmed pulmonary TB. RePORT-Brazil study sites are located in Manaus (Amazonas state, Northern region), Salvador (Bahia state, Northeastern region), and Rio de Janeiro (Rio de Janeiro state, Southeastern region), with a total of five health units: Instituto Nacional de Infectologia Evandro Chagas, Clínica da Família Rinaldo Delamare, and Secretaria Municipal de Saúde de Duque de Caxias (Rio de Janeiro), Instituto Brasileiro para Investigação da Tuberculose, Fundação José Silveira (Bahia), and Fundação de Medicina Tropical Doutor Heitor Vieira Dourado (Amazonas), representing both a heterogeneous population and the Brazilian cities with highest TB burden (17, 18).

Data Collection – RePORT-Brazil

Between 2015 and 2019, TB cases were interviewed for sociodemographic, clinical and epidemiological data such as age, sex, race/ethnicity (self-reported, based on the guidelines of the Ministry of Health of Brazil (19, 20), body mass index (BMI), income, smoking status, passive smoking status (living with someone who smokes), alcohol and illicit drug use, and clinical data such as presence of TB symptoms (cough, fever, weight loss, fatigue, night sweats, chest pain) and had the following tests performed: chest X-ray, HIV serologic test (the test was not performed if the individuals had a previous diagnosis of HIV), CD4 and viral load (if HIV serology was positive or previous diagnosis of HIV-infection), complete blood count, glycated hemoglobin (HbA1c), sputum smear microscopy, Xpert-MTB-RIF (if available) and mycobacterial culture (Lowenstein-Jensen medium or BD BACTEC MGIT). Patients who received TB treatment or fluoroquinolones for >7 days in the 30 days prior to TB diagnosis and pregnant women were excluded. We only analyzed information collected at the study baseline.

Notifiable Diseases Information System (SINAN), Brazilian Ministry of Health

SINAN is a system for the notification of transmissible diseases, including TB, that has been implemented, supported, and maintained by the Brazilian Ministry of Health (21). Data were collected from TB patients ≥ 18 years old with information about "diabetes status", between 2015 and 2019. Persons who were homeless, prisoners, pregnant, or had extrapulmonary TB were excluded, resulting in a population of 279,143 individuals. TB was diagnosed according to the Brazilian Ministry of Health criteria, detailed in the Manual of Recommendations for the TB Control in Brazil (22). After TB diagnosis, the information collected at the baseline and the laboratory results were recorded on a standardized form that, individual characteristics (sex, age, race, education level, alcohol consumption, illicit drug use, smoking habits, and comorbidities), the presence of DM condition ("yes" or "no" options) and HIV-infection, among others (22).

Study Definitions

In pulmonary TB cases from RePORT-Brazil, participants with HbA1c ≥ 5.7% were classified as dysglycemic and those with HbA1c < 5.7% were considered normoglycemic. Study participants were also classified as having DM (HbA1c ≥ 6.5%), PDM (HbA1c = 5.7–6.4%) or normoglycemia (HbA1c < 5.7%), following American Diabetes Association (ADA) guidelines (23).

Data Analysis

Categorical variables were presented as proportions and compared using a two-sided Pearson's chi-square test (with Yates's correction) or Fisher's two-tailed test in 2 × 3 or 2 × 2 tables, respectively. Continuous variables were presented as median and interquartile range (IQR) and compared using the Mann Whitney *U* (between 2 groups) or Kruskal Wallis test (between ≥2 groups). Viral load values and CD4 count were transformed to log10 for analyses. Multinomial and binomial logistic regression models with stepwise method (Wald) were performed to evaluate independent associations between clinical characteristics of pulmonary TB cases and presence of diabetes and/or prediabetes in the Report-Brazil and SINAN cohorts. Parameters with *p*-values ≤ 0.2 in univariate analyses were included in multivariable models. *P*-values < 0.05 were considered statistically significant. All the analyses were pre-specified. Statistical analyses were performed using SPSS 24.0 (IBM statistics), Graphpad Prism 9.0 (GraphPad Software, San Diego, CA) and R 3.1.0 (R Foundation, Austria).

RESULTS

Characteristics of the Study Participants

RePORT-Brazil enrolled 1,162 patients with culture-positive pulmonary TB during 2015-2019 from the five centers of the consortium. The prevalence of dysglycemia at TB diagnosis was 61.5% (95%CI: 58.6–64.2). Compared to normoglycemic individuals, those with dysglycemia were more likely male (68.8 vs. 61.8%, $p = 0.018$) and older (39, IQR: 29–52 years, $p < 0.001$). Among TB-DM cases, 122/275 (44.4%) had previous diagnosis of DM. The dysglycemia group also exhibited higher frequency of self-reported *pardo* race ($n = 388$, 54.4%, $p = 0.007$), a higher median of BMI value (20.5, IQR:18.4–23.1; $p < 0.001$) and a higher frequency of self-reported weight loss ($n = 597$, 93%; $p = 0.016$) but not of other TB symptoms (**Supplementary Table 1**).

Characteristics of TB Cases by Glycemic Status

In RePORT-Brazil, the DM and PDM prevalence at TB diagnosis was 23.7% (95%CI: 21.31–26.2%) ($n = 275$), and 37.8% (95%CI: 35.0–40.6%) ($n = 439$), respectively

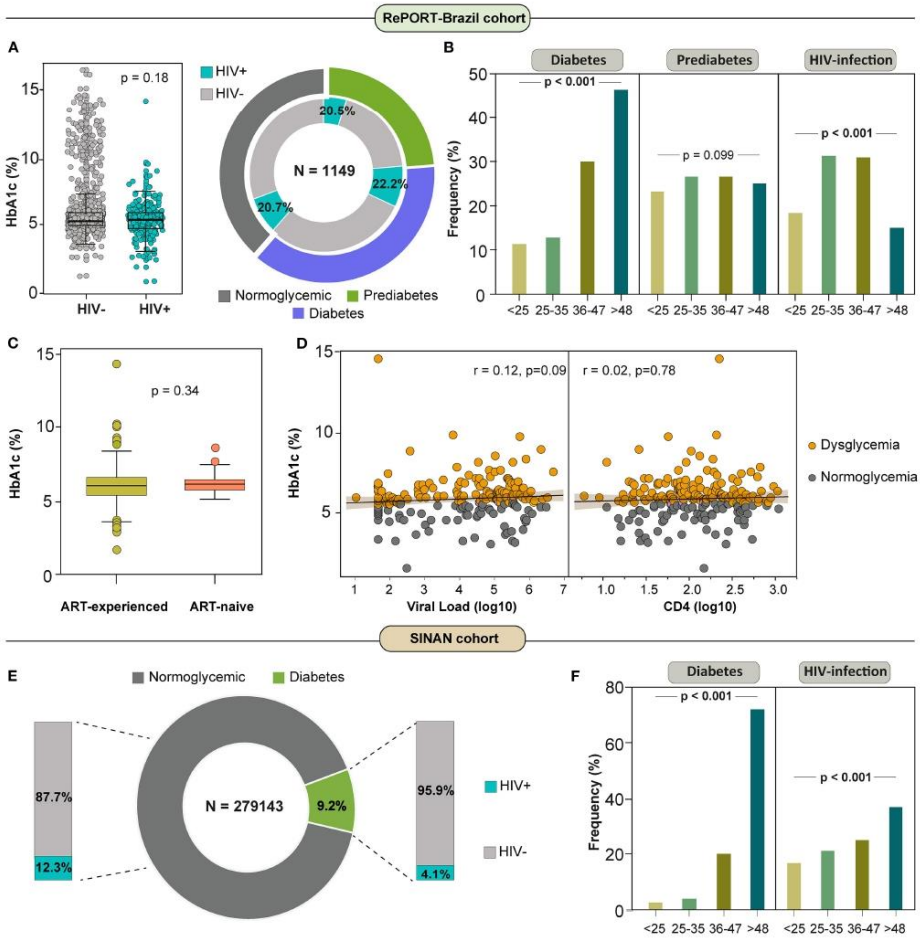

FIGURE 1 | HIV infection among dysglycemic patients with active tuberculosis in RePORT-Brazil and SINAN cohorts. **(A)** Left panel: Scatter plot comparing distribution of HbA1c levels between subgroups of pulmonary TB cases per HIV infection status. Data were compared using the Mann-Whitney *U* test. Left panel: Total frequency of HIV infection among diabetic TB patients was 20.5%, among prediabetics was 22·2% and among normoglycemic patients was 20.7% (chi-square test $p > 0{\cdot}05$). **(B)** Frequency of individuals with diagnosis of diabetes, prediabetes and HIV infection in the indicated age category (in years) among pulmonary TB patients is shown. Data were compared using the Pearson's chi-square test. **(C)** Box plot comparing distribution of HbA1c levels between subgroups of pulmonary TB cases per ART-experience and ART-naive status. Data were compared using the Mann-Whitney *U* test. **(D)** Spearman correlation between HbA1c and viral load (log10) levels (Left panel) and CD4 (log10) levels (Right panel) at baseline in pulmonary TB patients grouped according to the dysglycemic status. Line and shaded area represent linear curve fit with 95% confidence interval. **(E)** Total frequency of HIV infection among diabetic TB patients was 4.1% and among normoglycemic patients was 12.3% (chi-square test $p > 0{\cdot}05$). The statistical analyzes were carried out only with the available data, omitting the cases with missing information (14 patients were removed due to lack in HIV status). **(F)** Frequency of individuals with diagnosis of diabetes and HIV infection in the indicated age category (in years) among pulmonary TB patients is shown. Data were compared using the Pearson's chi-square test. ART, antiretroviral therapy.

(**Supplementary Figure 1A**). Several clinical characteristics differed between normoglycemic and dysglycemic TB patients, with significant differences in frequency of sex ($p = 0.027$), age ($p < 0.001$) race/ethnicity ($p < 0.001$), BMI values ($p < 0.001$) and the frequency of self-reported weight loss as a symptom ($p = 0.033$) between the three groups (**Supplementary Table 2**).

To evaluate these differences in more detail, we performed pair-wise comparisons between the groups. The highest median age was observed in the DM group (46 years; IQR: 36–55), which was significantly higher than PDM (36, IQR: 26–47) and normoglycemia (31, IQR: 23–42). We also observed differences between PDM and normoglycemia, with $p < 0.001$ in both comparisons (**Supplementary Figure 1B**). In addition, the DM group had higher median BMI (21.6, IQR: 19.1–24.4) than PDM (19.9, IQR: 18.4–21.80, $p < 0.001$) and normoglycemia (19.8, IQR: 17.9–22.0, $p < 0.001$), but there was no difference between PDM and normoglycemic individuals ($p = 0.53$) (**Supplementary Figure 1B**). TB patients with DM more frequently presented with positive smear ($p = 0.037$), weight loss ($p = 0.027$) and cough ($p = 0.038$) than those with normoglycemia (**Supplementary Figure 1C**). Patients with PDM similarly exhibited higher frequency of weight loss ($p = 0.027$) compared with persons with normoglycemia at baseline (**Supplementary Figure 1C**). Of note, 44.4% ($n = 122$) of the participants with DM already knew about their diagnosis of DM before being enrolled in the study (**Supplementary Figure 1D**, **Supplementary Table 2**).

To assess whether the results obtained from the analyses of the RePORT-Brazil cohort mirrored the data from the overall Brazilian TB population, we characterized the TBDM cases reported to the SINAN registry (**Supplementary Figure 2**). Of 279,143 pulmonary TB cases reported between 2015 and 2019, 25,765 had DM (self-reported), resulting in a prevalence of 9.2% (95%CI: 9.1–9.3%) (**Supplementary Table 3**, **Supplementary Figure 2A**). Patients with TB-DM were older (55 years, IQR:46–64) than normoglycemic patients (40 years, IQR:29–54; $p < 0.001$) (**Supplementary Figure 2B**), had a higher frequency of abnormal chest X-ray ($p < 0.001$), positive smear ($p < 0.001$), positive culture ($p < 0.001$) and were new cases more frequently reported ($p < 0.001$) than in normoglycemic patients (**Supplementary Figure 2C**, **Supplementary Table 3**). In contrast, normoglycemic persons were more frequently men ($p < 0.001$), reported greater consumption of alcohol ($p < 0.001$) and illegal drug use ($p < 0.001$) and more frequent tobacco use ($p < 0.001$) than those with DM. Finally, normoglycemic TB patients were mainly black/*pardo* ($p < 0.001$) and more frequently had drug-sensitive TB than TB-DM participants ($p < 0.001$) (**Supplementary Table 3**).

Characteristics of HIV Status Among TB Cases With Dysglycemia

In RePORT-Brazil, the association between HIV-infection status and dysglycemia at baseline in participants with active pulmonary TB was analyzed according to age, presence of DM or PDM as well as to HbA1c levels (**Figure 1**).

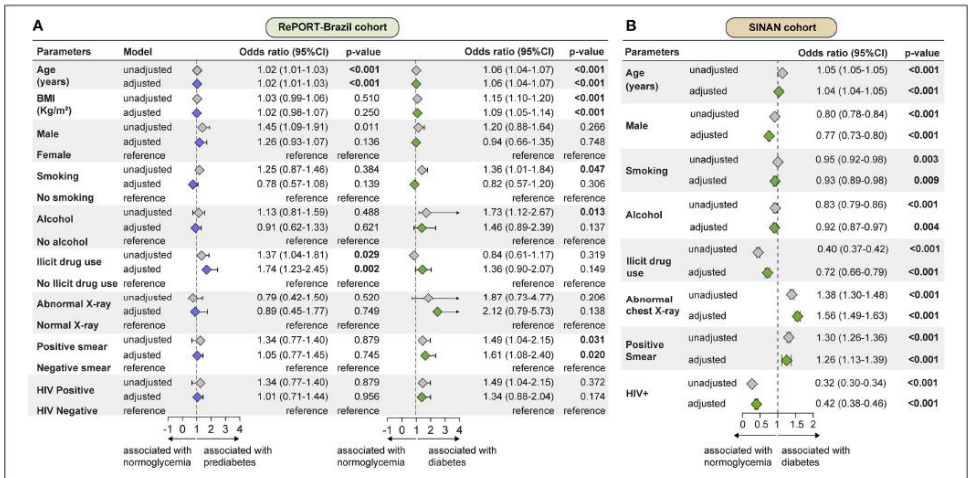

FIGURE 2 | Factors associated with dysglycemia in patients with active pulmonary tuberculosis in RePORT-Brazil and SINAN cohorts. **(A)** A multinomial logistic regression analyses were used to test association between indicated characteristics of pulmonary TB patients and presence of prediabetes (left panel) or diabetes (right panel). Variables included in the adjusted model exhibited univariate *p*-values ≤ 0·2 (See **Supplementary Table 2** for details). **(B)** Binomial logistic regression to test association between indicated characteristics of TB patients and presence of diabetes. Only variables with significant p-value in the adjusted model are shown. Variables included in the adjusted model exhibited univariate *p*-values ≤ 0.2 (See **Supplementary Table 3** for details). BMI, Body Mass Index.

Importantly, the distribution of HbA1c values among persons with TB did not differ significantly according to HIV-infection status (**Figure 1A**, left panel). In fact, HIV-infection was present in the minority of the active TB cases in all sub-categories of glycemic status. The HIV-infection prevalence in the TB-dysglycemia group was 21.4% (95%CI: 18.6–4.3%) (**Figure 1A**, right panel). There was a significant difference in the frequency of TB patients with either DM ($p < 0.001$) or HIV-infection ($p < 0.001$) according to age category (**Figure 1B**), whereas there was no significant difference in the distribution of PDM among the different age categories ($p = 0.099$) (**Figure 1B**). Of note, the subgroup of older participants (>48 years-old) exhibited the highest frequency of DM (**Figure 1B**).

Further comparisons revealed no differences in the distribution of HbA1c values between PLWH undertaking antiretroviral therapy (ART) and those who were ART-naïve at the time of study enrollment (**Figure 1C**). There was a non-significant positive correlation between HbA1c levels and HIV viral load (**Figure 1D**, left panel) and also between HbA1c concentrations and CD4 T-cell counts (**Figure 1D**, right panel) when all PLWH were considered regardless of the glycemic status (**Figure 1D**, left panel). In contrast, in the SINAN cohort, we found a prevalence of HIV-infection in the DM sub-group of 4.1% (95% CI: 3.8–4.3%) (**Figure 1E**), lower than what was observed in the RePORT-Brazil cohort. Moreover, older TB patients (age >48 years) were more frequently found in in the DM and HIV-infection subgroups ($p < 0.001$) than other age groups (**Figure 1F**).

Factors Associated With Dysglycemia in Patients With Active Pulmonary TB

Multinomial logistic regression analyses were performed to test associations between characteristics of active pulmonary TB

TABLE 1 | Characteristics of TB cases by DM status in RePORT-Brazil cohort.

Characteristics	TBDM-HIV (*n* = 56)	TBPDM-HIV (*n* = 97)	TB-HIV (*n* = 91)	TBDM (*n* = 217)	TBPDM (*n* = 341)	TB (*n* = 350)	*p*-value
Sex male – no. (%)	43 (76.8)	75 (77.3)	67 (73.6)	137 (63.1)	232 (68.0)	209 (59.7)	**0.002**
Age – median (IQR)	36 (31–42)	35 (28–43)	34 (26–42)	49 (38–57)	36 (25–49)	30 (22–42)	**<0.001**
Race/Ethnicity – no. (%)							**<0.001**
White	6 (10.7)	26 (26.8)	11 (12.1)	37 (17.1)	66 (19.4)	95 (27.1)	
Black	11 (19.6)	12 (12.4)	16 (17.6)	46 (21.3)	103 (30.2)	106 (30.3)	
Asian	0 (0.0)	2 (2.1)	3 (3.3)	4 (1.9)	3 (0.9)	4 (1.1)	
Pardo	39 (69.6)	57 (58.8)	61 (67.0)	127 (58.8)	164 (48.1)	145 (41.4)	
Indigenous	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	5 (1.5)	0 (0.0)	
BMI– (kg/m^2) – median (IQR)	20.5 (17.5–22.5)	20.2 (18.7–21.8)	19.9 (17.9–22.7)	21.9 (19.9–25.2)	19.8 (18.1–21.8)	19.9 (17.9–21.8)	**<0.001**
Smoking – no. (%)	36 (64.3)	60 (61.9)	56 (61.5)	120 (55.3)	171 (50.1)	164 (46.9)	**0.009**
Alcohol consumption – no. (%)	53 (94.6)	91 (93.8)	81 (89.0)	187 (86.2)	271 (79.5)	276 (78.9)	**<0.001**
Illicit drug use – no. (%)	30 (53.6)	47 (48.5)	53 (58.2)	47 (21.7)	123 (36.1)	85 (24.3)	**0.023**
Positive smear – no. (%)	37 (66.1)	58 (61.1)	49 (55.1)	182 (83.9)	262 (77.3)	271 (78.3)	**<0.001**
Previous diagnosis of diabetes – no. (%)	9 (16.1)	22 (22.9)	19 (21.3)	41 (19.2)	52 (15.3)	55 (15.8)	**<0.001**
Abnormal chest X–ray – no. (%)	52 (92.9)	81 (83.5)	79 (86.8)	215 (99.1)	335 (98.2)	344 (98.3)	**<0.001**
Drug–susceptibility testing (DST) – no. (%)							
Rifampicin–isoniazid resistance	2 (3.9)	5 (5.8)	3 (4.0)	6 (3.0)	3 (1.0)	7 (2.3)	0.165
Rifampicin resistance	4 (7.8)	5 (5.8)	3 (4.0)	6 (3.0)	3 (1.0)	10 (3.3)	0.057
Isoniazid resistance	7 (13.7)	12 (14.0)	8 (10.7)	14 (7.1)	19 (6.3)	16 (5.3)	**0.036**
Sensitive	45 (88.2)	77 (89.5)	69 (92)	177 (89.4)	248 (82.4)	265 (87.5)	0.115
Symptoms of TB–no. (%)							
Hemoptysis	6 (15.8)	8 (10.4)	8 (13.1)	57 (29.1)	78 (26.3)	81 (27.6)	0.175
Cough	38 (74.5)	78 (89.7)	61 (81.3)	196 (99.0)	298 (98.3)	295 (95.8)	**0.004**
Fever	45 (88.2)	71 (81.6)	63 (84.0)	150 (75.8)	240 (79.2)	228 (74.0)	0.846
Weight loss	49 (96.1)	82 (94.3)	65 (86.7)	185 (93.4)	279 (92.1)	272 (88.9)	**0.018**
Fatigue	48 (94.1)	73 (83.9)	68 (90.7)	165 (83.3)	240 (79.2)	237 (76.9)	0.364
Night sweats	31 (60.8)	63 (72.4)	47 (62.7)	142 (72.1)	213 (70.3)	214 (69.7)	0.448
Chest pain	31 (60.8)	47 (54.0)	33 (44.0)	134 (68.0)	201 (66.3)	212 (69.1)	**0.108**

Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Kruskal-Wallis test and categorical variables were using the Pearson's chi-square test. Bold values represent statistically significant. Definition of alcohol consumption: Past or current any consumption of alcohol. Definition of smoking: Past or current cigarette smoker. Definition of passive smoking: Living with someone who smokes. Definition of illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin or crack). Definition of persistence of symptoms: Patients who in the initial evaluation interview (baseline) reported indicated symptom and in the evaluation of visit 2 (month 2) still reported having such symptom. Definition of Pardo ethnicity: mixture of European, black and Amerindian. TB, tuberculosis; BMI, Body Mass Index.

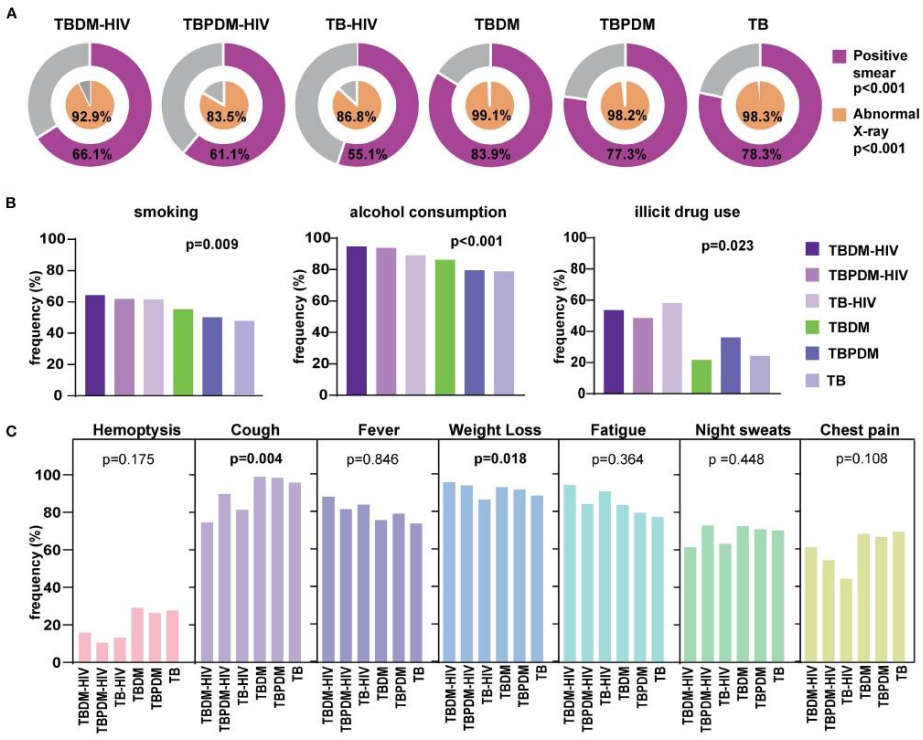

FIGURE 3 | Clinical Characteristics of people with TB according glycemic and HIV status in the RePORT-Brazil cohort. **(A)** Proportion of positive smears and abnormal X-rays in each study group. **(B)** Frequency of TB cases according glycemic and HIV status regarding smoking habit, alcohol consumption and illicit drug use (smoking, alcohol, and illicit drug: in the past or at the time of evaluation before anti-TB treatment). **(C)** Frequency of TB classical symptoms in each study group. The data were compared between the groups using the Pearson's chi-square test. Comparisons with significant p-values are displayed in bold. TB, tuberculosis; DM, diabetes; PDM, prediabetes.

patients and the presence of PDM or DM in RePORT-Brazil participants. Results demonstrated that increases in age (per 1-year increase) were independently associated with an increased odds of PDM (adjusted odds ratio [aOR]: 1.02, IQR: 1.01–1.03, $p < 0.001$) or DM (aOR: 1.06, IQR: 1.04–1.07, $p < 0.001$). Furthermore, self-reported illicit drug use (aOR: 1.74, IQR: 1.23–2.45, $p = 0.002$) was related to increased odds of PDM but not DM. Higher BMI values (per 1Kg/m^2 increase; aOR: 1.09, IQR: 1.05–1.14, $p < 0.001$) and presence of positive smear at baseline (aOR: 1.61, IQR: 1.08–2.40, $p < 0.001$) were both independently associated with increased odds of DM but not PDM. Of note, no association was found between presence of HIV-infection and odds of presenting with PDM ($p = 0.956$) or DM ($p = 0.174$) in the RePORT-Brazil cohort (**Figure 2A**).

To test associations between characteristics of TB and the presence of DM in the SINAN cohort, a binomial logistic regression analysis was performed. In this cohort, aging (per 1-year increase; aOR: 1.04, IQR: 1.04–1.05, $p < 0.001$), positive smear (aOR: 1.26, IQR: 1.13–1.39, $p < 0.001$) and abnormal chest X-ray (aOR: 1.56, IQR: 1.49–1.63, $p < 0.001$) at baseline were independently associated with presence of DM. In contrast, male sex (aOR: 0.77, IQR: 0.73–0.80, $p < 0.001$), current smoking (aOR: 0.93, IQR:0.89-0.98, p <0.001), alcohol consumption (aOR: 0.92, IQR: 0.87–0.97, $p < 0.001$), use of illicit drugs (aOR: 0.72, IQR: 0.66–0.79, $p < 0.001$) and to live with HIV (aOR: 0.42,

IQR: 0.38–0.46, $p < 0.001$) were all associated with a decreased odds of DM (**Figure 2B**).

Clinical and Epidemiologic Profiling According to the Glycemic Status and HIV

In the RePORT-Brazil cohort, the TBDM-HIV, TBPDM-HIV and TB-HIV groups presented similar frequencies for male sex (≈75.9%, $p = 0.002$). Interestingly, the highest median age was in the TBDM group (49 years), followed by 36 years in the TBDM-HIV and TBPDM groups, with the lowest median age observed in the TB group (30 years) ($p < 0.001$) (**Table 1**). *Pardo* race was the most reported in the TBDM-HIV group (69.6%). Drug resistance to isoniazid was more frequently observed in the groups with HIV coinfection ($p = 0.036$) (**Table 1**).

TB cases with HIV comorbidity displayed lower proportions of abnormal chest radiographs ($p < 0.001$) and of smear-positive sputum samples ($p < 0.001$) (**Figure 3A**, **Table 1**). We observed that tobacco use (64.3%) and alcohol consumption (94.6%) were significantly more reported in the TBDM-HIV group when compared to the clinical groups without HIV (**Figure 3B**, **Table 1**). As expected, regarding to the TB classic symptoms, the participants from the TBDM-HIV group presented a lower frequency of cough ($p = 0.004$) and a higher percentage of patients with weight loss ($p = 0.018$) (**Figure 3C**, **Table 1**).

We found a similar clinical profile in the SINAN cohort, where the TBDM-HIV group was characterized by a higher frequency of male sex (70.1%). Furthermore, the highest median age was 55 years among TBDM cases, followed by 49 years in the TBDMHIV group ($p < 0.001$) (**Table 2**). Such as in RePORT-Brazil, the *pardo* race was the most self-reported in all groups. Remarkably, the TBDM-HIV group presented a slight proportion of drug resistance cases, and especially to rifampicin and isoniazid (8.1%) ($p < 0.001$).

Similar to the abovementioned results on the RePORT-Brazil, in the SINAN cohort we found a low frequency of positive smear in the TBDM-HIV (61.8%) and TB-HIV (55%) groups ($p < 0.001$) as well as of abnormal X-rays (89.1 and 87.9%, respectively) ($p < 0.001$) (**Figure 4A**, **Table 2**). Furthermore, the positive culture results were also less frequently reported in the groups with HIV comorbidity when compared to the groups of individuals non-exposed to HIV ($p < 0.001$) (**Figure 4B**, **Table 2**). Finally, TBDM-HIV cases more frequently reported the tobacco smoking (27.9%) and alcohol consumption (28.4%) ($p < 0.001$) (**Figure 4C**, **Table 2**).

DISCUSSION

Characterizing the association between TB, dysglycemia and HIV is important to understand the influence of metabolic and immunologic dysregulation in the presentation of the TB disease. The TB-DM association is frequent worldwide; currently, more TB patients live with DM than with HIV (24). In the RePORT-Brazil cohort, the prevalence of dysglycemia among TB patients at baseline was 61.5% (37.8% PDM and 23.7%

TABLE 2 | Characteristics of TB cases by DM and HIV status in SINAN cohort.

Characteristics	TBDM-HIV ($n = 1051$)	TB-HIV normoglycemia ($n = 31073$)	TB DM ($n = 18591$)	TB normoglycemia ($n = 172939$)	*p*-value
Sex male – no. (%)	737 (70.1)	22339 (71.9)	11684 (62.8)	116122 (67.1)	**<0.001**
Age – median (IQR)	49 (40–57)	39 (31–46)	55 (46–63)	40 (28–54)	**<0.001**
ART use – no. (%)	468 (69.1)	13883 (72.8)	–	–	**<0.001**
Race/Ethnicity – no. (%)					**<0.001**
White	341 (34.3)	9920 (34.1)	6220 (35.2)	54881 (33.4)	
Black/*Pardo*	647 (65.0)	18919 (65.0)	11171 (63.1)	105690 (64.4)	
Indigenous	2 (0.2)	112 (0.4)	150 (0.9)	2314 (1.5)	
Asian	5 (0.5)	169 (0.6)	149 (0.8)	1357 (0.8)	
Abnormal chest X-ray – no. (%)	772 (89.1)	22204 (87.9)	14824 (94.9)	133615 (93.4)	**<0.001**
Alcohol consumption – no. (%)	282 (28.4)	6548 (21.5)	2703 (14.9)	30972 (18)	**<0.001**
Illicit drug use – no. (%)	173 (18.5)	5798 (19.8)	767 (4.4)	17305 (10.4)	**<0.001**
Smoking – no. (%)	265 (27.9)	6374 (21.6)	3353 (19.1)	33647 (20.2)	**<0.001**
Positive smear – no. (%)	431 (61.8%)	10937 (55.0)	11010 (77.1)	93512 (73.1)	**<0.001**
Positive culture – no. (%)	195 (59.3%)	5266 (58.3)	3667 (65.4)	32453 (64.3)	**<0.001**
Drug-susceptibility testing (DST) –no. (%)					**<0.001**
Rifampicin resistance	4 (4.0)	91 (3.4)	31 (1.7)	290 (1.8)	
Isoniazid resistance	3 (3.0)	137 (5.1)	95 (5.2)	791 (5.0)	
Rifampicin-Isoniazid resistance	8 (8.1)	119 (4.4)	92 (5.1)	644 (4.1)	
Sensitive	84 (84.8)	2360 (87.2)	1602 (88.0)	14089 (89.1)	

Data represent no. (%), except for age, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Mann-Whitney U test and categorical variables were using the Fisher's exact test (ART use) or Pearson's chi-square test. Bold values represent statistically significant. Definition of Pardo ethnicity: mixture of European, black and Amerindian. TB, tuberculosis; ART, antiretroviral therapy.

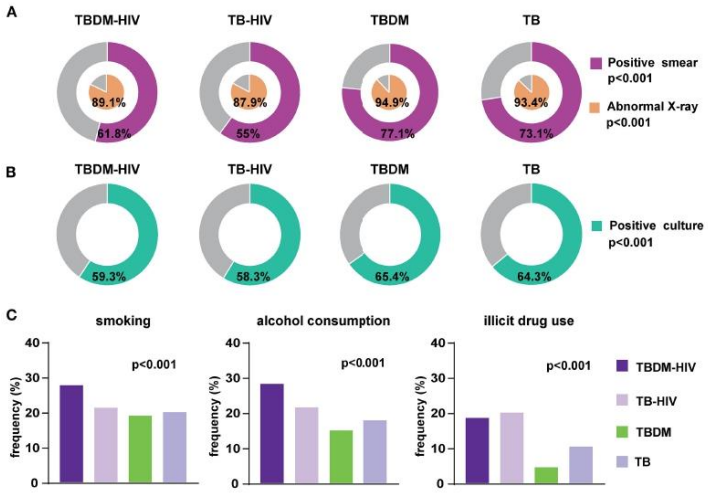

FIGURE 4 | Clinical Characteristics of people with TB according glycemic and HIV status of the SINAN cohort. **(A)** Proportion of positive smears and abnormal X-rays in each study group. **(B)** Frequency of positive cultures. **(C)** TB cases according glycemic and HIV status regarding smoking habit, alcohol consumption and illicit drug use (smoking, alcohol, and illicit drug: in the past or at the time of evaluation before anti-TB treatment). The data were compared between the groups using the Pearson's chi-square test. Comparisons with significant *p*-values are displayed in bold. TB, tuberculosis; DM, diabetes; PDM, prediabetes.

DM). This prevalence was higher than that recently reported in Ghana (25), Peru (26) and in the South of Brazil (27). The RePORT-Brazil cohort is large and composed by individuals from different regions of Brazil, and we have recently shown that it is representative of Brazilian patients with TB (18). The present work reports findings consistent with the literature, where TB-dysglycemia (mainly DM) patients have increased BMI values and higher prevalence of weight loss than normoglycemic patients (28). TB-DM patients in RePORT-Brazil exhibited similar characteristics to those in a large cohort of 709,000 Brazilians with TB from 2007 to 2014: mostly men, mean age >40 years and self-reported black or *pardo* (29).

TB patients more frequently reported smoking and use of illicit drugs and alcohol, which are shared risk factors not only for TB but also for DM (30, 31). The multinomial regression analysis demonstrated that illicit drug use was associated with increased odds of PDM, whereas alcohol use and smoking were associated with DM in the unadjusted model. Also in this analysis, aging was associated with both PDM and DM, and higher BMI was associated with presence of DM. These are factors already described as risk factors for TB in patients with DM, in addition to a lack of glycemic control (32). The majority (55.6%) of the TB-DM patients in the RePORT-Brazil study had no previous diagnosis of dysglycemia, which can be related to a lack of glycemic control that may be contributing to a more severe symptomatology (32), considering that coughing was a symptom associated with DM. The rate of newly diagnosed patients was high compared to other studies (33), representing 66% of DM cases in RePORT Brazil cohort, demonstrating the importance of DM screening at the time of TB diagnosis.

Using data from SINAN, we observed that between 2015 and 2019, the frequency of TB-DM in Brazil was only 9.2%, lower than the global prevalence of 15% and higher than the South American prevalence of 7.7%, calculated from a meta-analysis of more than 200 studies recently conducted around the world (8). When comparing our original data with the results obtained through SINAN, in RePORT-Brazil, patients with TB-DM were more likely to be male, black/*pardo*, older and more frequently to have a positive sputum smear than persons without DM, reinforcing the idea that the results obtained with RePORT-Brazil are representative of the country's population. However, in contrast to RePORT-Brazil, in SINAN, TB-DM patients had a significantly lower frequency of HIV-infection than those who did not report DM. This difference found in SINAN may be since glycemic control is performed in all the study participants diagnosed with dysglycemia, whereas it is only recommended, and not mandatory, in the national guidelines. In addition, there is a potential underreporting of cases in SINAN, and only DM cases, but not PDM, are notified. We have discussed this limitation in the SINAN database previously (18), where the performance of health and epidemiological indicators was substantially higher in RePORT-Brazil than in the cases notified to SINAN. In the SINAN cohort, there was a lower proportion of males in the TBDM group, probably due to the higher percentage

of women diagnosed with diabetes (34). On the other hand, the lower frequency of alcohol, smoking and illicit drug use could be attributed to the fact that this information is self-reported by patients rather than formally investigated (35).

In RePORT-Brazil, most patients with DM or PDM were HIV-seronegative. Other studies had shown this low frequency of HIV-infection in association with DM in Brazil (28, 29). HbA1c levels were also similar in TB patients stratified by HIV status. There is scarce evidence describing the interaction of HbA1c values and HIV in patients with TB. One study described that HbA1c could underestimate real glycemia values in PWLH (36). Furthermore, dysglycemia risk in PLWH has been shown to be increased after initiating ART (37), which could be a potential confounding factor, but HIV-infection was not associated with occurrence of dysglycemia in our study in both cohorts, even when stratified by age. Of note, in the SINAN cohort, presence of HIV-infection was linked to increased likelihood of normoglycemia in the population with pulmonary TB. Thus, the findings presented here from both large cohorts analyzed in this study argue that HIV-infection does not appear to be a determinant of dysglycemia in patients with pulmonary TB in Brazil.

To investigate whether HIV had any influence on dysglycemia in the RePORT-Brazil cohort, we tested for correlations between HbA1c and HIV-1 viral load or CD4 T-cell counts. We found just weak and non-significant correlations, indicating that HIV progression may not influence the occurrence of significant hyperglycemia. A study in PLWH that used fasting plasma glucose to measure glycemia reported that CD4 T-cell counts, and HIV viral load could influence blood glucose levels (38). Further studies are necessary to clarify whether HIV disease progression affects glycemic control by measuring several laboratory parameters simultaneously, such as HbA1c, fasting glucose levels or oral glucose tolerance tests. Our findings clearly corroborate the idea that despite the effect of HIV-infection on the immune system, glucose metabolism does not seem to be highly affected by this infection or disease progression.

We show the groups according to the glycemic status and by HIV infection and we identified that the group of persons with TBDM-HIV present with some peculiar characteristics. Male sex, smoking and alcohol consumption were higher in the TBDM-HIV group. We did not find specific literature to be able to contrast to our results. However, a study in 132 people with HIV described that the male population has a strong association with smoking, and in turn there is a strong interaction between smoking and alcohol consumption in infected men with HIV (39) which is consistent with the results of our study. Immunodeficiency and a decreased inflammatory response can inhibit sputum production in individuals with HIV; such cases also tend to have fewer atypical findings on radiographs (40), which coincides with the overall low percentage of cough and lower frequency of abnormal x-rays found in the TBDM-HIV, TBPDM-HIV and TB-HIV groups. Among the groups of individuals living with HIV, the TBDM-HIV presented a higher proportion of abnormal x-rays and self-reported cough. We hypothesize that presence of DM may boost immunopathological mechanisms that lead to tissue damage and inflammation which results in abnormal radiographs and cough. Reinforcing this idea, we have previously reported that the transcriptome of TB-DM patients exhibits increased representation of neutrophilic inflammation pathways (41), which may contribute at least in part to lung damage leading to cough and altered x-rays.

The present study has some limitations. In RePORT-Brazil, dysglycemia was investigated by means of HbA1c levels; we did not perform fasting glucose levels or oral glucose tolerance tests. Although glycated hemoglobin levels have been reliably used to estimate dysglycemia in several studies, it is possible that the final numbers of DM and PDM would have differed if additional laboratory assessments had been used. In addition, the use of anti-DM drugs was not uniformly recorded. In SINAN, diabetes condition is notified without differentiating if it was self-reported or if it had a laboratory confirmation. Therefore, the accuracy of DM diagnosis may have been affected. Another limitation was that in the RePORT-Brazil cohort, the type of DM was type 2 and in the SINAN cohort the type of DM is not specified in the notification system.

Regardless of its limitations, the present study adds important knowledge to the study of dysglycemia in TB patients in a large well-characterized multicenter cohort from Brazil, enabling the identification of factors associated with PDM and DM in this population. We also demonstrate that the majority of patients with TB-DM had no previous diagnosis of dysglycemia, which may be associated with an underreporting of DM in the SINAN database, and that HIV-infection was not significantly associated with dysglycemia in TB patients. It is important to systematically screen for DM in TB patients and initiate appropriate therapy for both diseases to reduce the dual burden of these major diseases. In 2019, screening for DM in patients diagnosed with TB was implemented in the Brazilian guidelines as a programmatic activity (20), in order to control TB transmission, monitor glycemia and ensure a favorable treatment result. However, the results of this strategy are still being evaluated to find a functional system in the comprehensive care of patients with TB.

THE REPORT BRAZIL CONSORTIUM

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The RePORT-Brazil protocol, informed consent, and study documents were approved by the institutional review boards at each study site and at Vanderbilt University Medical Center (CAAE: 25102414.3.2009.5543). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TS, MF, MC-S, VR, and BA: Conceptualization. MA, MA-P, AQ, MMSR, and BA: Data curation. MA, MA-P, BB-D, CS, JM-P, EVN, BN, MSR, AS, AB, JdO, AM, RS-G, MF, BD, JL-e-S, AK, SC, VR, TS, MC-S, and BA: Investigation. MA, MA-P, BB-D, and BA: Formal analysis. BD, JL-e-S, AK, SC, VR, TS, MC-S, MF, and BA: Funding acquisition. MA, MA-P, BB-D, and BA: Methodology. MF, TS, and BA: Project administration. MA, MA-P, BB-D, TS, and BA: Resources. MA, MA-P, AQ, MMSR, MF, TS, and BA: Software. TS, and BA: Supervision. MA, MA-P, BB-D, JM-P, CS, EVN and BA: Writing—original draft. All authors Writing—review and editing. All authors have read and agreed to the submitted version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.804173/full#supplementary-material

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Supplementary Material

Supplementary Table 1. Characteristics of TB cases by glycemic status in RePORT- Brazil cohort

Characteristics	Dysglycemia (n=714)	Normoglycemia (n=558)	p-value
Male sex – no. (%)	491 (68.8)	277 (61.8)	**0.018**
Age – median (IQR)	39 (29-52)	31 (23-42)	**<0.001**
HIV infection – no. (%)	153 (21.5)	91 (20.7)	0.798
Race/Ethnicity – no. (%)			**0.007**
White	135 (18.9)	107 (23.9)	
Black	174 (24.4)	128 (28.6)	
Asian	7 (1.0)	0 (0.0)	
Pardo	388 (54.4)	206 (46.0)	
Indigenous	9 (1.3)	7 (1.6)	
BMI- (kg/m^2) – median (IQR)	20.5 (18.4-23.1)	19.8 (17.9-22.0)	**<0.001**
Smoking – no. (%)	350 (54.6)	224 (50.0)	0.140
Alcohol consumption – no. (%)	605 (84.7)	364 (81.2)	0.141
Illicit drug use – no. (%)	247 (34.6)	142 (31.7)	0.331
Positive smear – no. (%)	542 (76.4)	324 (73.1)	0.232
Previous diagnosis of diabetes – no. (%)	128 (17.9)	8 (1.79)	**<0.001**
Abnormal chest X-ray – no. (%)	686 (96.1)	430 (96.0)	0.480
Drug-susceptibility testing (DST) – no. (%)			
Rifampicin-Isoniazid resistance	16 (2.5)	10 (2.6)	1.000
Rifampicin resistance	18 (2.82)	13 (3.37)	0.756
Isoniazid resistance	52 (8.14)	25 (6.48)	0.392
Sensitive	628 (86.5)	400 (87.6)	1.000
Symptoms of TB– no. (%)			
Hemoptysis	151 (24.7)	91 (25.2)	0.924
Cough	613 (95.5)	363 (92.8)	0.096
Fever	509 (79.3)	298 (76.2)	0.280
Weight Loss	597 (93.0)	344 (88.4)	**0.016**
Fatigue	529 (82.4)	311 (79.5)	0.289
Night sweats	452 (70.5)	266 (64.1)	0.476
Chest pain	415 (64.7)	250 (64.1)	0.888

Table note: TB cases were divided in two groups based on the glycemic status in normoglycemia or dysglycemia, which included both diabetes and prediabetes. Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were using the Fisher's exact test (2x2) or Pearson's chi-square test.
Definition of alcohol consumption: Past or current any consumption of alcohol. *Definition of passive smoking:* Living with someone who smokes. *Definition of illicit drug use:* Past or current illicit drug use (marijuana, cocaine, heroin or crack). *Definition of Pardo ethnicity*: mixture of European, black and Amerindian
Abbreviations: TB: tuberculosis, BMI: Body Mass Index

Supplementary Material

Supplementary Table 2. Characteristics of TB cases by DM status in RePORT-Brazil cohort

Characteristics	Diabetes (n=275)	Prediabetes (n=439)	Normoglycemia (n=448)	p-value
Sex male – no. (%)	182 (66.2)	309 (70.4)	277 (61.8)	**0.027**
Age – median (IQR)	46 (36-55)	36 (26-47)	31 (23-42)	**<0.001**
HIV infection – no. (%)	56 (20.5)	97 (22.2)	91 (20.7)	0.821
Race/Ethnicity – no. (%)				**<0.001**
White	43 (15.7)	92 (21.0)	107 (23.9)	
Black	58 (21.2)	116 (26.4)	128 (28.6)	
Asian	2 (0.73)	5 (1.14)	0 (0.0)	
Pardo	167 (60.9)	221 (50.3)	206 (46.0)	
Indigenous	4 (1.46)	5 (1.14)	7 (1.56)	
BMI (kg/m^2)-median (IQR)	21.6 (19.1-24.4)	19.9 (18.4-21.8)	19.8 (17.9-22.0)	**<0.001**
Smoking – no. (%)	158 (57.6)	232 (52.8)	224 (50.0)	0.150
Alcohol consumption – no. (%)	242 (88.0)	363 (82.7)	364 (81.2)	0.053
Illicit drug use – no. (%)	77 (28.0)	170 (38.8)	142 (31.7)	**0.007**
Positive Smear – no. (%)	220 (80.3)	332 (74.0)	324 (73.1)	0.077
TB clinical form– no. (%)				0.591
Pulmonary	248 (90.2)	388 (88.2)	399 (88.7)	
Pulmonary + Extrapulmonary	27 (9.8)	52 (11.8)	51 (11.3)	
Previous diagnosis of diabetes – no. (%)	122 (44.4)	6 (1.4)	8 (1.8)	**<0.001**
Abnormal chest X-ray– no. (%)	269 (97.8)	417 (95.0)	430 (96.0)	0.168
Drug-susceptibility testing (DST) – no. (%)				
Rifampicin resistance	10 (4.0)	8 (2.1)	13 (3.4)	0.331
Isoniazid resistance	21 (8.4)	31 (8.0)	25 (6.5)	0.608
Rifampicin-Isoniazid resistance	8 (3.2)	8 (2.1)	10 (2.6)	0.666
Sensitive	236 (84.4)	392 (87.8)	400 (87.5)	1.000
Symptoms of TB– no. (%)				
Hemoptysis	64 (27.2)	87 (23.1)	91 (25.2)	0.515
Cough	235 (94.0)	378 (96.4)	363 (92.8)	0.083
Fever	196 (78.4)	313 (79.8)	298 (76.2)	0.466
Weight Loss	235 (94.0)	362 (92.3)	344 (88.4)	**0.033**
Fatigue	214 (85.6)	315 (80.4)	311 (79.5)	0.131
Night sweats	174 (69.9)	278 (70.9)	266 (68.2)	0.708
Chest paint	165 (66.3)	250 (63.8)	250 (64.1)	0.796

Table note: Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Kruskal-Wallis test and categorical variables were using the Pearson's chi-square test. Bold values represent statistically significant.

Definition of alcohol consumption: Past or current any consumption of alcohol. *Definition of smoking:* Past or current cigarette smoker. *Definition of passive smoking:* Living with someone who smokes. *Definition of illicit drug use:* Past or current illicit drug use (marijuana, cocaine, heroin or crack)

Definition of persistence of symptoms: Patients who in the initial evaluation interview (baseline) reported indicated symptom and in the evaluation of visit 2 (month 2) still reported having such symptom.

Definition of Pardo ethnicity: mixture of European, black and Amerindian

Abbreviations: TB: tuberculosis, BMI: Body Mass Index

Supplementary Material

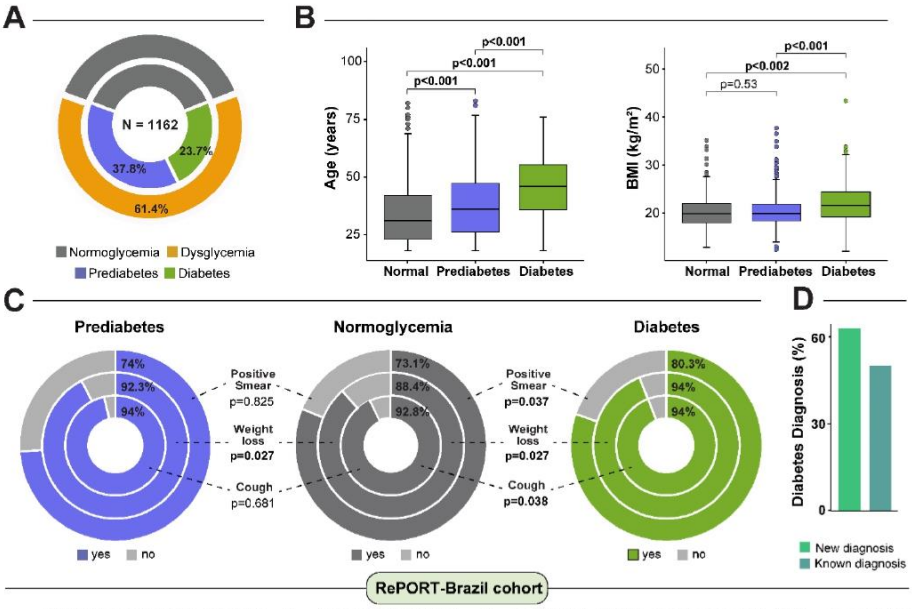
Supplementary Table 3. Characteristics of TB cases by DM status in SINAN cohort

Characteristics	Diabetes (n=25765)	Normoglycemia (n=253378)	p-value
Male sex – no. (%)	16172 (62.8)	171638 (67.7)	**<0.001**
Age – median (IQR)	55.0 (46.0-64.0)	40.0 (29.0-54.0)	**<0.001**
HIV infection – no. (%)	1051 (4.08)	31073 (12.3)	**<0.001**
ART use – no. (%)	484 (11.2)	14175 (27.8)	**<0.001**
Race/Ethnicity – no. (%)			**<0.001**
White	8243 (33.8)	77442 (32.4)	
Black/*Pardo*	15750 (64.6)	156749 (65.5)	
Indigenous	181 (0.74)	2997 (1.25)	
Asian	210 (0.86)	1953 (0.82)	
Abnormal chest X-ray – no. (%)	20113 (79.3)	190895 (76.7)	**<0.001**
Alcohol consumption – no. (%)	3820 (14.9)	45548 (18.0)	**<0.001**
Illicit drug use – no. (%)	1116 (4.35)	26696 (10.6)	**<0.001**
Smoking – no. (%)	4526 (17.7)	47877 (19.0)	**<0.001**
Positive smear – no. (%)	14649 (56.9)	128692 (50.8)	**<0.001**
TB clinical form– no. (%)			**<0.001**
Pulmonary	23443 (91.0)	217256 (85.7)	
Extrapulmonary	1322 (5.1)	21203 (8.4)	
Pulmonary + Extrapulmonary	1001 (3.9)	14919 (5.9)	
Positive culture – no. (%)	4527 (17.6)	42879 (16.9)	**0.003**
Drug-susceptibility testing (DST) – no. (%)			0.116
Rifampicin resistance	40 (1.8)	428 (2.1)	
Isoniazid resistance	117 (5.4)	1048 (5.1)	
Rifampicin-Isoniazid resistance	113 (5.2)	857 (4.2)	
Sensitive	1906 (87.6)	18211 (88.6)	

Table note: Data represent no. (%), except for age, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were using the Fisher's exact test (2x2) or Pearson's chi-square test. Bold values represent statistically significant
Definition of Pardo ethnicity: mixture of European, black and Amerindian
Abbreviations: TB: tuberculosis, ART: antiretroviral therapy

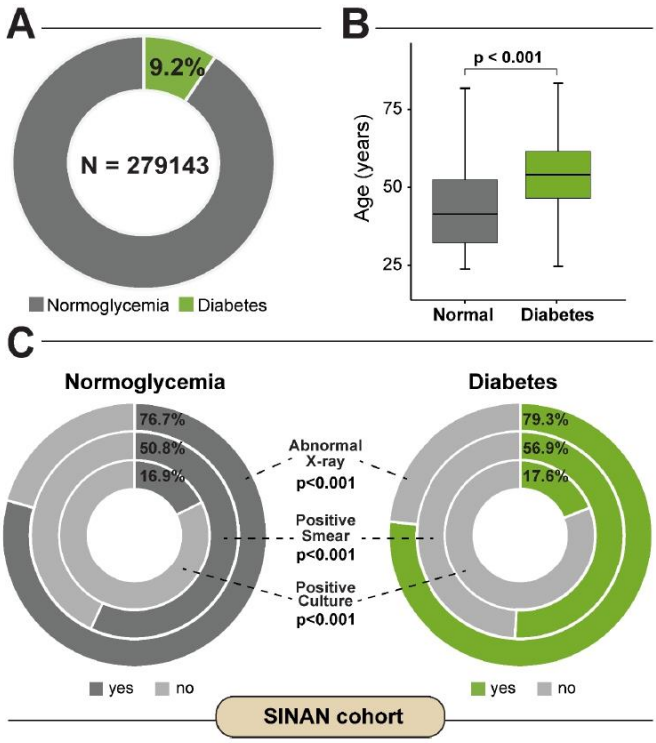
Supplementary Material

1 Figure Legends



Supplementary Figure 1. Characteristics of patients with pulmonary TB according to dysglycemia status in RePORT-Brazil cohort. (A) Among all the individuals with active pulmonary TB (n=1162), 61.4% had dysglycemia: 37.8% pre-DM and 23.7% DM. **(B)** Comparison of Age and BMI between groups were performed using Mann-Whitney *U* test. **(C)** Characteristics of the pulmonary TB cases stratified according to the presence of diabetes or prediabetes were compared with those from patients with normoglycemia using the Fisher's exact test (additional comparisons are displayed in **Supplementary Table 2**). **(D)** Frequency of new cases of DM diagnosis. The statistical analyzes were carried out only with the available data, omitting the cases with missing information. Abbreviations: TB: tuberculosis, BMI: Body Mass Index.

Supplementary Material



Supplementary Figure 2. Characteristics of patients with pulmonary TB according to DM status in SINAN-TB cohort. (A) Among all the individuals with active pulmonary TB (n=287581) between 2015 and 2019 in Brazil, 9.2% had DM. **(B)** Comparison age between groups were performed using Mann-Whitney *U* test. **(C)** Characteristics of the pulmonary TB cases stratified according to the presence of diabetes were compared with those from patients with normoglycemia using the Fisher's exact test (additional comparisons are displayed in **Supplementary Table 3**). The statistical analyzes were carried out only with the available data, omitting the cases with missing information.

6.7 MANUSCRITO VII

The Effect of Diabetes and Prediabetes on Mycobacterium tuberculosis Transmission to Close Contacts.

DM é um fator de risco para o desenvolvimento de TB ativa em pacientes ILTB. Entretanto, nada havia sido descrito sobre a associação entre DM ou pré- DM e transmissão de TB. Esse trabalho avaliou as características epidemiológicas e clínicas de pacientes com TB pulmonar confirmada por cultura e seus contatos próximos, participantes do RePORT-Brasil quanto ao diagnóstico de ILTB através do teste de QuantiFERON.

Resumo dos resultados: Contatos de pacientes com TB pulmonar e disglicemia apresentaram risco aumentado de ter ILTB. Aqueles contatos de pacientes com TB e pré-DM apresentaram um alto risco de QuantiFERON positivo, no início do estudo. Por outro lado, contatos de pacientes que tinham TBDM apresentaram um risco aumentado de ter uma conversão (QuantiFERON negativo no início para QuantiFERON positivo no mês 6). O aumento do foco em tais contatos poderia melhorar o controle da TB no país.

O manuscrito foi apresentado no *TB RiCC Webinar - RePORT Brazil*, novembro 2020 e no *Keystone Tuberculosis: Science Aimed at Ending the Epidemic*, dezembro - 2020

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The Journal of Infectious Diseases

MAJOR ARTICLE

The Effect of Diabetes and Prediabetes on *Mycobacterium tuberculosis* Transmission to Close Contacts

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Background. It is unknown whether dysglycemia is associated with *Mycobacterium tuberculosis* transmission.

Methods. We assessed epidemiological and clinical characteristics of patients with culture-confirmed pulmonary tuberculosis and their close contacts, enrolled in a multicenter prospective cohort in Brazil. Contacts were investigated at baseline and 6 months after enrollment. QuantiFERON positivity at baseline and conversion (from negative to positive at month 6) were compared between subgroups of contacts according to glycemic status of persons with tuberculosis (PWTB) as diabetes mellitus (DM) or prediabetes. Multivariable mixed-effects logistic regression models were performed to test independent associations with baseline QuantiFERON positive and QuantiFERON conversion.

Results. There were 592 PWTB (153 DM, 141 prediabetes, 211 normoglycemic) and 1784 contacts, of whom 658 were QuantiFERON-positive at baseline and 106 converters. Multivariable analyses demonstrated that tuberculosis-prediabetes cases, acid-fast bacilli-positive, pulmonary cavities, and living with someone who smoked were independently associated with QuantiFERON positive in contacts at baseline. DM, persistent cough, acid-fast bacilli-positive, and pulmonary cavities in tuberculosis source cases were associated with QuantiFERON conversion.

Conclusions. Contacts of persons with pulmonary tuberculosis and dysglycemia were at increased risk of being QuantiFERON positive at baseline or month 6. Increased focus on such close contacts could improve tuberculosis control.

Keywords. diabetes; prediabetes; quantiFERON; interferon-γ releasing assay; *Mycobacterium tuberculosis*.

Understanding factors associated with *Mycobacterium tuberculosis* transmission is an important component for tuberculosis control. *M. tuberculosis* is transmitted via aerosols generated by people with active pulmonary tuberculosis, through speaking, coughing, or sneezing [1]. Individuals with more severe pulmonary tuberculosis may emit higher numbers of infectious droplet nuclei. Vigorous and persistent cough, as well as cavitary lung lesions, may increase the emission of infectious droplets [2]. Other drivers of *M. tuberculosis* transmission include biological characteristics of *M. tuberculosis* [3], the number of contacts, the proximity and duration of contact, delays in tuberculosis diagnosis in the source case, and environmental factors such as closed indoor spaces with low air circulation and no ultraviolet light [2]. Other factors are associated with higher risk of developing tuberculosis, such as human immunodeficiency virus (HIV) infection, diabetes mellitus (DM), smoking, alcohol abuse, and malnutrition [2, 3]. Although DM is associated with an increased risk of developing active disease once infected with *M. tuberculosis* [4], the effect of DM on *M. tuberculosis* transmission has not been evaluated.

Previous studies have found that persons with DM (PWDM) and tuberculosis more frequently present with extensive or cavitary pulmonary tuberculosis than normoglycemic patients [5]. Furthermore, persons with tuberculosis (PWTB) with DM exhibit a higher bacillary load in sputum [6, 7], more persistent cough [8], and delayed mycobacterial clearance compared to persons without DM [7, 8]. Although DM has the potential to increase *M. tuberculosis* transmission, to our knowledge no studies have directly investigated this hypothesis. We therefore investigated whether contacts of persons with pulmonary

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tuberculosis and dysglycemia were at increased risk of *M. tuberculosis* infection compared to contacts of normoglycemic PWTB.

METHODS

Ethics Statement

The study was conducted according to the principles of the Declaration of Helsinki. The RePORT-Brazil protocol was approved by the institutional review boards at each study site and at Vanderbilt University Medical Center. Participation in RePORT-Brazil was voluntary and written informed consent was obtained from all participants.

Study Design

This was a multicenter prospective observational cohort study of individuals ≥18 years old with culture-confirmed pulmonary tuberculosis and their close contacts. Description of RePORT sites and data collection is presented in Supplementary Methods and in [9].

For this protocol, close contacts were defined as having ≥4 hours of contact/week with the tuberculosis index case at any time in the previous 6 months [10]. Contacts identified who agreed to participate in the study were evaluated at 2 visits: baseline and 6 months after enrollment. They were also contacted by phone at months 12, 18, and 24 to see if they developed active tuberculosis. At the baseline visit QuantiFERON (QTF) testing was performed, and at month 6 a repeat QTF was performed if the initial QTF result was negative. Individuals whose QTF result was indeterminate (at either the baseline or month 6 visit) or who did not have a second QTF performed at month 6 (if negative at baseline) were excluded from the analysis. For tuberculosis index cases for whom close contacts were excluded from this study, data from the index case were not included in the statistical analyses.

Study Definitions

In PWTB, DM was defined according to baseline hemoglobin A1c (HbA1c), following American Diabetes Association guidelines [11]. Patients were classified as having DM (HbA1c ≥ 6.5%), prediabetes (PDM; HbA1c = 5.7%–6.4%), or normoglycemia (HbA1c < 5.7%). HbA1c ≥ 5.7% was classified as dysglycemia. For tuberculosis close contacts, DM status was obtained by self-report or by HbA1c when available. To investigate *M. tuberculosis* transmission, we considered a positive result of the first (baseline) or second QTF (month 6) test an indicator of *M. tuberculosis* infection.

Data Analysis

Categorical variables were presented as proportions and compared using a 2-sided Pearson χ^2 test (with Yates correction) or Fisher 2-tailed test. Continuous variables were presented as median and interquartile range and compared using the Mann-Whitney *U* (between 2 groups) or Kruskal-Wallis test (between ≥2 groups). To evaluate independent associations between clinical characteristics of pulmonary tuberculosis index cases and presence of diabetes and/or PDM, we used unadjusted and multivariable-adjusted binomial logistic regression models. Variables were selected using the stepwise method (Wald) with backward selection criteria. We additionally assessed associations between clinical characteristics of PWTB and contacts and QTF results (positive at baseline or QTF conversion, compared to contacts who were QTF negative at both baseline and month 6) using unadjusted and multivariable-adjusted mixed-effects logistic regression models [12]. The "tuberculosis case" variable was included as the random effect term to address clustering of tuberculosis cases with more than one contact. Parameters with *P* values ≤.2 in univariate analyses were included in multivariable models. For the analysis of clinical characteristics of PWTB and contact QTF result, we also used bootstrapping to estimate a bias-corrected coefficient, addressing potential bias due to small sample size [13]. Over 1000 bootstrap iterations, we sampled with replacement from the data and estimated coefficients within the bootstrap sample; the unit of resampling was "the contacts from the same tuberculosis case." The distribution of those coefficient estimates over the 1000 bootstrap iterations were used to estimate the mean and 95% confidence intervals (CI) of the bias-corrected coefficient estimates. *P* values <.05 were considered statistically significant. Statistical analyses were performed using SPSS 24.0 (IBM Statistics), Graphpad Prism 6.0 (GraphPad Software), and R 3.1.0 (R Foundation).

RESULTS

Characteristics of Study Participants

RePORT-Brazil enrolled 1038 patients with culture-positive pulmonary tuberculosis during the study period, of whom 592 had close contacts who enrolled in the study. Of the 1038, 643 (62%) had dysglycemia at baseline (Figure 1). Additional information is provided in Supplementary Table 1. Among all dysglycemic PWTB, 61.1% had PDM (n = 393, 37.9% of all PWTB) and 38.9% had DM (n = 250, 24.1% of all PWTB). Details are in Supplementary Table 2 and Supplementary Table 3. Among PWTB, 446 (43%) did not have a close contact enrolled into our study. Of the 592 PWTB who reported contacts, an average of 3 contacts per PWTB were enrolled. PWTB who had contacts were stratified according to glycemic status at the time of diagnosis: tuberculosis-dysglycemia (n = 381, 64.4%) and tuberculosis-normoglycemia (n = 211, 35.6%) (Figure 1).

There were 609 contacts of 211 normoglycemic PWTB and 1186 close contacts of 381 dysglycemic PWTB. There were 47 contacts with indeterminate QTF results either at baseline or at the month 6 visit, who were excluded. There were an additional 175 contacts considered lost to follow-up because they missed the second QTF test; they were also excluded. The sample size with which all further analyses were performed was 1573 close tuberculosis contacts: 537 close contacts of 198 normoglycemic

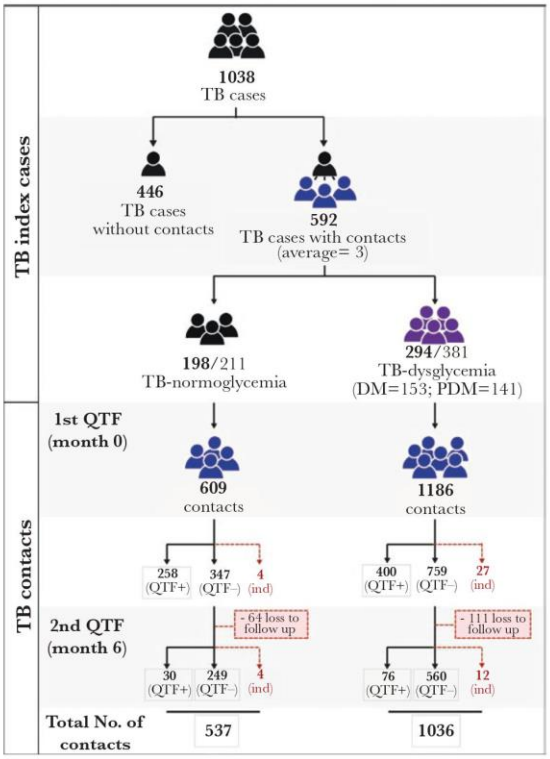

Figure 1. Study flow chart. The main objective of the study was to compare incident tuberculosis (TB) infection among contacts from pulmonary tuberculosis patients with or without dysglycemia. Data were obtained from 1038 individuals diagnosed with culture-confirmed pulmonary tuberculosis enrolled into the RePORT Brazil study protocol. Of those, 592 (57%) had close contacts (average of 3 contacts per tuberculosis index case) who enrolled and were included in the analyses. During the clinical and laboratory evaluation (hemoglobin A1c levels) of the tuberculosis index cases, 141 had prediabetes (PDM), 153 had type-2 diabetes (DM), and 211 were normoglycemic. In 609 contacts of 198 tuberculosis-normoglycemic patients and 1186 contacts of 294 tuberculosis-dysglycemic patients the first QuantiFERON (QTF) test was performed. The close contacts enrolled of each tuberculosis index case were evaluated, and screening for *Mycobacterium tuberculosis* infection was performed with clinical and radiographic examination as well as with QTF testing. Those who had negative QTF result at baseline underwent repeat QTF testing at 6 months to assess for QTF conversion. For the present study, individuals whose QTF result was indeterminate (ind; first or second QTF) or those who did not have a second QTF test performed at month 6 of follow-up were excluded from the analysis.

PWTB and 1036 contacts of 294 dysglycemic PWTB (DM = 153 and PDM = 141) (Figure 1).

Characteristics of Tuberculosis Close Contacts

Tuberculosis close contacts were next grouped according to the glycemic status of their tuberculosis index case. Contacts of normoglycemic PWTB more frequently had DM (P = .011) and reported illicit drug use than contacts of PWTB with diabetes or PDM (Figure 2A). Other detailed comparisons among the subgroups of tuberculosis close contacts are shown in Supplementary Table 3. The Sankey diagram shown in Figure 2B describes the QTF results, the number of tuberculosis close contacts with QTF conversion from negative to positive, and active tuberculosis incidence. Close contacts of normoglycemic PWTB more frequently exhibited a positive QTF at the baseline visit than contacts from PWDM or PDM (Figure 2C). The different groups of tuberculosis close contacts could be distinguished by frequency of QTF conversion (Figure 2D). The highest tuberculosis incidence values were found in QTF-positive individuals who were close contacts of tuberculosis index cases with PDM or normoglycemia (0.44 and 0.38 persons-years, respectively).

The final set of analyses stratified tuberculosis close contacts into 3 groups according to the final QTF test result: (1) those who tested positive at the baseline visit (QTF positive, n = 658), (2) those who tested negative at both baseline and month 6 visit (QTF negative, n = 809), and (3) those who tested negative at the baseline visit and positive at the month-6 visit (QTF conversion, n = 106). Comparisons of characteristics of these study subgroups of tuberculosis contacts are described in Supplementary Table 4. The frequency of smokers was significantly higher in the positive QTF group (29.5%) versus negative QTF (22.9%) (P = .001). Individuals with QTF conversion were more frequently contacts of PWTB with DM, whereas those with a negative QTF more commonly were contacts of prediabetic PWTB (Figure 3A). QTF-positive participants were generally contacts of normoglycemic PWTB (Figure 3A). Additional analyses revealed that HIV infection was more frequently detected in tuberculosis index cases who had QTF-negative contacts (P < .001; Figure 3B). Of note, tuberculosis index cases who had acid-fast bacilli (AFB)-positive sputum smears and exhibited cavitary lung lesions were more likely to have contacts who were QTF positive or converted the QTF result at month 6 visit (P < .001; Figure 3B). Moreover, QTF-positive contacts were on average older than those who were QTF negative and those who experienced QTF conversion (P < .001; Figure 3C). The subgroup of tuberculosis contacts with QTF conversion more frequently reported smoking. No participant from this latter group had DM.

A multivariable mixed-effects logistic regression with a random effect per "tuberculosis case" tested associations between characteristics of PWTB, or of tuberculosis contacts and positivity of the QTF test at baseline or conversion of the QTF in tuberculosis contacts. The results demonstrated that PDM (adjusted odds ratio [aOR], 1.54; 95% CI, 1.25–1.65; P = .002), passive smoking (aOR, 1.44; 95% CI, 1.25–1.82; P = .003), AFB smear positive (aOR, 1.54; 95% CI, 1.19–1.99; P = .001), cavitary lung lesions (aOR, 1.68; 95% CI, 1.32–2.13; P < .001), and age (aOR, 1.01; 95% CI, 1.01–1.03; P < .001) were important characteristics of PWTB associated with positive QTF in contacts, independent of other confounding factors (Figure 3D, left). Interestingly, this model also revealed characteristics of tuberculosis index cases

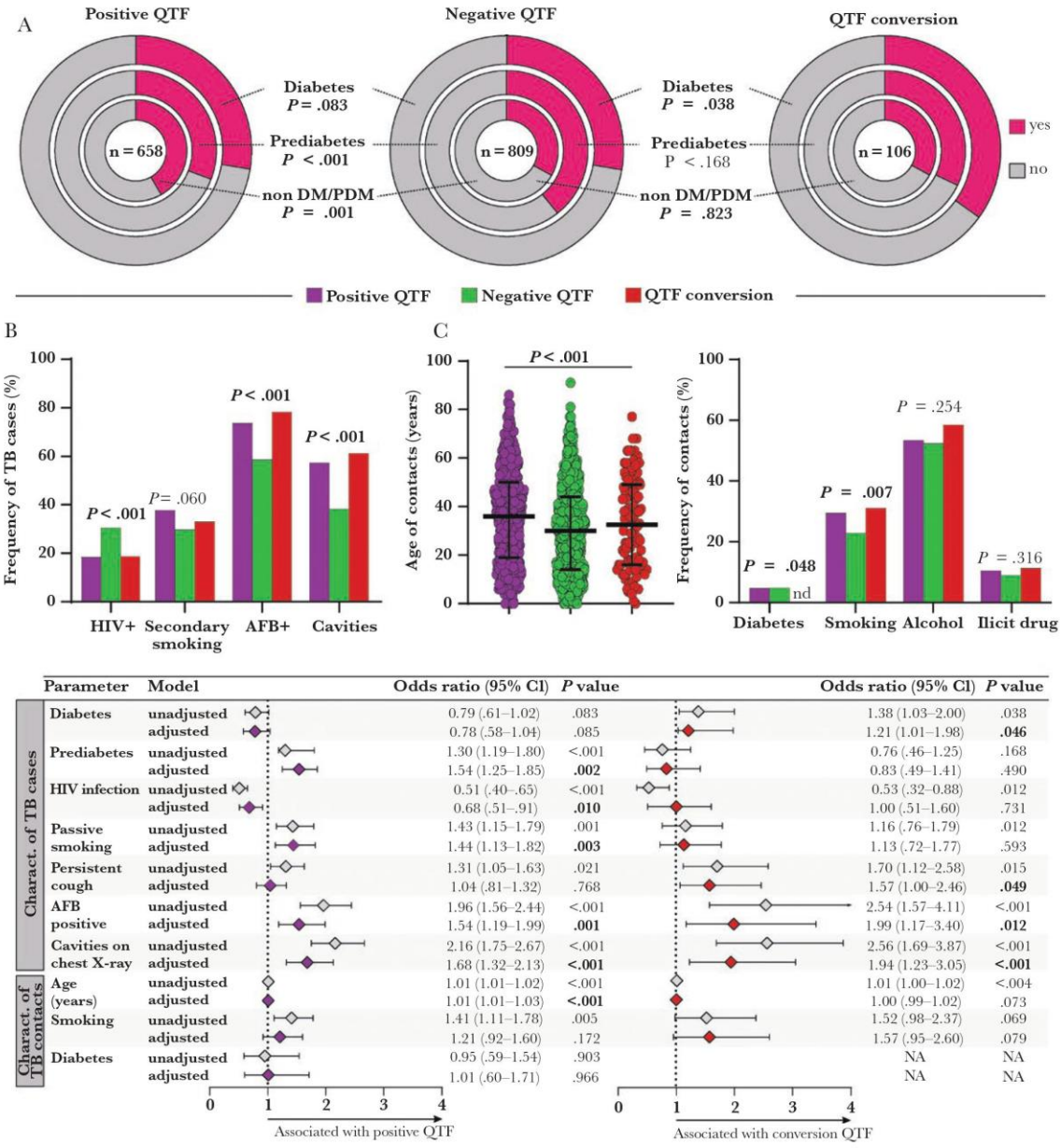

Figure 3. Factors associated with tuberculosis infection in contacts of pulmonary tuberculosis patients with diabetes and prediabetes. *A*, Characteristics of the close contacts of pulmonary tuberculosis patients stratified according to the QTF test result were compared using the Fisher exact test (additional comparisons are displayed in Supplementary Table 3). *B*, Frequency of indicated characteristics of the pulmonary tuberculosis index cases stratified based on the QTF results of the contacts was compared using the Pearson χ^2 test. *C*, Left, scatter plot shows distribution of age (median and interquartile range) among the subgroups of contacts of persons with tuberculosis based on the QTF result. Data were compared using the Kruskal-Wallis test with Dunn multiple comparisons ad hoc test. The difference in median age values between the groups of positive QTF and of QTF conversion was statistically significant. Right, frequency of close tuberculosis contacts with the indicated characteristics was compared between the subgroups based on the QTF result was compared using the Pearson χ^2. *D*, A multivariable mixed-effects logistic regression with a random effect per "tuberculosis case" (to decrease the possible selection bias, because 1 "tuberculosis case" can have more than 1 contact, with different QTF results) was used to test association between indicated characteristics of pulmonary tuberculosis index patients or of the tuberculosis close contacts and positivity of the baseline QTF test or conversion of the QTF result in tuberculosis contacts. Variables included in the adjusted model exhibited univariate *P* values≤.2 (see Supplementary Table 4 for details). *A*, *B*, and *C*, *P* values were adjusted for clustering by index case. Passive smoking was defined as living with someone who smokes. Persistent cough was defined as patients who reported cough at the initial evaluation (month 0) and also at the month 2 visit. Abbreviations: AFB, acid-fast bacilli; CI, confidence interval; DM, diabetes; HIV, human immunodeficiency virus; NA, not applicable; nd, not detected; PDM, prediabetes; QTF, QuantiFERON; TB, tuberculosis.

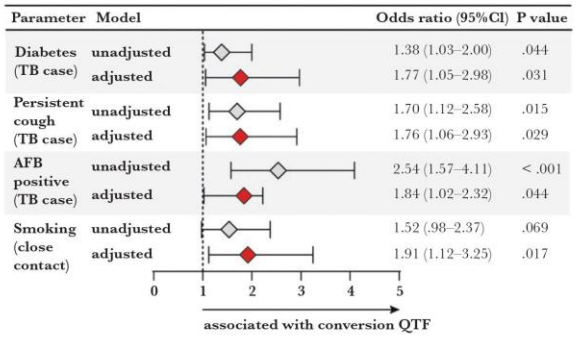

Figure 4. Factors associated with QTF conversion in contacts of pulmonary tuberculosis patients. A multivariable mixed-effects logistic regression with a random effect per "tuberculosis case." Estimates are bias-corrected based on 1000 bootstrap iterations to account for the small sample size. Estimates (in terms of odds ratios) reflect associations between indicated characteristics of pulmonary tuberculosis index patients or of the tuberculosis close contacts and conversion of the QTF result (incident tuberculosis infection) in tuberculosis contacts. Variables included in the adjusted model exhibited univariate *P* values ≤.2 (see Supplementary Table 4 for details). Persistent cough was defined as patients who reported cough in the initial evaluation interview (month 0) and also in the month 2 visit. Abbreviations: AFB, acid-fast bacilli; CI, confidence interval; QTF, QuantiFERON; TB, tuberculosis.

DISCUSSION

Identifying whether DM affects *M. tuberculosis* transmission is important to guide tuberculosis control strategies. Previous studies have found that dysglycemia in tuberculosis contacts can make them more susceptible to infection [4, 14–16] but to date it had not been investigated whether tuberculosis-DM increases the risk of contacts acquiring *M. tuberculosis* infection. In the current study, 62% of PWTB presented with dysglycemia (PDM or DM) and 37.9% had DM. This prevalence is higher than recently reported in Ethiopia [17], Peru [18], and India [19], as well as in a previous study of our group, from a smaller subpopulation from Northeastern Brazil [20]. In the previous study, we observed a 63.1% prevalence of dysglycemia, which is comparable to the present study, but the DM prevalence was lower (25%). This difference could be explained by the heterogeneity of the population in the country. The current cohort is larger and includes individuals from different regions of the country (5 sites of RePORT Brazil, located in 3 states), while the previous cohort included individuals from just one state. That said, the cohort in the present study is more representative of Brazilian PWTB [21]. In spite of the different frequency of PWDM, the present work had findings consistent with the previous one, such as higher body mass index (BMI) and higher prevalence of cough and weight loss in patients with dysglycemia, particularly in PWDM [20].

Tuberculosis-DM patients exhibited similar characteristics to those in a large cohort of 709 000 Brazilians with tuberculosis from 2007 to 2014: mostly men, mean age >40 years, self-reported black or pardo, and low frequency of HIV-infection [22, 23].

Tuberculosis-DM patients more frequently reported smoking and alcohol consumption, which are shared risk factors for both diseases [3, 24, 25]. This corroborates the relationship described in populations from Peru, Mexico, and South Africa [6, 18], where PWTB with DM and PDM were older and had an increased BMI compared to normoglycemic PWTB.

There were 1573 contacts followed up in this study. Only 1% (n = 16) of the close contacts had a confirmed diagnosis of tuberculosis at the baseline visit, while 42% (n = 658) were diagnosed with latent tuberculosis infection (LTBI). The findings are comparable with what has been reported in low to middle-income countries, including Brazil, where the prevalence of active tuberculosis in contacts was 1.4%, while the prevalence of LTBI was 51.5% [26].

Only 81 (5%) tuberculosis contacts were diagnosed with DM. This prevalence is 12 times lower than that reported in household tuberculosis contacts from India [27], but could be an underestimate, because HbA1c was not routinely measured in all contacts and many DM diagnoses were self-reported. In our study, these individuals were primarily contacts of normoglycemic PWTB.

Among those who had a negative QTF at baseline, 106 (6.7%) converted to positive QTF at the 6-month visit. An Ethiopian study [28] using QTF-tuberculosis Gold to follow tuberculosis household contacts for 1 year demonstrated that nearly half of negative QTF individuals at the first visit became positive after 12 months and for this reason the authors suggested that repeated screening of QTF-negative contacts may be needed for early diagnosis of LTBI. Because the second QTF in our study was carried out once, at 6 months after baseline, this may explain the lower conversion rate.

Regarding factors that could potentially increase *M. tuberculosis* transmission, tuberculosis-DM index cases had a significantly higher frequency of positive AFB sputum smears, consistent with previous publications [3, 29]. However, there was no significant difference in presence of cavities between the DM, PDM, and normoglycemic tuberculosis index cases subgroups. Although this was not expected based on the prior literature, it has been described before in a Brazilian retrospective cohort study [8]. Similarly, persistent cough was unexpectedly more common in the normoglycemic PWTB group. A possible explanation for both findings could be an earlier diagnosis of tuberculosis in Brazilian PWDM, self-reported response, other conditions that can stimulate or inhibit cough (use of medications, smoking, or neuroperipheral lesions among others) may be related to this result. In fact, most patients were newly diagnosed (156, 62.4%) and were not taking anti-DM drugs. Brazil has a decentralized public health care system and PWDM, who are already in the system and followed by family medicine teams, may have easier access to healthcare to evaluate symptoms. Furthermore, tuberculosis-DM patients had significantly more symptoms such as weight loss and fatigue, which is associated with earlier health care-seeking behavior and diagnosis of tuberculosis [20].

When assessing PWTB-related factors associated with baseline positive QTF in contacts, DM was not found to be a significant factor, whereas normal HbA1c, positive AFB, and presence of cavities on X-ray were associated with a significantly increased risk of LTBI. While these findings have clinical importance, a positive QTF at baseline may not be the most accurate measure for the purpose of this study, as the positivity can be related to a previous exposure. In this scenario, QTF conversion within 6 months of follow-up may be a better measure of recent exposure and infection. After adjusting for confounders, the following index case-related factors significantly increased the risk of QTF conversion: DM, persistent cough, AFB positive, and presence of cavitary lung lesions. Contacts with a tuberculosis-DM index case were 1.21 times more likely to be infected with *M. tuberculosis* compared to contacts of a normoglycemic tuberculosis index case. These findings confirm our hypothesis that tuberculosis-DM increased *M. tuberculosis* transmission and corroborates previous studies that reported persistent cough, AFB positivity, and presence of cavitation on chest X-ray increase *M. tuberculosis* transmission risk [2, 30]. The differing results regarding tuberculosis index case diabetes and prediabetes, and baseline QTF and QTF conversion, require further evaluation in additional cohorts.

After adjusting for confounders, the only individual characteristics of tuberculosis contacts significantly associated with an increased risk of QTF conversion was increased age. Other factors previously found to increase the risk of acquiring tuberculosis (DM, HIV, smoking, and alcohol use) were not confirmed in this study [31].

The present study had some limitations. Dysglycemia was investigated by means of HbA1c levels; we did not perform fasting glucose levels or oral glucose tolerance tests. Although glycated hemoglobin levels have been reliably used to estimate dysglycemia in several studies, it is possible that the final numbers of DM and PDM would have differed if additional laboratory assessments had been used. In this prospective cohort, additional measurements of HbA1c were not performed at other study time points. Thus, it was not possible to investigate whether transient versus persistent dysglycemia over the course of antituberculosis treatment had differential impact on *M. tuberculosis* transmission to close contacts. The tuberculosis close contacts were not systematically screened for DM using HbA1c in all study sites, and DM was recorded based only on self-report. The use of anti-DM drugs was not uniformly recorded, and it is possible that patients with dysglycemia receiving medication to lower the glucose levels may have exhibited a differential impact on *M. tuberculosis* transmission. Finally, we did not have data on whether the pulmonary lesions in the tuberculosis index case were upper versus lower lobe; this information could help determine why tuberculosis index cases with DM were less likely to have cavitary disease.

The present study adds important knowledge to the field by demonstrating that dysglycemic PWTB were at higher risk of transmitting *M. tuberculosis* to close contacts in a well-characterized, large, multicenter cohort in Brazil. In addition, the follow-up of contacts of PWTB with the highest probability of transmitting *M. tuberculosis* can optimize strategies focused on controlling the disease [32]. Actions focused on disease control among contacts [33, 34] is one of the main pillars for reducing tuberculosis incidence.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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SUPPLEMENTARY MATERIAL

Supplementary Methods

RePORT Brazil

RePORT-Brazil study sites are located in Manaus (Amazonas state, Northern region), Salvador (Bahia state, Northeastern region), and Rio de Janeiro (Rio de Janeiro state, Southeastern region), with a total of five health units: Instituto Nacional de Infectologia Evandro Chagas, Clínica da Familia Rinaldo Delamare, and Secretaria de Saúde de Duque de Caxias (Rio de Janeiro), Instituto Brasileiro para Investigação da Tuberculose (Bahia), and Fundação de Medicina Tropical Doutor Heitor Vieira Dourado (Amazonas), representing both a heterogeneous population and the Brazilian cities with among the highest TB burden [1]

Data collection

TB cases were interviewed for sociodemographic data such as age, sex, HIV-infection status, race/ethnicity (self-reported), body mass index (BMI), income, smoking status, passive smoking status (living with someone who smokes), alcohol consumption and illicit drug use, and clinical data such as presence of TB symptoms (cough, fever, weight loss, fatigue, night sweats, chest pain), persistence of symptoms (if still present at the month 2 visit or later) and had the following tests performed: chest X-ray, HIV test, CD4 and viral load (if HIV positive), complete blood count, glycated hemoglobin (HbA1c), sputum smear microscopy, Xpert-MTB-RIF (if available) and mycobacterial culture (Lowenstein-Jensen medium or BD BACTEC MGIT). TB patients had visits at month 0 (baseline), 2 and end of the treatment, when clinical status was reassessed, and new smear/culture tests performed. Patients who received TB treatment or fluoroquinolones for >7 days in the 30 days prior to TB diagnosis were excluded.

For this protocol, close contacts were defined as having ≥4 hours of contact/week with the TB index case at any time in the previous 6 months. Contacts identified who agreed to participate in the study were evaluated at two visits: baseline and 6 months after enrollment. They were also contacted by phone at months 12, 18, and 24, to see if they developed active TB. At the baseline visit QuantiFERON (QTF) testing was performed, and at month 6 a repeat QTF was performed if the initial QTF result was negative. Individuals whose QTF result was indeterminate (at either the baseline or month 6 visit) or who did not have a second QTF performed at month 6 (if negative at baseline) were excluded from the analysis.

SUPPLEMENTARY TABLES

Supplementary Table 1. Characteristics of TB close contacts of the TB index cases

Characteristics	Contacts excluded (n=220)	Contacts included (n=1573)	p-value
Characteristics of the TB contacts			
Age – median (IQR)	27.1 (15.4-42.6)	32.5 (16.1-47.1)	0.010
Sex male – no. (%)	95 (42.8)	635 (40.4)	0.512
Race/Ethnicity – no. (%)			0.063
White	38 (17.2)	316 (20.1)	
Black	37 (16.7)	321 (20.4)	
Asian	0 (0)	4 (0.3)	
Pardo	143 (64.7)	922 (58.6)	
Indigenous	3 (1.4)	10 (0.60)	
BMI (kg/m2)-median (IQR)	23.5 (19.1-28.4)	24.4 (20.3-28.7)	0.189
BCG scar – no. (%)	207 (93.2)	1398 (88.9)	0.050
HIV-infection	7 (3.2)	38 (2.4)	0.491
Smoking – no. (%)	56 (25.3)	412 (26.2)	0.870
Passive smoking – no. (%)	65 (29.5)	510 (32.5)	0.397
Alcohol consumption – no. (%)	119 (53.6)	838 (53.3)	0.943
Illicit drug use – no. (%)	31 (14.0)	154 (9.8)	0.060
Comorbidity – no. (%)	60 (27.0)	358 (22.8)	0.175
Diabetes– no. (%)	17 (7.7)	71 (4.5)	0.056
Hypertension– no. (%)	33 (14.9)	185 (11.8)	0.188
Characteristics of TB index cases			
Age – median (IQR)	36.00 (25-45)	34.00 (25-45)	0.934
Sex male – no. (%)	130 (59.1)	984 (62.6)	0.358
HIV-infection – no. (%)	58 (26.1)	389 (24.7)	0.063
Race/Ethnicity – no. (%)			0.516
White	42 (18.9)	300 (19.1)	
Black	39 (17.6)	323 (20.5)	
Asian	2 (0.9)	6 (0.4)	
Pardo	132 (59.5)	901 (57.3)	
Indigenous	7 (3.2)	43 (2.7)	
BMI (kg/m2)-median (IQR)	20.5 (18.2-23.8)	20.5 (18.2-22.3)	0.217
Income – no. (%)			0.050
More than a minimum wage	79 (35.7)	522 (33.3)	
Equal or less than a minimum wage	88 (39.8)	538 (34.3)	
Without income	54 (24.4)	507 (32.4)	
Smoking – no. (%)	101 (45.5)	801 (50.9)	0.133
Passive smoking – no. (%)	76 (34.9)	522 (33.4)	0.647
Alcohol consumption – no. (%)	172 (74.3)	1282 (81.5)	0.277
Illicit drug use – no. (%)	70 (31.5)	541 (34.4)	0.449
Status Diabetes			0.938
Diabetes	59 (45.0)	453 (45.0)	
Prediabetes	0 (0.0)	583 (0.0)	
Normoglycemia	72 (55.0)	537 (55.0)	

Positive AFB – no. (%)	163 (73.4)	1042 (76.8)	0.060
Cavities on chest X-ray– no. (%)	92 (41.8%)	531 (47.8)	0.043
Positive culture – no. (%)	222 (100.0)	1573 (100)	NA
Drug-susceptibility testing (DST) – no. (%)			0.08
Sensitive	205 (94.0)	1412 (91.0)	
Rifampicin-Isoniazid resistance	4 (1.8)	25 (1.6)	
Rifampicin resistance	0 (0.0)	2 (0.1)	
Isoniazid resistance	9 (4.1)	113 (7.3)	
Symptoms of TB– no. (%)			
Hemoptysis	45 (24.2)	373 (25.1)	0.858
Cough	203 (92.3)	1488 (94.6)	0.059
Fever	179 (80.6)	1257 (79.9)	0.802
Weight Loss	188 (88.3)	1442 (92.0)	0.067
Fatigue	192 (86.5)	1257 (79.9)	0.023
Night sweats	154 (69.4)	1044 (66.5)	0.403
Chest paint	149 (67.1)	1025 (65.2)	0.598
Persistence of symptoms			
Cough	58 (31.0)	537 (36.1)	0.195
Fever	5 (100)	53 (100)	NA
Weight Loss	10 (4.5)	135 (8.6)	0.035
Fatigue	31 (17)	360 (26.3)	0.006
Night sweats	105 (47.3)	779 (49.5)	0.566
Chest paint	163 (89.6)	1189 (86.5)	0.294

Table note: Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Mann Whitney test and categorical variables were using the Pearson's chi-square test.

Definition of alcohol consumption: Past or current any consumption of alcohol. *Definition of smoking:* Past or current cigarette smoker. *Definition of passive smoking:* Living with someone who smokes. *Definition of illicit drug use:* Past or current illicit drug use (marijuana, cocaine, heroin or crack)

Definition of persistence of symptoms: Patients who in the initial evaluation interview (month 0) reported indicated symptom and in the evaluation of visit 2 (month 2) still reported having such symptom.

Definition of Pardo ethnicity: mixture of European, black and Amerindian

Abbreviations: TB: tuberculosis, BMI: Body Mass Index, AFB: acid fast bacilli, NA: Not applicable

Supplementary Table 2. Characteristics of PWTB by glycemic status

Characteristics	Dysglycemia (n=643)	Normoglycemia (n=395)	p-value
Male sex – no. (%)	441 (68.7)	246 (62.3)	0.034
Age – median (IQR)	39 (29-51)	31 (23-42)	<0.001
Age – categories (years)			<0.001
<25	109 (17.0)	124 (31.40)	
25-35	151 (23.5)	133 (33.7)	
36-47	177 (27.6)	69 (17.5)	
>48	205 (31.9)	69 (17.5)	
HIV infection – no. (%)	138 (21.5)	77 (19.5)	0.440
Race/Ethnicity – no. (%)			<0.001
White	114 (17.8)	94 (23.8)	
Black	160 (25.0)	111 (28.1)	
Asian	6 (0.9)	0 (0.0)	
Pardo	352 (54.9)	183 (46.3)	
Indigenous	9 (1.4)	7 (1.8)	
BMI- (kg/m^2) – median (IQR)	20.4 (18.4-22.9)	19.8 (17.9-21.9)	0.022
Income – no. (%)			0.024
More than a minimum wage	201 (32.1)	126 (32.9)	
Equal or less than a minimum wage	249 (39.7)	177 (46.2)	
Without income	177 (28.2)	80 (20.9)	
Smoking – no. (%)	350 (54.5)	194 (49.1)	0.091
Passive smoking – no. (%)	246 (38.6)	147 (37.3)	0.688
Alcohol consumption – no. (%)	551 (85.8)	322 (81.5)	0.065
Illicit drug use – no. (%)	230 (35.9)	127 (32.2)	0.220
Hypoglycemic drugs – no. (%)	25 (3.9)	0 (0.0)	NA
AFB grade – no. (%)			0.388
1+	165 (25.7)	94 (23.8)	
2+	160 (24.9)	84 (21.3)	
3+	152 (23.7)	95 (24.1)	
Scanty	50 (7.8)	37 (9.4)	
Negative	115 (17.9)	85 (21.5)	
Cavities on chest X-ray – no. (%)	314 (49.1)	201 (51.4)	0.480
Positive culture – no. (%)	643 (100.0)	395 (100.0)	
Drug-susceptibility testing (DST) – no. (%)			0.500
Rifampicin-Isoniazid resistance	16 (2.5)	10 (2.6)	
Rifampicin resistance	2 (0.3)	3 (0.8)	
Isoniazid resistance	35 (5.5)	15 (3.9)	
Sensitive	585 (91.7)	359 (92.8)	
Symptoms of TB– no. (%)			
Hemoptysis	151 (24.7)	92 (25.2)	0.863
Cough	613 (95.5)	367 (92.9)	0.078
Fever	509 (79.3)	301 (76.2)	0.244
Weight Loss	596 (92.8)	347 (88.3)	0.013

Characteristics	Dysglycemia (n=643)	Normoglycemia (n=395)	p-value
Fatigue	529 (82.4)	314 (79.5)	0.244
Night sweats	452 (70.5)	269 (68.3)	0.446
Chest paint	416 (64.9)	253 (64.2)	0.823
Persistence of symptoms – no. (%)			
Cough	224 (36.5)	165 (45.0)	0.009
Fever	20 (100.0)	25 (100.0)	NA
Weight Loss	48 (7.5)	33 (8.4)	0.609
Fatigue	141 (24.4)	85 (23.3)	0.698
Night sweats	317 (49.4)	185 (46.8)	0.426
Chest paint	84 (14.5)	45 (12.4)	0.345

Table note: TB index cases were divided in two groups based on the glycemic status in normoglycemia or dysglycemia, which included both diabetes and prediabetes. Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were using the Fisher's exact test (2x2) or Pearson's chi-square test.

Age categories: based on the study population quartiles.

Definition of alcohol consumption: Past or current any consumption of alcohol. *Definition of passive smoking:* Living with someone who smokes. *Definition of illicit drug use:* Past or current illicit drug use (marijuana, cocaine, heroin or crack)

Definition of persistence of symptoms: Patients who in the initial evaluation interview (month 0) reported indicated symptom and in the evaluation of visit 2 (month 2) still reported having such symptom.

Definition of Pardo ethnicity: mixture of European, black and Amerindian

Hypoglycemic drug: Metformin, glyburide, gluformin, sitagliptin, glipizide and insulin.

No patient reported statin use at baseline.

Missing information was identified in six variables: HIV infection (3 [0.5%]), Race/Ethnicity (2 [0.3%]), income (16 [2.5%]), AFB grade (1 [0.2%]), X-ray (15 [2.3%]) and drug-susceptibility testing (DST) (5 [0.8%]). The statistical analyzes were carried out only with the available data, omitting the cases with missing information.

Abbreviations: TB: tuberculosis, BMI: Body Mass Index, AFB: acid-fast bacilli, NA: Not applicable

Supplementary Table 3. Characteristics of TB index cases or close contacts by diabetes status of the TB index cases

Characteristics	Diabetes (n=250)	Prediabetes (n=393)	Normoglycemia (n=395)	p-value
Characteristics of TB index cases				
Sex male – no. (%)	166 (66·4)	276 (70·2)	246 (62·3)	0·062
Age – median (IQR)	46 (35-55)	35 (26-47)	31 (23-42)	<0·001
Age – categories (years)				<0·001
<25	23 (9·2)	86 (21·9)	124 (31·4)	
25-35	40 (16·0)	112 (28·5)	133 (33·7)	
36-47	73 (29·2)	104 (26·5)	69 (17·5)	
>48	114 (45·6)	91 (23·2)	69 (17·5)	
HIV infection – no. (%)	51 (20·4)	88 (22·4)	77 (19·5)	0·681
Race/Ethnicity – no. (%)				0·008
White	38 (15·3)	77 (19·6)	94 (23·8)	
Black	54 (21·7)	106 (27·0)	111 (28·1)	
Asian	1 (0·4)	5 (1·3)	0 (0·0)	
Pardo	152 (61·0)	200 (50·9)	183 (46·3)	
Indigenous	4 (1·6)	5 (1·3)	7 (1·8)	
BMI (kg/m^2)-median (IQR)	21·5 (19·1-24·4)	19·8 (18·3-21·8)	19·8 (17·9-21·9)	<0·001
Income – no. (%)				0·233
More than a minimum wage	91 (36·5)	110 (29·1)	126 (32·9)	
Equal or less than a minimum wage	91 (36·5)	158 (41·8)	177 (46·2)	
Without income	67 (26·9)	110 (29·1)	80 (20·9)	
Smoking – no. (%)	144 (57·6)	207 (52·7)	194 (49·1)	0·036
Passive smoking – no. (%)	100 (40·0)	147 (37·8)	147 (37·3)	0·514
Alcohol consumption – no. (%)	221 (88·4)	331 (84·2)	322 (81·5)	0·021
Illicit drug use – no. (%)	75 (30·0)	156 (39·8)	127 (32·2)	0·018
Hypoglycemic drugs – no. (%)	24 (9.6)	1 (0.3)	0 (0·0)	0.001
AFB grade – no. (%)				0·041
1+	65 (26·0)	101 (25·7)	94 (23·8)	
2+	64 (25·6)	96 (24·4)	84 (21·3)	
3+	66 (26·4)	86 (21·9)	95 (24·1)	
Scanty	18 (7·2)	32 (8·1)	37 (9·4)	
Negative	37 (14·8)	78 (19·8)	85 (21·5)	
Cavities on chest X-ray– no. (%)	118 (47·4)	196 (50·1)	201 (51·4)	0·333
Positive culture – no. (%)	250 (100·0)	393 (100·0)	395 (100·0)	NA
Drug-susceptibility testing (DST) – no. (%)				0·360
Rifampicin resistance	2 (0·8)	0 (0·0)	3 (0·8)	
Isoniazid resistance	13 (5·2)	23 (5·9)	15 (3·9)	
Rifampicin-Isoniazid resistance	8 (3·2)	8 (2·1)	10 (2·6)	
Sensitive	226 (90·8)	359 (92·1)	359 (92·8)	
Symptoms of TB– no. (%)				
Hemoptysis	64 (27·2)	87 (23·1)	92 (25·2)	0·678
Cough	235 (94·0)	379 (96·4)	367 (92·9)	0·087
Fever	196 (78·4)	314 (79·9)	301 (76·2)	0·423

Weight Loss	235 (94·0)	362 (92·1)	347 (88·3)	0·010
Fatigue	214 (85·6)	316 (80·4)	314 (79·5)	0·066
Night sweats	174 (69·9)	279 (71·0)	269 (68·3)	0·598
Chest paint	165 (66·3)	251 (63·9)	253 (64·2)	0·637
Persistence of symptoms				
Cough	91 (38·7)	133 (35·1)	165 (45·0)	0·021
Fever	10 (100·0)	10 (100·0)	25 (100·0)	NA
Weight Loss	27 (10·8)	21 (5·3)	33 (8·4)	0·037
Fatigue	63 (28·5)	78 (21·8)	85 (23·3)	0·219
Night sweats	124 (49·6)	193 (49·1)	185 (46·8)	0·465
Chest paint	35 (15·8)	49 (13·7)	45 (12·4)	0·241
Characteristics of TB close contacts				
Age – median (IQR)	31·8 (14·8-45·8)	33·8 (16·2-47·7)	31·7 (17·9-48·5)	0·414
Sex male – no. (%)	188 (42·5)	237 (40·2)	210 (38·8)	0·242
Race/Ethnicity – no. (%)	373 (84·4)	463 (78·5)	407 (75·2)	<0·001
White	65 (14·7)	123 (20·8)	128 (23·7)	
Black	89 (20·1)	114 (19·3)	118 (21·8)	
Asian	1 (0·2)	2 (0·3)	1 (0·2)	
Pardo	284 (64·3)	349 (59·2)	289 (53·4)	
Indigenous	3 (0·7)	2 (0·3)	5 (0·9)	
Income – no. (%)	297 (68·4)	349 (61·7)	286 (55·0)	<0·001
More than a minimum wage	137 (31·6)	217 (38·3)	234 (45·0)	
Equal or less than a minimum wage	190 (43·8)	239 (42·2)	202 (38·8)	
Without income	107 (24·7)	110 (19·4)	84 (16·2)	
BCG scar – no. (%)	390 (88·2)	524 (88·8)	484 (89·5)	0·541
HIV-infection – no. (%)	13 (2·9)	17 (2·9)	8 (1·5)	0·124
Smoking – no. (%)	132 (29·9)	143 (24·2)	137 (25·3)	0·128
Passive smoking – no. (%)	146 (33·0)	190 (32·3)	174 (32·4)	0·843
Alcohol consumption – no. (%)	239 (54·1)	303 (51·4)	296 (54·7)	0·785
Illicit drug use – no. (%)	62 (14·0)	38 (6·4)	54 (10·0)	0·057
Comorbidity – no. (%)	77 (17·4)	138 (23·4)	143 (26·4)	0·001
Diabetes*– no. (%)	11 (2·5)	28 (4·7)	32 (5·9)	0·034
Hypertension– no. (%)	43 (9·7)	66 (11·2)	76 (14·0)	0·090

Table note: Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Kruskal-Wallis test and categorical variables were using the Pearson's chi-square test.
Age categories: based on the population quartile
Definition of alcohol consumption: Past or current any consumption of alcohol. *Definition of smoking:* Past or current cigarette smoker. *Definition of passive smoking:* Living with someone who smokes. *Definition of illicit drug use:* Past or current illicit drug use (marijuana, cocaine, heroin or crack)
Definition of persistence of symptoms: Patients who in the initial evaluation interview (month 0) reported indicated symptom and in the evaluation of visit 2 (month 2) still reported having such symptom.
Definition of Pardo ethnicity: mixture of European, black and Amerindian
Hypoglycemic drug: Metformin, glyburide, gluformin, sitagliptin, glipizide and insuline.
No patient reported statin use at baseline.
*p-value was calculated with information of diabetes and prediabetes groups.
Diabetes: This information was self-reported and only 31 close contacts had available HbA1c result.
Abbreviations: TB: tuberculosis, BMI: Body Mass Index, AFB: acid fast bacilli, NA: Not applicable

Supplementary Table 4. Characteristics of TB close contacts and of the TB index cases by final QuantiFERON result of the TB contacts

Characteristics	Positive (n=658)	Negative (n=809)	Conversion (n=106)	p-value
Characteristics of the TB contacts				
Age – median (IQR)	36 (19·2-50·1)	30 (14·3-43·9)	32·1 (16·3-48·6)	<0·001
Sex male – no. (%)	239 (36·3)	350 (43·3)	46 (43·4)	0·275
Race/Ethnicity – no. (%)				0·175
White	113 817·2)	189 (23·4)	14 (13·2)	
Black	160 (24·3)	137 (16·9)	24 (22·6)	
Asian	3 (0·5)	1 (0·1)	0(0)	
Pardo	378 (57·4)	476 (58·8)	68 (64·2)	
Indigenous	4 (0·6)	6 (0·7)	0 (0)	
Income – no. (%)				0·775
More than a minimum wage	218 (34·3)	325 (41·6)	45 (43·7)	
Equal or less than a minimum wage	287 (45·1)	301 (38·5)	43 (41·7)	
Without income	131 (20·6)	155 (19·8)	15 (14·6)	
HIV-infection – no. (%)	11 (1·7)	24 (3·0)	3 (2·8)	0·463
Smoking – no. (%)	194 (29·5)	185 (22·9)	33 (31·1)	0·007
Passive smoking – no. (%)	237 (36·2)	241 (29·8)	32 (30·5)	0·238
Alcohol consumption – no. (%)	352 (53·5)	424 (52·4)	62 (58·5)	0·254
Illicit drug use – no. (%)	69 (10·5)	73 (9·0)	12 (11·3)	0·316
Comorbidity – no. (%)	168 (25·5)	170 (21·0)	20 (18·9)	0·659
Diabetes– no. (%)	31 (4·7)	40 (4·9)	0 (0·0)	NA
Hypertension– no. (%)	95 (14·4)	80 (9·9)	10 (9·4)	0·318
Characteristics of the TB index cases				
HbA1c (%)- median (IQR)	5·9 (5·4-6·6)	6 (5·5-6·6)	6·45 (5·6-7·1)	0·248
Status Diabetes				0·002
Diabetes	182 (27·7)	223 (27·6)	48 (45·3)	
Prediabetes	218 (33·1)	337 (41·7)	28 (26·4)	
Normoglycemia	258 (39·2)	249 (30·8)	30 (28·3)	
HIV-infection	121 (18·4)	248 (30·7)	20 (18·9)	<0·001
Age – median (IQR)	34 (24-44)	35 (25-45)	34 (24-47)	0·296
Sex male – no. (%)	402 (61·1)	515 (63·7)	67 (63·2)	0·623
Race/Ethnicity – no. (%)				0·388
White	125 (19·0)	161 (19·9)	14 (13·2)	
Black	160 (24·3)	135 (16·7)	28 (26·4)	
Asian	3 (0·5)	3 (0·4)	0 (0·0)	
Pardo	356 (54·1)	495 (61·2)	60 (56·6)	
Indigenous	14 (2·2)	15 (1·9)	4 (3·8)	
BCG scar – no. (%)	582 (88·4)	722 (89·2)	94 (88·7)	0·732
BMI (kg/m2)-median (IQR)	20 (18·22·5)	20·4 (18·7-22)	20·3 (18·3-22·5)	0·647
Income – no. (%)				0·203
More than a minimum wage	205 (31·4)	280 (34·6)	37 (35·2)	

Characteristics	Positive (n=658)	Negative (n=809)	Conversion (n=106)	p-value
Equal or less than a minimum wage	244 (37·4)	253 (31·3)	41 (39·0)	
Without income	204 (31·3)	276 (34·1)	27 (25·7)	
Smoking – no. (%)	350 (53·2)	402 (49·7)	49 (46·2)	1·000
Passive smoking – no. (%)	248 (37·8)	239 (29·8)	35 (33·0)	0·060
Alcohol consumption – no. (%)	527 (80·1)	667 (82·4)	88 (83·0)	0·718
Illicit drug use – no. (%)	233 (35·4)	271 (33·5)	37 (34·9)	0·581
Positive AFB – no. (%)	483 (73·6)	475 (58·7)	83 (78·3)	<0·001
Cavities on chest X-ray	374 (57·3)	307 (38·3)	65 (61·3)	<0·001
Positive culture – no. (%)	658 (100·0)	809 (100·0)	106 (100·0)	NA
Drug-susceptibility testing (DST) – no. (%)				0·085
Rifampicin-Isoniazid resistance	8 (1·2)	15 (1·9)	2 (1·9)	
Rifampicin resistance	1 (0·2)	1 (0·1)	0 (0·0)	
Isoniazid resistance	33 (5·0)	72 (9·1)	8 (7·6)	
Sensitive	612 (93·6)	705 (88·9)	95 (90·5)	
Symptoms of TB – no. (%)				
Cough	630 (95·7)	754 (93·2)	104 (98·1)	0·009
Fever	537 (81·6)	637 (78·7)	83 (78·3)	0·633
Weight Loss	610 (93·4)	735 (91·0)	97 (91·5)	0·386
Fatigue	520 (79·0)	654 (80·8)	83 (78·3)	0·390
Night sweats	459 (70·0)	517 (63·9)	68 (64·2)	0·294
Chest paint	436 (66·3)	514 (63·5)	75 (70·8)	0·098
Persistence of symptoms – no. (%)				
Cough	244 (38·7)	246 (32·6)	47 (45·2)	0·003
Fever	30 (100·0)	21 (100·0)	2 (100·0)	NA
Fatigue	63 (9·6)	67 (8·3)	5 (4·7)	0·517
Weight Loss	161 (27·2)	178 (26·0)	21 (22·6)	0·708
Night sweats	356 (54·1)	379 (46·8)	59 (55·7)	0·011
Chest paint	79 (13·3)	94 (13·6)	13 (14·0)	0·997

Table note: Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Kruskal-Wallis test and categorical variables were using the Pearson's chi-square test.

Definition of alcohol consumption: Past or current any consumption of alcohol. *Definition of smoking:* Past or current cigarette smoker. *Definition of passive smoking:* Living with someone who smokes. *Definition of illicit drug use:* Past or current illicit drug use (marijuana, cocaine, heroin or crack)

Definition of persistence of symptoms: Patients who in the initial evaluation interview (month 0) reported indicated symptom and in the evaluation of visit 2 (month 2) still reported having such symptom.

Definition of Pardo ethnicity: mixture of European, black and Amerindian

Abbreviations: TB: tuberculosis, BMI: Body Mass Index, AFB: acid fast bacilli, NA: Not applicable

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6.8 MANUSCRITO VIII

Divergence in Accuracy of Diabetes Screening Methods in Tuberculosis Patients: A Cross-Sectional Study from Brazil and Peru

A associação TB-DM é altamente preocupante no contexto da infecção por TB, principalmente em países de baixa e média renda. No Brasil e Peru, é recomendada a triagem para DM para aqueles que apresentam TB ativa, assim como triagem para TB em pessoas com DM. Esse trabalho avaliou a precisão de métodos distintos de rastreamento de DM em pessoas com TB ativa.

Resumo dos resultados: As coortes estudadas apresentaram diferenças quanto aos valores de exames para diagnóstico da DM. Enquanto a coorte do Brasil apresentou níveis significativamente mais elevados de HbA1c, a do Peru apresentou níveis elevados de ambos antes do tratamento anti-TB. As análises realizadas demonstraram que esses testes apresentaram precisão distinta para identificar disglicemia na população com TB ativa em cada país, destacando a necessidade de reanalisar os critérios diagnósticos de DM/PDM em indivíduos com TB.

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Divergence in Accuracy of Diabetes Screening Methods in Tuberculosis Patients: A Cross-Sectional Study from Brazil and Peru

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Short title: Diagnosis of dysglycemia in tuberculosis

ABSTRACT

Objective: To evaluate the accuracy of distinct diabetes mellitus (DM) screening methods in persons with active tuberculosis (PWTB)

Methods: Levels of fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) at the time of tuberculosis diagnosis at the study clinics were assessed from two distinct retrospective cohorts of PWTB from Brazil (n=116) and Peru (n=136) to evaluate accuracy for detecting preDM and DM cases. Additionally, we investigated the association of clinical and sociodemographic factors with tuberculosis and pre-DM or DM in each country.

Results: When comparing FPG and HbA1c values of PWTB from Brazil and Peru, Peruvian individuals presented higher FPG levels at baseline (median [IQR]: 91 [81–106] vs 95 [88.4–102.1]; p=0.02), while those from Brazil had significant higher levels of HbA1c (median [IQR]: 6.3 [5.7-7.15] vs 5.1 [4.9-5.4]; p<0.01). Additional analysis using the receiver operating characteristic (ROC) curve revealed that the markers showed distinct accuracy to identify dysglycemia among PWTB in each country.

Conclusion: Our findings indicate that there are significant differences in the total accuracy of the glycemic screening methods evaluated between PWTB from two highly endemic countries from South America, highlighting the need to revisit the diagnostic criteria of DM/PDM in PWTB.

Keywords: fasting plasma glucose, hemoglobin A1c, diabetes mellitus, prediabetes, tuberculosis.

INTRODUCTION

Tuberculosis (TB) is a major public health concern at global level. In 2019, The World Health Organization (WHO) estimated 10 million new cases and 1.4 million deaths caused by TB [1]. Notably, among risk factors associated with TB morbidity and mortality, it is a common knowledge that glycemic disorders such as diabetes mellitus (DM) and prediabetes (PDM), exhibit critical influence over immune pathology and systemic inflammation, thus increasing risk of worse clinical outcomes [2–4]. Moreover, it is known that DM triples active TB risk and exacerbates TB clinical presentation resulting in early mortality rates (death within 100 days of starting anti-TB treatment) and increasing the odds of unfavorable TB treatment outcomes [2–6]. On the converse, TB may lead to infection-related hyperglycemia, often decompensating glycemic control in diabetics [4,5]. Hence, the relationship between dysglycemic states and TB is bidirectional, establishing a mutual harmful association.

TB and DM convergence results in a significant disease worldwide, especially in low and middle-income countries [3,7]. Indeed, despite all TB therapeutic strategies and preventive support improvement, Brazil remains among the 20 countries with the highest disease burden in the world and number one in the Americas, followed by Peru [1,8]. While Brazil is responsible for the largest number of absolute cases for its large population, Peru has the second highest incidence rate in the Americas (123/100.000 versus 45/100.000 in Brazil) [8]. In Brazil, 7.6% of incident TB cases are associated to DM [9]. As an effort to decrease the impact caused by TB-DM syndemic, the WHO as well as the Peruvian and the Brazilian National TB Program (NTP and PNCT, respectively) recommend screening for DM those presenting with active TB and frequent screening for TB symptoms in persons with DM (PWDM) [1,10,11].

In the clinical practice, fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) are the most frequent tests used to diagnose DM, followed by the oral glucose tolerance test (OGTT) [5,12]. OGTT is considered the gold standard for DM diagnosis, but it has some expressive limitations as a mass screening test, due to the uncertainty of the fasting state, the time-consuming nature of the test,

poor reproducibility of the results and need of a standard 75g glucose load, which is a challenge in primary care settings in resource-limited countries [5,13,14]. Nevertheless, the accuracy of HbA1c and FPG can be limited by issues such as accuracy variation among subjects of different ethnicity [15]. Of note, previous investigations assessing accuracy of these laboratory parameters for screening of DM in PWTB exposed conflicting results in different populations, especially in those from South America [13,16]. This could result from blood tests being affected by ethnicity and genetic variations influencing hemoglobin concentrations in peripheral blood [17], strengthening the hypothesis that unique features determined by genetic background might have an impact on the choice of the most reliable DM screening method.

In the present study, we investigated the performance of HbA1c and FPG in identifying PDM and DM cases among PWTB from two South American countries with high burden for both TB and DM, Brazil, and Peru. Differences in associations of clinical and sociodemographic characteristics with TB and dysglycemia between the countries were also examined.

METHODS

Ethics statement

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. In Brazil, the study was approved by the Ethics Committee of the Maternidade Clímério de Oliveira, Federal University of Bahia (protocol number: 037/2011, Ethics Committee approval number: 034/11). Peruvian research was approved by the Institutional Committee of Ethics for Humans (CIEI, approval number: 158–22–16), the Universidad Peruana Cayetano Heredia. Written informed consent was obtained from all participants or their legally responsible guardians.

Study design and population in Brazil

We conducted a retrospective cross-sectional study of data retrieved from a prospective cohort conducted between May 2010 and June 2011 in the Instituto Brasileiro para Investigação da Tuberculose (IBIT), Fundação José Silveira, Salvador, Brazil, which aimed to examine the association between glucose metabolism disorder and pulmonary TB [18]. For the present study, the inclusion criteria were patients ≥18 years of age, diagnosed with TB according to the Brazilian Manual of Recommendations for TB Control [10] and who were not undertaking anti-TB drugs for more than 5 days, whereas incomplete medical report was considered as the exclusion criteria. Sociodemographic and clinical characteristics were collected by trained physicians during each patient visit and recorded in standardized electronic forms, which are part of the Brazilian National TB control program. Moreover, as part of the laboratory investigation, three sputum smears stained by Ziehl–Neelsen and examined by microscopy at the IBIT's microbiology referral laboratory, processed by the modified Petroff's method and cultured on Lowenstein-Jensen medium. Diagnosis of DM or PDM was performed at the time of TB diagnosis (baseline visit) in agreement with American Diabetes Association (ADA) guidelines [19], and was based on fasting plasma glucose (FPG), glycated hemoglobin (HbA1c) and oral glucose tolerance test (OGTT) as previously described [18]. Further details about the study site and data management are described in previously published studies [18,20].

Study design and population in Peru

We retrospectively analyzed data of 136 individuals diagnosed with pulmonary TB, from a larger prospective cohort study conducted over February and November 2017 with patients from North Lima, Peru [2]. TB diagnosis was performed by the National TB Program (all patients had microbiologically confirmed TB) and inclusion criteria comprised patients with age ≥ 18 years and who were not receiving anti-TB treatment or had started in no more than 5 days. Information on sociodemographic and clinical evaluation was retrieved from the medical records. All enrolled participants provided sputum samples for acid-fast bacilli (AFB) smear, which were stained by Ziehl–Neelsen and examined by microscopy. Then sputum specimens were cultured by Lowenstein-Jensen medium and BD MGIT 960 System (liquid culture). Smear and cultures were graded according to AFB and colonies numbers following standard guidelines [21]. Evaluation of glycemic markers, FPG, HbA1c and OGTT, was performed to establish DM or PDM diagnosis according to ADA criteria [19]. Such procedures were performed at the baseline clinical visit when TB was diagnosed. Measurement of HbA1c in blood was conducted using TRI-stat™ platform (Trinity Bio- tech, Ireland). FPG and OGTT were performed following standard methods. Supplementary information about procedures and patient management, are well described in previous publications [2,6].

Epidemiological characteristics of TB and DM in Brazil and Peru.

Overall distribution of TB and DM cases in both countries was described accordingly with the data gathered from the international reports published by the WHO [8] and International Diabetes Federation [22]. Such distribution is shown in **Figure 1**.

Data analysis

Descriptive analysis was performed with categorical variables presented as frequency and percentages and compared using the Fisher's exact test (between 2 groups) or Pearson's chi-square test (more than 2 groups), when appropriate. Quantitative variables were expressed as median with interquartile range (IQR) and compared using the Mann-Whitney *U* test, for two groups, or the Kruskal Wallis test with Dunn's multiple comparisons posttest for more than two groups.

Analyses of stratified or matched categorical data were performed with Cochran-Mantel-Haenszel test. To quantitatively assess the accuracy of the HbA1c and FPG, receiver operator characteristics (ROC) curves analysis were performed in each country. The Kappa (k) statistic test was calculated to assess agreement between FPG or HbA1c as diagnostic test for DM/PDM in both countries. Kappa statistic results were interpreted using the Landis and Koch criteria [23]. All tests were pre-specified, two-tailed and differences were considered statistically significant with $p \leq 0.05$. Data analysis was performed using SPSS 24.0 (IBM statistics), Graphpad Prism 7.0 (GraphPad Software, San Diego, CA) and JMP 13.0 (SAS, Cary, NC, USA).

RESULTS

TB and DM burden in Brazil and Peru

The overall distribution of TB and DM cases using the most updated report containing estimated data from both countries, performed in 2019, is shown in **Figure 1** [8,22]. Brazil led the burden of TB in South and Central America, with a total of 96,000 TB cases reported and a rate of 46 cases per 100,000 inhabitants, while Peru had a total of 39,000 TB cases estimated and a rate of 119/100,000. Regarding DM distribution, more than 16.8 million cases were reported among Brazilians, with a rate of 80 cases per 100,000 estimated in 2019 [1] and among Peruvian approximately 22 cases per 100,000 [24]. Furthermore, the cohort explored in the present study was located in state of Bahia, represented in the map with an incidence of TB-DM of 9 cases per 100 inhabitants. Similarly, the Province of Lima, from where our Peruvian cohort was followed, had an incidence of 10 cases per 100 inhabitants of TB-DM comorbidity in 2019. Therefore, our cohorts are originated from relevant endemic areas with relatively high burden of both TB and DM.

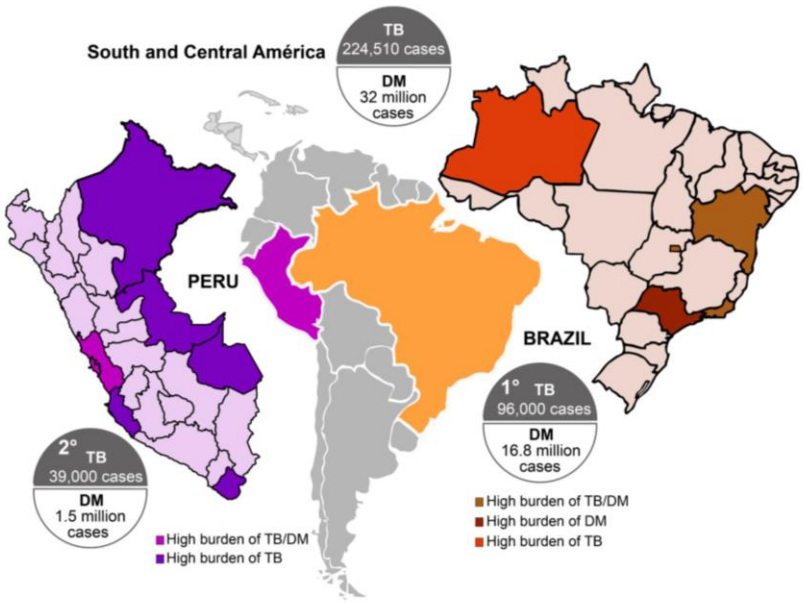

Figure 1. Epidemiological distribution of TB and DM cases across Brazil and Peru. The figure shows the distribution of TB and DM burden by Country. Inside the Countries, in the Map, it is displayed the distribution of TB and DM overload by state/province.

Characteristics of the study populations

Brazilian participants were significantly older than the Peruvians, (median age [IQR]: 45 years [31–55] vs. 29 years [IQR: 23–45], respectively; $p < 0.01$) (**Table 1**). Distribution of sex was similar between the cohorts (**Table 1**). With respect to clinical presentation, we found that Brazilian participants presented more frequently with cough ($p<0.01$), fever (<0.01) and weight loss ($p=0.03$), whereas individuals from Peru more often had hemoptysis ($p<0.01$) and lack of appetite ($p=0.02$) (**Table 1** and **Supplementary Figure 1**). Moreover, Peruvians exhibited higher FPG levels (median [IQR]: 95mg/dL [88.4–102.1] vs 91 mg/dL [81–106]; $p = 0.02$), while Brazilian displayed more elevated HbA1c values (median [IQR]: 6.3% [5.7-7.15] vs 5.1% [4.9-5.4]; $p<0.01$). There was no difference in median OGTT level among the two populations (**Table 1**). Smoking history was more commonly reported in patients from Brazil (39.7% vs 21.5%, p< 0.01), while

243 current illicit drug use and alcohol consumption were more frequent in Peruvians
244 (p< 0.01) (**Table 1**). Metformin use was more frequently documented in Peruvian
245 participants than that in those from Brazil (11.4% vs 1.3%, p< 0.01). Finally,
246 Peruvians more often were BCG vaccinated than Brazilians (93.3% vs 75.4%,
247 p<0.01). Additional comparisons are depicted in **Table 1**.
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Table 1. Characteristics of study populations stratified according to countries

Characteristics	n/N	Brazil n=116	Peru n=136	p-value
Sex	116/136			0.37
Male		64 (55.2)	83 (61)	
Female		52 (44.8)	53 (39)	
Age (years)	116/136	45 (31-55)	29 (23-45)	**<0.01**
BMI (Kg/m²)	115/132	22.94 [20-26.81]	22.67 [20.57-25.31]	0.46
Cough	116/136	115 (99.1)	123 (90.4)	**<0.01**
Fever	116/136	76 (65.5)	63 (46.3)	**<0.01**
Malaise	116/136	83 (71.6)	105 (77.2)	0.31
Loss of weight	116/136	98 (84.5)	99 (72.8)	**0.03**
Night sweats	116/136	79 (68.1)	78 (57.4)	0.09
Hemoptysis	116/136	24 (20.7)	57 (41.9)	**<0.01**
Lack of Appetite	116/136	87 (75)	82 (60.3)	**0.02**
Dyspnea	116/136	70 (60.3)	88 (64.7)	0.52
Comorbidities	116/136	17 (14.7)	16 (11.8)	0.58
Smoking History	116/135	46 (39.7)	29 (21.5)	**<0.01**
Illicit drug use	116/135	4 (3.4)	21 (15.6)	**<0.01**
Alcohol consumption	116/135	11 (9.5)	70 (51.9)	**<0.01**
Glycemic Status	116/136			**<0.01**
DM		49 (42.2)	19 (14)	
PDM		48 (41.4)	42 (30.9)	
Normoglycemic		19 (16.4)	75 (55.1)	
Metformin use	21/132	10 (1.3)	7 (11.4)	**<0.01**
FPG (mg /dL)	116/136	91 [81-106]	95 [88.4-102.1]	**0.02**
HbA1c (%)	116/134	6.3 [5.7-7.15]	5.1 [4.9-5.4]	**<0.01**
OGTT (mg/dL)	84/112	118 [94-154.5]	112.8 [91.45-127.85]	0.06
Prior TB	116/136	23 (19.8)	23 (16.9)	0.62
BCG vaccination	114/135	86 (75.4)	126 (93.3)	**<0.01**
TB contact	116/136	31 (26.7)	52 (38.2)	0.06
AFB smear	116/130			0.99
Negative		50 (43.1)	60 (46.2)	
Scanty		0 (0)	0 (0)	
1+		27 (23.3)	27 (20.8)	
2+		18 (15.5)	15 (11.5)	
3+		21 (18.1)	28 (21.5)	
L-J culture	108/131			0.27
Negative		4 (3.7)	38 (29)	
Scanty		2 (1.9)	14 (10.7)	
+1		48 (44.4)	63 (48.1)	
+2		33 (30.6)	9 (6.9)	
+3		21 (19.4)	7 (5.3)	

Data are represented as median with interquartile range [25th - 75th percentile] or frequency (percentage). Groups were compared using Mann-Whitney *U* test for quantitative variables and the Pearson's qui-square test or Fisher's exact test for categorical variables. P < 0.05 was considered statistically significant. Comorbidities: Renal disease and/or Asthma and/or Hypertension; Smoking history: Past or current cigarette smoker; Illicit Drugs Use: Past or

current illicit drug use (marijuana, cocaine, heroin or crack); Chronic Alcoholism: Past or current any consumption of alcohol; Metformin use: Metformin use in patients with dysglycemia; Prior TB: previous diagnosis of active tuberculosis; DM: Diabetes; PDM: Prediabetes; FPG Fasting Plasma Glucose; HbA1c Glycated Hemoglobin; OGTT Oral Glucose Tolerance Test; BMI: Body Mass Index; BCG: Bacillus Calmette–Guérin; AFB Acid-Fast Bacilli; L-J Löwenstein-Jensen.

Distribution of TB cases according to glycemic status in Brazil and Peru

We next stratified the study participants in both countries based on the final diagnosis of the glycemic status (e.g., normoglycemic, PDM and DM). In Brazil, 42.2% of the PWTB had also DM and 41.4% had PDM (**Table 2**). In contrast, in Peru, 13.9% of the PWTB had comorbid DM, followed by 31% who had PDM (**Table 2**). DM was associated with older age in both countries and the group with highest median age were Brazilians individuals with DM (50.1 [IQR: 45–59], $p<0.01$) (**Table 2**). Among the TB clinical symptoms, hemoptysis was more prevalent in Peruvian patients with DM (47.4%; $p<0.01$) (**Table 2**). When all the TB patients were considered, we found HbA1c ($p<0.01$) and OGTT ($p<0.01$) values higher in Brazil, while FPG levels ($p<0.01$) higher in Peru (**Table 2**). Sputum culture grade values tended to be higher following hyperglycemia degree, with Brazilian patients exhibiting a greater frequency of higher culture grades ($p<0.01$).

Table 2. Characteristics of pulmonary TB cases stratified according to countries and glycemic status.

Characteristics	TOTAL			BRAZIL			PERU			
	DM	PDM	Normoglycemic	DM	Pre-DM	Normoglycemic	DM	Pre-DM	Normoglycemic	p-value
	n=68	n=90	n=94	n=49	n=48	n=19	n=19	n=42	n=75	
Sex										0.79
Male	42 (61.8)	51 (56.7)	54 (57.4)	33 (67.3)	24 (50)	7 (36.8)	9 (47.4)	27 (64.3)	47 (62.7)	
Female	26 (38.2)	39 (43.3)	40 (42.6)	16 (32.7)	24 (50)	12 (63.2)	10 (52.6)	15 (35.7)	28 (37.3)	
Age (years)	50.1 [42.8-58.6]	39.5 [26.0 - 52.0]	27.7 [22.2-33.0]	50.81 [45.0-59.0]	39.3 [26.0-52.3]	33.0 [27.7-44.7]	46.4 [36.6-58.3]	39.8 [26.7-51.4]	25.8 [21.0-31.0]	**<0.01**
BMI (Kg/m²)	22.68 [20.02-26.36]	23.0 [20.6 - 26.0]	22.4 [20.2-26.1]	22.94 [20.0-26.4]	22.5 [20.2-27.1]	23.32 [19.6-28.4]	22.3 [21.4-26.4]	23.2 [21.2-25.1]	22.3 [20.3-25.4]	0.81
Cough	67 (98.5)	85 (94.4)	86 (91.5)	49 (100.0)	47 (97.9)	19 (100.0)	18 (94.7)	38 (90.5)	67 (89.3)	0.16
Fever	36 (52.9)	50 (55.6)	53 (56.4)	30 (61.2)	29 (60.4)	17 (89.5)	6 (31.6)	21 (50)	36 (48)	0.91
Malaise	52 (76.5)	66 (73.3)	70 (74.5)	37 (75.5)	32 (66.7)	14 (73.7)	15 (78.9)	34 (81)	56 (74.7)	0.90
Loss of weight	58 (85.3)	72 (80.0)	67 (71.3)	43 (87.8)	37 (77.1)	18 (94.7)	15 (78.9)	35 (83.3)	49 (65.3)	0.90
Night sweats	48 (70.6)	55 (61.1)	54 (57.4)	36 (73.5)	32 (66.7)	11 (57.9)	12 (63.2)	23 (54.8)	43 (57.3)	0.23
Hemoptysis	21 (30.9)	20 (22.2)	40 (42.6)	12 (24.5)	6(12.5)	6 (31.6)	9 (47.4)	14 (33.3)	34 (45.3)	**<0.01**
Lack of appetite	51 (75.0)	61 (67.8)	57 (60.6)	39 (79.6)	32 (66.7)	16 (84.2)	12 (63.2)	29 (69.0)	41 (54.7)	0.16
Dyspnea	39 (57.4)	54 (60)	65 (69.1)	27 (55.1)	29 (60.4)	14 (73.7)	12 (63.2)	25 (59.5)	51 (68.0)	0.25
Comorbidities	9 (13.2)	17 (18.8)	31 (32.9)	4 (8.9)	12 (25)	1 (5.3)	5 (26.3)	5 (11.9)	6 (8)	0.85
Smoking History	28 (41.2)	28 (31.5)	19 (20.2)	24 (49)	18 (37.5)	4 (21.1)	4 (21.1)	10 (24.4)	15 (20)	0.15
Illicit drug use	3 (4.4)	8 (9)	14 (14.9)	2 (4.1)	1 (2.1)	1 (5.3)	1 (5.3)	7 (17.1)	13 (17.3)	0.83
Alcohol consumption	11 (16.2)	32 (36)	38 (40.4)	7 (14.3)	3 (6.3)	1 (5.3)	4 (21.1)	29 (70.7)	37 (49.3)	**<0.01**
Metformin use	17 (42.5)	0 (0)	0 (0)	10 (47.6)	0 (0)	0 (0)	7 (36.8)	0 (0)	0 (0)	**<0.01**
FPG (mg/dL)	148.2 [102.2-286.8]	93.15[82.6 - 100.8]	89 [84.0-93.7]	122 [95-231]	85 [79-92]	81 [78.0-89.0]	254.1 [150.4-311.6]	100.7 [95.7-104.2]	89.9 [85.7-94.7]	**<0.01**
HbA1c (%)	8.1 [6.8-12.9]	5.7 [5.3 - 6.1]	5.1 [4.7-5.3]	7.6 [6.7-11.9]	6 [5.7-6.2]	5.5 [4.8-5.6]	10.8 [7.4-13.5]	5.1 [5.0-5.6]	5 [4.7-5.2]	**<0.01**
OGTT (mg/dL)	141 [111-189]	127.1 [105.8 - 156.3]	101.6 [83.3-117.7]	152 [109.0-196.5]	121 [100.0-153.0]	92.5 [75.0-109.0]	119.5 [119.5-119.5]	132.7 [108.5-157.4]	105.2 [85.8-121.4]	**<0.01**
Prior TB	17 (25)	15 (16.7)	14 (14.9)	12 (24.5)	7 (14.6)	4 (21.1)	5 (26.3)	8 (19.0)	10 (13.3)	0.23

BCG vaccination	50 (73.5)	76 (85.4)	86 (91.5)	33 (67.3)	38 (79.2)	15 (78.9)	17 (89.5)	38 (92.7)	71 (94.7)	**<0.01**
TB contact	16 (23.5)	24 (26.7)	43 (45.7)	13 (26.5)	15 (31.3)	3 (15.8)	3 (15.8)	9 (21.4)	40 (53.3)	**<0.01**
AFB smear										0.28
Negative	22 (32.4)	40 (44.4)	48 (51.6)	17 (34.7)	25 (52.1)	8 (42.1)	5 (26.3)	15 (35.7)	40 (54.1)	
Scanty	1 (1.5)	2 (2.2)	2 (2.2)	0 (0)	0 (0)	0 (0)	1 (5.3)	2 (4.8)	2 (2.7)	
1+	20 (29.4)	16 (17.8)	18 (19.4)	17 (34.7)	7 (14.6)	3 (15.8)	3 (15.8)	9 (21.4)	15 (20.3)	
2+	12 (17.6)	10 (11.1)	11 (11.8)	9 (18.4)	4 (8.3)	5 (26.3)	3 (15.8)	6 (14.3)	6 (8.1)	
3+	13 (19.1)	22 (24.4)	14 (15.1)	6 (12.2)	12 (25.0)	3 (15.8)	7 (36.8)	10 (23.8)	11 (14.9)	
L-J culture										**<0.01**
Negative	6 (8.8)	11 (12.5)	25 (27.5)	2 (4.1)	2 (4.2)	0 (0)	4 (21.1)	9 (22.5)	25 (34.7)	
Scanty	2 (2.9)	6 (6.8)	8 (8.8)	1 (2)	1 (2.1)	0 (0)	1 (5.3)	5(12.5)	8 (11.1)	
1+	31 (45.6)	39 (44.3)	41 (45.1)	19 (38.8)	21 (43.8)	8 (42.1)	12 (63.2)	18 (45)	33 (45.8)	
2+	22 (32.4)	13 (14.8)	7 (7.7)	20 (40.8)	9 (18.8)	4 (21.1)	2 (10.5)	4 (10)	3 (4.2)	
3+	4 (5.9)	17 (19.3)	7 (7.7)	4 (8.2)	13 (27.1)	4 (21.1)	0 (0)	4 (10)	3 (4.2)	

Data are represented as median with interquartile range [25th - 75th percentile] or frequency (percentage). Comparison of TB patients between Brazil and Peru and glycemic groups was performed using Kruskal-Wallis Test for quantitative variables and the Mantel-Haenszel Test for categorical variables. $P < 0.05$ was considered statistically significant. Comorbidities: Renal disease and/or Asthma and/or Hypertension; Smoking history: Past or current cigarette smoker; Illicit Drugs Use: Past or current illicit drug use (marijuana, cocaine, heroin or crack); Chronic Alcoholism: Past or current any consumption of alcohol; Metformin use: Metformin use in patients with dysglycemia; Prior TB: previous diagnosis of active tuberculosis; DM: Diabetes; PDM: Prediabetes; FPG Fasting Plasma Glucose; HbA1c Glycated Hemoglobin; OGTT Oral Glucose Tolerance Test; BMI: Body Mass Index; BCG: Bacillus Calmette–Guérin; AFB Acid-Fast Bacilli; L-J Löwenstein-Jensen.

Heterogeneity in values from the glycemic screening laboratory tests between persons with TB from Brazil and Peru

FPG and HbA1c value distribution in patients from both countries are shown in **Figure 2**. To better understand the value distribution obtained in the distinct screening tests in the study populations, we initially segregated participants in two groups, including: (i) those with normoglycemia and (ii) individuals with dysglycemia (PDM or DM). Dysglycemia was more prevalent among Brazilian participants (83.6%) (**Figure 2A**). However, FPG levels in this group showed that most individuals with dysglycemia presented values under the reference baseline, whereas, in Peru, 70.5% of patients with DM/PDM exhibited values above the limit for dysglycemia with this marker (**Figure 2A**). Comparison of FPG median values also displayed differences between countries ($p<0.05$), with higher levels found in the Peruvian cohort (**Figure 2C**). On the other hand, HbA1c levels had an inverse distribution in both populations (**Figure 2B**), in which Brazilians presented the vast majority of values above the reference for DM/PDM diagnosis. In addition, the median values of HbA1c showed to be significantly increased among Brazilians in comparison with Peru ($p<0.001$) **(Figure 2D)**. These results suggest that the glycemic screening methods showed a distinct behavior according to the country.

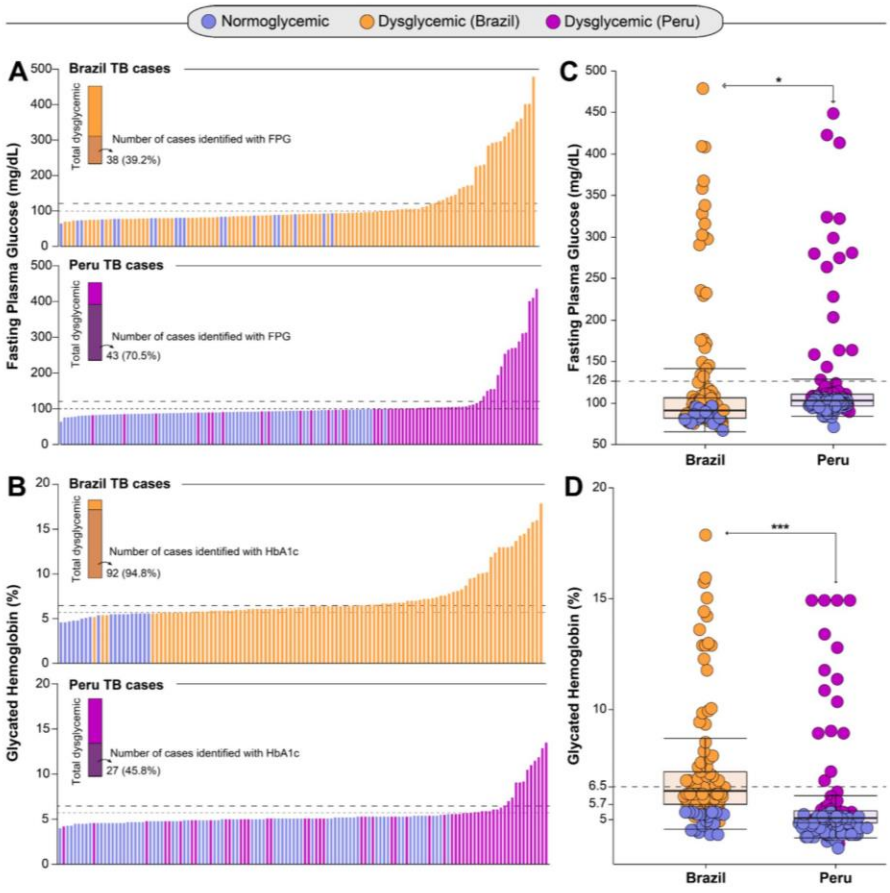

Figure 2. Differences in distribution of Fasting Plasma Glucose and Glycated Hemoglobin levels in TB patients stratified by country. (A) Distribution of FPG levels of TB patients in Brazilian and Peruvian populations are shown. (B) Distribution of values obtained in HbA1c test in TB cases in Brazil and Peru are exhibited. The patients are colored according to the glycemic status. Reference intervals marking dysglycemia are displayed by transversal lines, where lower limit representing its reference for prediabetes, and upper limit representing its reference for diabetes. Box plots depicting the distribution of the FPG values (C) as well as levels of HbA1c (D) in the subgroups of Brazilian and Peruvian populations amongst TB patients are shown. The differences in median values (and IQR) of FPG and HbA1c between groups were compared using

the Mann-Whitney *U* test. (*p<0.05, ***p<0.001). Dysglycemic: prediabetes and diabetes; FPG: Fasting Plasma Glucose; HbA1c: Glycated Hemoglobin.

Glycemic screening methods among TB cases

Next, we aimed to evaluate FPG and HbA1c level distribution according to the following groups: TB, TB-DM and TB-PDM. (**Figure 3**). Using a demographic density analysis with histograms, we found a similar distribution of FPG values and HbA1c percentage on both countries, where TB normoglycemic participants demonstrated a peak curve in lower FPG levels, followed by TBPDM (**Figure 3A**). Of note, our findings revealed that the TBDM group displayed wider distribution in both country curves (**Figure 3A**).

To better understand the differences in the glycemic markers according to TB-DM comorbidity between the two countries, we compared the levels of FPG and HbA1c in TB, TB-PDM and TB-DM groups in Brazil and Peru (**Figure 3B**). In all clinical groups, levels of FPG were higher among the Peruvians, whereas Brazilians displayed higher HbA1c values, except for the TBDM group (**Figure 3B**).

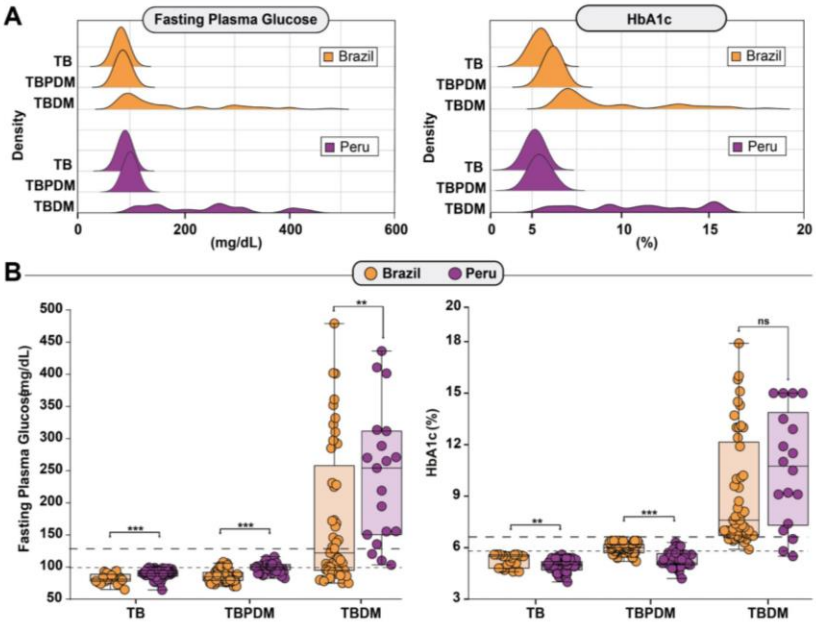

Figure 3. Dissimilarities over distribution of glycemic markers in TB patients stratified by glycemic status in Brazil and Peru. (A) Data show distribution of Fasting Plasma Glucose and Glycated Hemoglobin levels obtained in TB patients from both countries. TB patients were stratified according to glycemic status, in normoglycemic, Prediabetes and Diabetes Mellitus. (B) Box plot of glycemic markers represent distribution of the values obtained in Hb1Ac (left panel) and FPG (right panel) tests of TB patients stratified based on their DM status. Reference intervals marking dysglycemia are displayed by transversal lines, where lower limit points its reference for prediabetes, and upper limit its reference for diabetes. Box plots represent the distribution of the tests results between study groups (with medians, interquartile ranges, and top and lowest values). Differences between groups were tested using the Mann-Whitney U test (*p<0.05. **p<0.01. ***p<0.001). TB: Tuberculosis; TB-PDM: Tuberculosis and Prediabetes and TBDM: Tuberculosis and Diabetes Mellitus; non-DM/PDM: normoglycemic; PDM: prediabetes; DM: Diabetes Mellitus; FPG: Fasting Plasma Glucose (mg/dL; Y axis scale follows a geometric progression of ratio 2); HbA1c: glycated hemoglobin (%).

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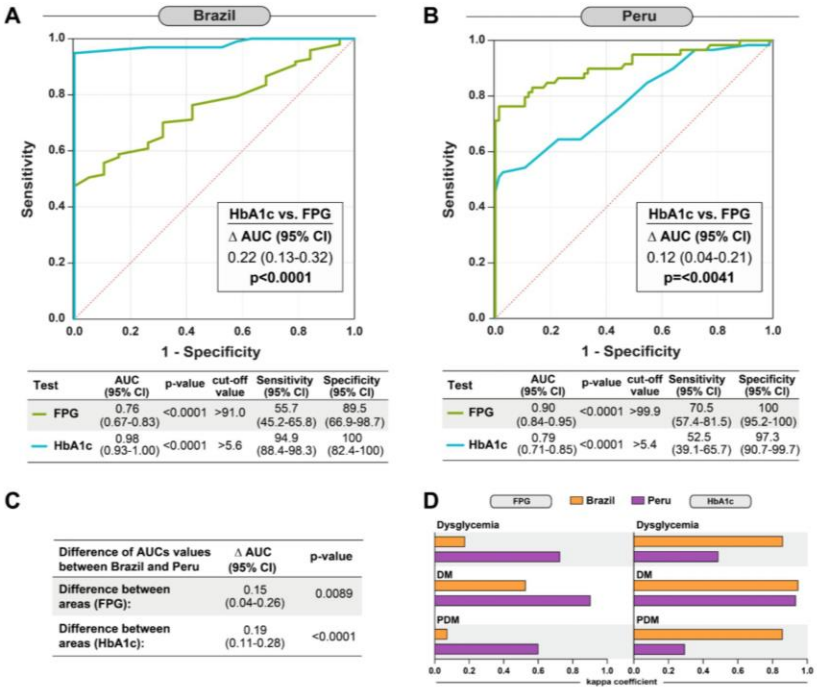
339 **Distinct accuracy of glycemic screening methods in dysglycemia diagnosis**
340 **among TB South American individuals.**
341 In order to extend our investigations concerning the discriminative performance
342 of glycemic markers to diagnose dysglycemia in TB patients, a receiver operating
343 characteristic (ROC) curve analysis using values of the glycemic markers was
344 employed in each country (**Figure 4**). HbA1c exhibited a good performance to
345 identify dysglycemia the Brazilian cohort, with an area under curve (AUC) of 0.98
346 (95% confidence interval (CI):0.93-1.00) (**Figure 4A**), whereas FPG
347 demonstrated superior performance among Peruvians (AUC: 0.90; 95%CI, 0.84-
348 0.95) (**Figure 4B**). We next compared the different cohorts with regard to the
349 performance of the FPG or HbA1c tests in distinguishing dysglycemia and found
350 substantial differences between the AUC ($p=0.0089$ and $p<0.0001$
351 correspondingly) (**Figure 4C**). This finding reinforces the idea that there are
352 important discrepancies in the overall accuracy of the FPG and of HbA1c tests to
353 identify individuals with prediabetes or diabetes between Brazilians and
354 Peruvians.
355
356 Finally, additional comparisons were made to narrow down the concordance
357 between HbA1c and FGP to detect diabetes or prediabetes in the study
358 populations. We noted that the FPG test had a good degree of agreement in the
359 Peruvian cohort for identification of dysglycemia cases ($k=0.77$) or PDM ($k=0.6$),
360 and very good degree for identification of DM individuals ($k=0.96$). Interestingly,
361 for Brazilian cohort the degree of concordance for identification of dysglycemia or
362 PDM was poor ($k=0.20$ and $k=0.08$, correspondingly) and for DM it was moderate
363 ($k=0.11$) (**Figure 4D**). In contrast, the HbA1c test exhibited a very good
364 agreement in the Brazilian cohort to detect dysglycemia ($k=0.83$), DM ($k=0.98$) or
365 PDM ($k=0.84$). Meanwhile, in the Peruvian cohort, the agreement for dysglycemia
366 was moderate ($k=0.44$), for DM it was very good ($k=0.97$) and for PDM it was just
367 fair ($k=0.35$).



Test	AUC (95% CI)	p-value	cut-off value	Sensitivity (95% CI)	Specificity (95% CI)
FPG	0.76 (0.67-0.83)	<0.0001	>91.0	55.7 (45.2-65.8)	89.5 (66.9-98.7)
HbA1c	0.98 (0.93-1.00)	<0.0001	>5.6	94.9 (88.4-98.3)	100 (82.4-100)

Test	AUC (95% CI)	p-value	cut-off value	Sensitivity (95% CI)	Specificity (95% CI)
FPG	0.90 (0.84-0.95)	<0.0001	>99.9	70.5 (57.4-81.5)	100 (95.2-100)
HbA1c	0.79 (0.71-0.85)	<0.0001	>5.4	52.5 (39.1-65.7)	97.3 (90.7-99.7)

Difference of AUCs values between Brazil and Peru	Δ AUC (95% CI)	p-value
Difference between areas (FPG):	0.15 (0.04-0.26)	0.0089
Difference between areas (HbA1c):	0.19 (0.11-0.28)	<0.0001

Figure 4. Accuracy disagreement on diagnose of glycemic disorders by FPG and HbA1c markers stratified by country. Receiver Operator Characteristics (ROC) curve analysis was employed to determine the accuracy of glycemic markers to predict dysglycemia in TB patients, using fasting glucose levels (FPG) and glycated hemoglobin (Hb1Ac), in Brazil (A) and Peru (B). Differences of area under the ROC curve (AUC) values were also assessed, with p-values and z statistic results referring to comparisons within Brazilian (A) and Peruvian (B) cohorts and between countries (C). (D) Kappa statistics was performed to analyze agreement of glycemic markers for diagnosis of dysglycemia, DM and PDM. Data represent the kappa coefficient in each country. Dysglycemic: prediabetes and diabetes; DM: diabetes mellitus; PDM: prediabetes; FPG: fasting Plasma Glucose; HbA1c: glycated Hemoglobin.

DISCUSSION

The findings presented here depict a detailed investigation of the performance of two tests widely used for assessment of dysglycemia among PWTB from Brazil and Peru. The studied countries represent an expressive portion of TB cases and around of 50% of Latin American cases in the world, with also elevated prevalence of DM and PDM [1,8,22]. As discussed, PWTB with concurrent uncontrolled glycemic status have an increased risk of increased morbidity and poor treatment outcomes [25,26]. Therefore, there is an urgent need for systematic screening of dysglycemia in PWTB, in order to reach those at highest risk of disease complications. Understanding the peculiarities of diagnosing dysglycemia in TB cases in different populations is key to develop focused control strategies adapted to local epidemiological trends.

Our analyses revealed that the accuracy of HbA1c and FPG to diagnose dysglycemia in PWTB differs between Brazil and Peru, with a better performance of HbA1c in Brazil and FPG in Peru. Findings from studies in other countries reinforce the idea that there is heterogeneity in performance of DM screening tests in PWTB. A study from India has demonstrated that HbA1c performed better than FPG with an AUC of 0.754 (0.682-0.828) for newly diagnosed DM among subjects with TB [13]. Furthermore, a Pakistan study showed that the proportion of participants falsely classified as positive was higher for FPG, although the performance of HbA1c and FPG had no differences in terms of diagnosing new DM cases [17]. In a recent study, FPG levels were able to detect more cases of PDM in PWTB from Peru than HbA1c [2]. In a Chinese study, FPG performed better than HbA1c in identifying newly diagnosed DM and PDM [27]. Such peculiarities in test performance to diagnose dysglycemia reported in different countries may be determined by genetics, environmental factors or a combination of both and should be explored in future mechanistic studies.

Previous studies have shown that HbA1c values vary according to ethnicity, even in individuals without dysglycemia [28,29]. Moreover, abnormalities of erythrocyte indices are considerable confounders in the analysis of HbA1c [30]. Possible explanations for this could be hemoglobin-related factors such as red cell turnover, variations in hemoglobin glycation, differences in the passage of

glucose mediated by GLUT1 transporter into the erythrocyte, higher prevalence of hemolytic conditions such as glucose-6-phosphate dehydrogenase deficiency or sickle cell trait, among others [29,31]. Genetic factors can also modulate HbA1c levels with heritability of 47% to 59% [32]. Interestingly, a genetic risk score, based on the 14 single nucleotide polymorphisms (SNPs) found that some people had a higher genetic risk of higher levels of fasting plasma glucose [33]. Regarding DM in PWTB, a multicentric prospective study compared the accuracy of random plasma glucose, point-of-care HbA1c, FPG, urine dipstick, risk scores and anthropometric measurements, using HbA1C as a golden standard. They also found heterogeneous performance of laboratory markers to diagnose DM across countries [12].

More than identifying the reasons for HbA1c variation among populations, it is essential to know what the clinical importance of these findings is. It is still under discussion how this variation in test performance can affect DM outcomes, but some studies have found no difference in long term risk for cardiovascular disease, final-stage renal disease and retinopathy [29,34,35]. To our knowledge, no studies to date have evaluated the influence of HbA1c accuracy variation in TB outcomes. A previous study reported higher HbA1c values being predictive of unfavorable outcomes in PWTB [36], but there was no comparison between populations with distinct genetic backgrounds.

The ADA guidelines for DM recommends that any of three diagnostic test mentioned in this study can be used to diagnose DM [19]. The Brazilian guidelines use the same criteria as ADA and the Peruvian guidelines have not included HbA1c as a diagnostic tool because of its low availability in the public health system and lack of standardization in the country [37,38]. Our findings suggest that the use of HbA1c should be used with caution in the diagnosis, as the cutoff is still inconsistent and may vary in dissimilar populations. It is possible that different thresholds need to be used in different populations.

More research needs to be done in evaluating the impact of variability in DM screening test accuracy in TB treatment outcome. Moreover, additional studies are required to define the most reliable screening methods for each population.

As an example, Grint D, et al tested a combination of two tests that increased DM diagnosis accuracy in PWTB from Peru and Indonesia, but not in other countries [12]. Meanwhile, standard diagnostic thresholds should be used with caution, particularly in the population with greater variability of tests results. Clinicians should also be attentive for factors that are predictors of high glycemia, such as older age, hypertension, and increased body mass index [28] and repeat or associate a different method when there is high pre-test probability of dysglycemia.

Common limitations of retrospective investigations should be acknowledged in our study. Our investigations could not determine the major factors responsible for the heterogeneity observed between countries, concerning ethnicity, severe anemia, and genetic variations in hemoglobin. Additionally, the dissonances found regarding the distinct glycemic status on each group analyzed may have affected the accuracy of our findings in terms of confidence intervals. Finally, there was not a gold standard such as OGTT test used for the evaluation of accuracy. Nevertheless, given our diversified and well characterized cohorts, our conclusions do extend the current knowledge in the field by demonstrating a significant variability in accuracy of FPG and HbA1c to diagnose dysglycemia in TB patients across countries.

Our findings provide relevant insights over the significance of intrinsic elements of each population when choosing the most reliable laboratory method for screening and diagnosis of glycemic disorders in PWTB. The analysis presented here demonstrate different discriminative results for dysglycemia diagnosis among individuals with TB, remarkable by a superior performance of HbA1c in Brazil, whilst FPG presented a better accuracy within Peruvians.

480 **NOTES**
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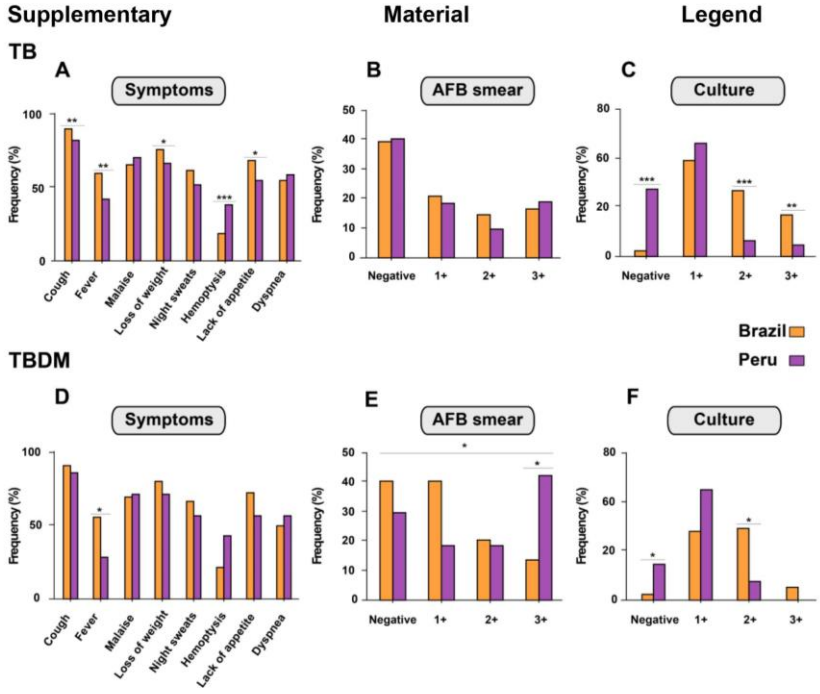

Supplementary Figure 1. Clinical and microbiological profiles of patients with TB and TB-DM compared between the Peruvian and Brazilian patients. Prevalence of indicated TB-related symptoms were compared between the study groups in all TB patients (A) and in TBDM comorbidity cases (D). AFB distribution profile in Peruvian and Brazilian patients in TB without DM (B) and in TBDM patients (E) was presented. Frequency of TB patients with different culture smear grades in sputum compared to the nationality is shown in TB (C) and TBDM groups (F). Data were analyzed using Pearson's chi-square test. TB: tuberculosis. TBDM: comorbidity tuberculosis and diabetes mellitus. AFB: acid-fast bacilli. BR: Brazil. PE: Peru. *p < 0.05. **p < 0.01. ***p < 0.001.

6.9 MANUSCRITO IX

High prevalence and heterogeneity of dysglycemia in patients with tuberculosis from Peru: a prospective cohort study

O estudo anterior demostrou as diferencias importantes entre os métodos diagnósticos entre o Brasil e o Peru. O Peru é o segundo país das Américas em incidência de TB. No programa nacional de controle à TB do país, a triagem para DM é altamente recomendada, dadas as complicações que têm sido observadas em pacientes com a associação TB-DM. Esse estudo expandiu nossas observações para termos de um melhor entendimento sobre a prevalência de DM e pré-DM pacientes com TB ativa atendidos em Lima, Peru.

Resumo dos resultados: Foi identificada uma alta prevalência de DM (13,97%) e de pré-DM (30,88%) em pacientes com TB. Nos contatos destes pacientes, a prevalência de Dm e pré-DM foram de 6,52% e 28,99%, respectivamente. A anemia esteve fortemente associada à TB-DM, o que possivelmente influenciou o desempenho diagnóstico da HbA1c nessa população.

O resumo do manuscrito foi aceito no *50th Union World Conference on Lung Health*, outubro 2019 e apresentado no Webinar -*Tuberculosis y Diabetes , Socios En Salud Sucursal Perú* em abril 2020

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RESEARCH ARTICLE Open Access

High prevalence and heterogeneity of Dysglycemia in patients with tuberculosis from Peru: a prospective cohort study

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Abstract

Background: The accuracy of different laboratory tests for diagnosis of diabetes mellitus (DM) and prediabetes (preDM) in populations exposed to tuberculosis (TB) remains poorly understood. Here, we examined the prevalence of DM and preDM in TB affected people in Lima, Peru.

Methods: A prospective cohort study of patients affected TB and their household contacts (HHC), was conducted between February and November 2017 in Lima, Peru. Fasting plasma glucose (FPG), HbA1c and oral glucose tolerance test (OGTT) were used to detect DM and preDM in a prospective cohort of TB patients ($n = 136$) and household contacts ($n = 138$). Diagnostic performance of the laboratory tests was analyzed. Potential effects of sociodemographic and clinical factors on detection of dysglycemia were analyzed.

Results: In TB patients, prevalence of DM and preDM was 13.97 and 30.88% respectively. Lower prevalence of both DM (6.52%) and preDM (28.99%) were observed in contacts. FPG, HbA1c and OGTT had poor agreement in detection of preDM in either TB cases or contacts. TB-DM patients had substantially lower hemoglobin levels, which resulted in low accuracy of HbA1c-based diagnosis. Classic sociodemographic and clinical characteristics were not different between TB patients with or without dysglycemia.

Conclusion: High prevalence of DM and preDM was found in both TB patients and contacts in Lima. Anemia was strongly associated with TB-DM, which directly affected the diagnostic performance of HbA1c in such population.

Keywords: Diabetes mellitus, Prediabetes, Tuberculosis, Comorbidity, Prevalence

Background

Tuberculosis kills 1–2 million people per year, especially in low and middle-income countries, and despite recent efforts to improve control programs, its incidence is declining at slow rates [1]. High-risk groups undermine the success of TB programs in the reducing the disease burden notwithstanding targeted interventions. One relevant aspect is diabetes mellitus (DM), which increases the risk of developing active TB in approximately three times [2]. More recently, prediabetes (preDM) has been also described as a risk factor for developing TB [3, 4]. Both the World Health Organization (WHO) as the Peruvian National TB Program (NTP) recommend screening for DM in people with active TB and for TB between household contacts [5]. Despite those indications, most individuals are unaware of their DM or pre-DM status. In 2017, the Peruvian NTP communicated a DM incidence of 6.2% with a testing coverage of 77.9% of all TB patients whereas other instances of the national government reported in 2016 a DM incidence around 10.4% (government communication). Those differences may reflect several limitations in the DM screening such as the use of only fasting plasma glucose (FPG) as the screening approach [5]. It is widely known that sensitivity of DM tests (such as HbA1c, fasting glucose and oral glucose tolerance) is variable [6–9]. It has been reported that HbA1c detects more people with DM [10] (or preDM) with higher sensitivity than other

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screening tests [11], so systematic use of FPG as screening tool, as observed in Peru, may result in incomplete record of TB-DM cases [12].

Due the discrepancies in sensitivity of DM screening tests and in order to determine the real prevalence of DM or preDM in TB patients and their household contact (HHC), we conducted a study in Lima, Peru, with the hypothesis that both DM and pre-DM are more frequent than previously officially reported. In addition, we compared the performance of different screening methods to detect DM and preDM in TB cases. Furthermore, we examined the associations between different other clinical and sociodemographic risk factors with the possible more extended comorbid TB-DM burden.

Methods

Study design

This was a prospective cohort study of patients affected TB and their household contacts (HHC), conducted between February and November 2017 in Lima, Peru. The recruitment details, as well as the procedures and investigations performed are outlined in Fig. 1a-b.

Study population

The study was carried out in the Public Hospital Sergio Bernales and outpatient health centers of Carabayllo and Comas districts. Patients with pulmonary TB with ≥16 years of age diagnosed by the NTP of public health centers, who are not receiving anti-TB treatment or have started it in a period of no more than 5 days, were included. In this study, HHC was defined as a person 12 years of age or older who shared at least household where they sleep or take their meals (at least one of them per day) with a study TB index patient. Exclusion criteria were patients or contacts diagnosed with HIV, pregnant women, who did not live permanently in the jurisdiction area of the study and patients who had infection or disease due to non-tuberculous mycobacteria. The follow-up of those patients was conducted up to 6 to 12 months after enrollment.

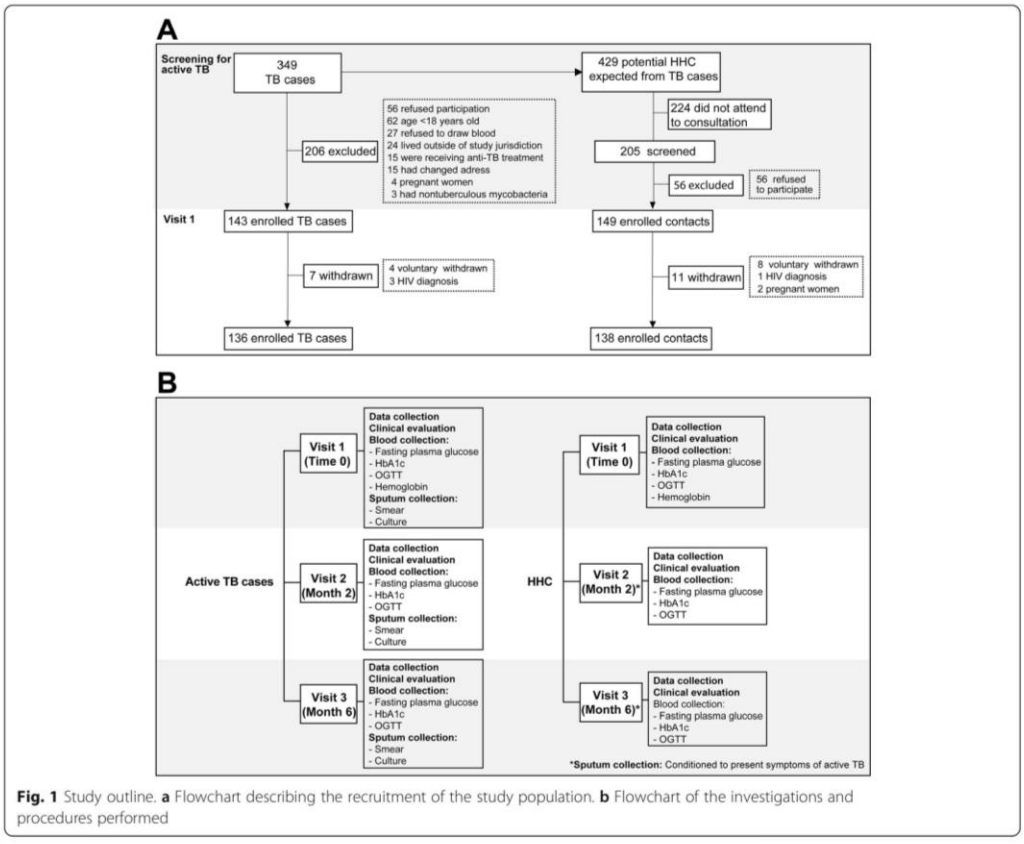

Fig. 1 Study outline. **a** Flowchart describing the recruitment of the study population. **b** Flowchart of the investigations and procedures performed

multiple comparisons (Bonferroni's method) were considered statistically significant. Statistical analyses were performed using SPSS 24.0 (IBM statistics), Graphpad Prism 7.0 (GraphPad Software, San Diego, CA) and JMP 13.0 (SAS, Cary, NC, USA).

Results

We initially screened 349 microbiologically-confirmed TB cases at the primary health care centers which were part of the present study, between February and November 2017. During the screening, 206 individuals were excluded for a number of reasons listed in Fig. 1a, and 143 patients with active TB were examined in the first study visit (Fig. 1a and Fig. 1b). At this stage, additional 7 persons were excluded due to HIV diagnosis ($n = 3$) and consent withdraw ($n = 4$), resulting in a cohort of 136 patients. During the search of HHCs of the TB index cases, 205 people were identified for screening and only 149 were effectively screened. Of those, 8 withdrew consent and 3 were excluded for having positive HIV status ($n = 1$) or pregnancy ($n = 2$) resulting in a total of 138 HHC participants (Fig. 1).

At enrollment, the DM prevalence was 13.97% (95% CI: 8.14, 19.80%) ($n = 19$) among TB patients (all of whom refereed DM diagnosed prior to study enrollment), while the prevalence of DM among HHC was 6.52% (95% CI: 2.40, 10.64%) ($n = 9$). The prevalence of preDM was 30.88% (95% CI: 23.81, 38.65%) in TB patients ($n = 42$) and 28.99% (95% CI: 21.42, 36.56%) among the HHC ($n = 40$). Diagnosis of preDM was performed at study enrollment. Comparisons at this timepoint revealed that TB and HHC groups exhibited similar frequencies of DM and preDM (Fig. 2a). After 2 months of antitubercular treatment (ATT) commencement, DM frequency was nearly double in TB vs. HHC whereas preDM was higher in the latter group (Fig. 2a). At month 6 of ATT, frequency of DM and preDM was once again not different between the study groups, although there was a remarkable 75% loss to follow-up in the HHC group at this timepoint (Fig. 2a).

Among the TB index cases at study baseline, DM individuals were on average older than preDM and normoglycemic individuals (median age: 46.41 yrs. IQR:33.5–54.8 vs. 39.8 yrs., IQR: 26.7–54.0 and 26.4 yrs. IQR: 22.3–34.7, respectively, $p < 0.01$) (Table 1). In addition,

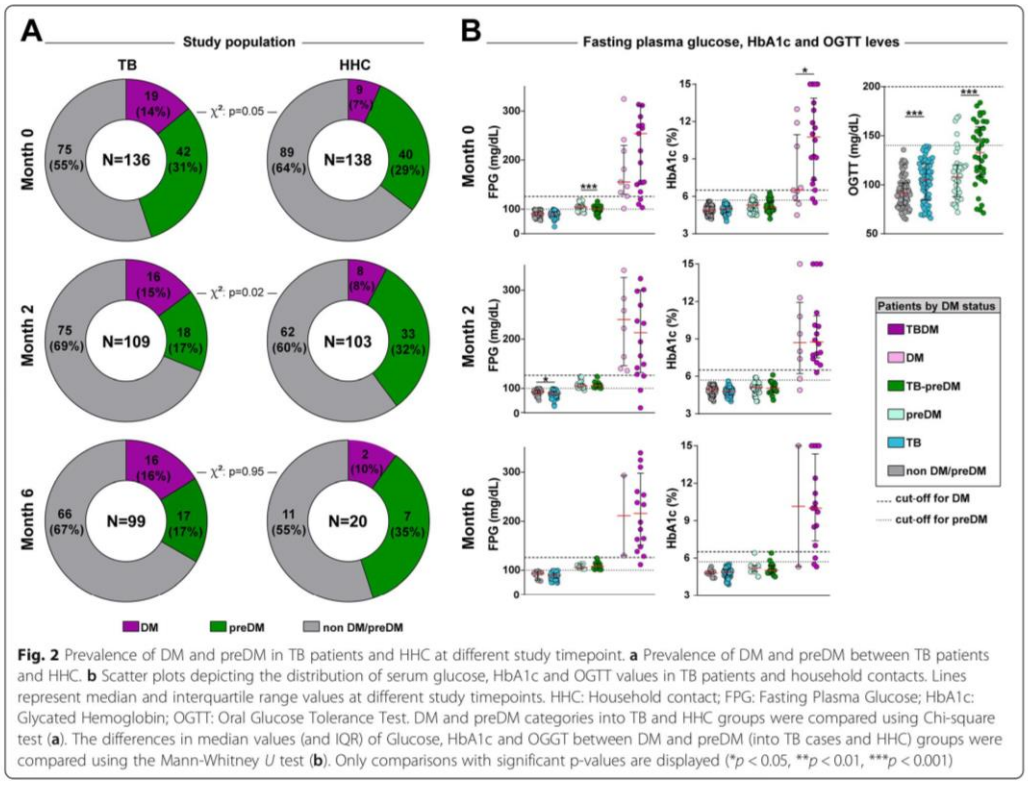

Fig. 2 Prevalence of DM and preDM in TB patients and HHC at different study timepoint. **a** Prevalence of DM and preDM between TB patients and HHC. **b** Scatter plots depicting the distribution of serum glucose, HbA1c and OGTT values in TB patients and household contacts. Lines represent median and interquartile range values at different study timepoints. HHC: Household contact; FPG: Fasting Plasma Glucose; HbA1c: Glycated Hemoglobin; OGTT: Oral Glucose Tolerance Test. DM and preDM categories into TB and HHC groups were compared using Chi-square test (**a**). The differences in median values (and IQR) of Glucose, HbA1c and OGGT between DM and preDM (into TB cases and HHC) groups were compared using the Mann-Whitney *U* test (**b**). Only comparisons with significant p-values are displayed (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$)

Table 1 Characteristics of pulmonary TB cases stratified according to glycemic status

Characteristics	n/N	TBDM	TBpreDM	Normoglycemic	*p*-value
		n = 19	*n* = 42	*n* = 75	
Age (years)-median (IQR)	136/136	46.41 (33.5–54.8)	39.8 (26.7–54.0)	26.4 (22.3–34.7)	**< 0.01**
Gender	136/136				0.354
Male	136/136	9 (47.4)	27 (64.3)	47 (62.7)	
Female	136/136	10 (52.6)	15 (35.7)	28 (37.3)	
Prior TB	136/136	5 (26.3)	8 (19.0)	10 (13.3)	0.158
BCG vaccination	135/136	17 (89.5)	38 (92.7)	71 (94.7)	0.411
Smoking	135/136	4 (21.1)	10 (24.4)	15 (20.0)	0.767
Smokers at home	135/136	2 (10.5)	4 (9.8)	5 (6.7)	0.499
Cannabis use	135/136	1 (5.3)	7 (17.1)	13 (17.3)	0.283
Illicit drug use	135/136	2 (10.5)	7 (17.1)	8 (10.7)	0.707
Alcohol use	135/136	4 (21.1)	29 (70.7)	37 (49.3)	0.348
Hypertension	135/136	4 (21.1)	3 (7.3)	0 (0.0)	**< 0.01**
Asthma	135/136	0 (0.0)	3 (7.3)	5 (6.7)	0.399
Renal disease	135/136	1 (5.3)	0 (0.0)	2 (2.7)	0.844
Slow scarring	135/136	3 (15.8)	9 (22.0)	7 (9.3)	0.186
Metformin use	132/136	7 (36.8)	0 (0.0)	0 (0.0)	**< 0.01**
BMI (kg/m2)-median (IQR)	132/136	22.3 (21.4–26.4)	23.2 (21.2–25.1)	22.3 (20.3–25.4)	0.749
Waist circumference (cm) -median (IQR)	132/136	85 (81–89)	88 (80–91)	83 (76–88)	0.058
Hb (g/dL) -median (IQR)	134/136	9.9 (7.6–13.4)	12.0 (10.8–13.1)	12.6 (11.3–13.4)	
Anemia	136/136	19 (100)	31 (73.8)	49 (66.2)	**0.006**
FPG (mg /dL) -median (IQR)	136/136	218.9 (147.7–298.1)	103.1 (100.4–106.3)	89.7 (85.6–93.9)	**< 0.01**
HbA1c (%)-median (IQR)	134/136	10.8 (7.4–13.5)	5.1 (4.8–5.5)	5.00 (4.6–5.1)	**< 0.01**
OGTT (mg/dL) -median (IQR)	112/136	119.5 (119.5–119.5)	128.5 (106.5–157.1)	105.2 (85.8–121.4)	**< 0.01**
AFB smear	135/136				**0.004**
Negative		5 (26.3)	15 (35.7)	40 (54.1)	
1+		3 (15.8)	9 (21.4)	15 (20.3)	
2+		3 (15.8)	6 (14.3)	6 (8.1)	
3+		7 (36.8)	10 (23.8)	11 (14.9)	
Scanty		1 (5.3)	2 (4.8)	2 (2.7)	
L-J culture	131/136				0.59
Negative		4 (21.1)	9 (22.5)	25 (34.2)	
1+		12 (63.2)	18 (45.0)	33 (45.2)	
2+		2 (10.5)	4 (10.0)	3 (4.2)	
3+		0 (0.0)	4 (10.0)	3 (4.2)	
colonies		1 (5.3)	5 (12.5)	8 (11.1)	
BD MGIT™ 960 System	78/136				0.11
Positive		8 (80.0)	22 (81.5)	34 (82.9)	
Negative		2 (20.7)	5 (18.5)	7 (17.1)	
MDR	76/136	2 (18.2)	3 (12.5)	4 (9.8)	0.451
Isoniazid-resistant	76/136	2 (18.2)	5 (20.8)	7 (17.1)	0.831
Rifampicin-resistant	76/136	2 (18.2)	4 (16.7)	5 (12.2)	0.55
TB treatment outcome	115/136				0.64
Poor		5 (27.8)	8 (23.5)	14 (22.2)	

Table 1 Characteristics of pulmonary TB cases stratified according to glycemic status *(Continued)*

Characteristics	n/N	TBDM	TBpreDM	Normoglycemic	*p*-value
		n = 19	*n* = 42	*n* = 75	
Cure		13 (72.2)	26 (76.5)	49 (77.8)	
Polyuria	136/136	9 (47.4)	16 (38.1)	28 (37.3)	0.493
Polydipsia	136/136	9 (47.4)	20 (47.6)	36 (48.0)	0.956

Data represent no. (%); IQR: Interquartile range. *BCG* Bacillus Calmette–Guérin, *BMI* Body Mass Index, *Hb* Hemoglobin, *FPG* Fasting Plasma Glucose, *HbA1c* Glycated Hemoglobin, *OGTT* Oral Glucose Tolerance Test, *AFB* Acid-Fast Bacilli, *L-J* Löwenstein-Jensen, *MDR* Multi Drug Resistant. Hypertension, asthma, renal disease and anemia as defined by the World Health Organization as described in Methods. Prior TB: diagnosis of active tuberculosis before of this

lower level of education (primary and secondary school years) was associated with presence of dysglycemia (DM or preDM) ($p < 0.01$; Table 1). Hypertension was more frequently in DM patients (21.1%) than that in normoglycemic TB cases (7.3%) ($p < 0.01$). The study groups were similar with regard to a number of other characteristics including sex, history of prior TB, asthma, renal disease and lifestyle habits (alcohol use, smoking and illicit drugs use) (Table 1).

When the cohort of HHC was stratified according to the glycemic status, we found once again that DM patients were on average older than those with preDM or normoglycemia (Table 2). In addition, the highest values of body mass index (BMI) and waist circumference were detected in the subgroup of preDM HHC (Table 2). Other characteristics were similar between the HHC subgroups.

The FPG and HbA1c tests were performed prospectively in all patients recruited (except OGTT for known DM cases). At the baseline visit, as expected, TB patients with coincident DM exhibited higher values of FPG and HbA1c than those diabetic but without TB (Fig. 2b). Such discrepancies in laboratory measurements were reduced at month 2 and 6 of ATT and no statistically significant differences were observed between diabetic patients with or without TB (Fig. 2b). The OGTT was performed only at baseline in patients without prior DM diagnosis. One individual was identified as having DM (from the HHC group). Once again, presence of TB was associated with higher values of OGTT results than in HHC individuals, suggesting that Mtb infection may drive inflammation-associated dysglycemia [19, 20] (Fig. 2b).

Moreover, the frequencies of TB-related symptoms between TB index cases with different degree of dysglycemia were compared and we found no statistically significant difference (Fig. 3a). Moreover, frequency patients presenting with increased acid-fast bacilli grades in sputum smears was higher in TB cases with DM compared to the other groups (chi-square $p = 0.004$; Fig. 3b). These findings indicate that TB clinical presentation is not worse in diabetics as we have previously demonstrated in different studies from Brazil [3, 19], but confirmed previously reported data showing increased mycobacterial loads in sputum smears [19].

Circulating hemoglobin levels were low in diabetic patients with coincident TB compared to those with preDM or normoglycemia (Fig. 4a and b). In fact, within the group of TB, anemia was detected in all diabetics but only in 73.8% of preDM ($n = 31$) and 66.2% of normoglycemic patients ($n = 49$) ($p = 0.006$). In HHC, diabetes was not associated with substantial changes in hemoglobin levels (Fig. 4a and b). Moreover, frequency of anemia was not different between the groups of TB contacts presenting with diverse degree of dysglycemia ($p = 0.08$). This finding suggested that a potential synergistic effect of DM and TB on the degree of anemia may exist. Indeed, results from FPG and HbA1c in TB patients demonstrated that values observed in DM were substantially higher than in preDM or normoglycemia, and similar trend was observed in OGTT between preDM and nondiabetics (Fig. 4c). Of note, in HHC, values of FPG and HbA1c were lower in anemic individuals compared to those with normal hemoglobin levels (Fig. 4c). Furthermore, OGTT levels were able to distinguish preDM from normoglycemia only in the subgroup of participants without anemia (Fig. 4c).

We next analyzed the overall accuracy of FPG and HbA1c in detecting DM or preDM cases in individuals stratified according to TB diagnosis (TB patients and HHC). FPG levels were able to detect more cases with preDM, but not with DM, than HbA1c did in the entire study population (Fig. 5a). When only TB cases were considered, again FPG was able to detect more preDM patients then HbA1c (Fig. 5b). Similar findings were observed in HHC (Fig. 5c). These results indicate that the laboratory tests examined here displayed different values of accuracy to detect DM or preDM in the study population. Summary of the accuracy and predictive values are shown in Additional file 1: Table S1. Concordance on DM diagnosis using either FPG or HbA1c levels was low, with lower performance of HbA1c (Fig. 6a). In addition, poor agreement was also observed between OGTT versus

Table 2 Characteristics of household contacts of pulmonary TB cases stratified glycemic status

Characteristics	n/N	DM	preDM	Normoglycemic	*p*-value
		n = 9	*n* = 40	*n* = 89	
Age (years) -median (IQR)	138/138	60.9 (57.5–68.0)	49.2 (40.0–57.3)	30.45 (65.83)	**< 0.01**
Gender	136/138				0.44
Male		5 (55.6)	21 (52.5)	30 (34.5)	
Female		4 (44.4)	19 (47.5)	57 (65.5)	
Education	138/138				0.207
Primary or secondary		9 (100.0)	33 (82.5)	71 (79.8)	
Technical or university		0 (0.0)	7 (17.5)	18 (20.2)	
Prior TB	135/138	2 (22.2)	3 (7.7)	9 (10.3)	0.618
BCG vaccination	135/138	9 (100.0)	36 (92.3)	84 (96.6)	0.752
Smoking	135/138	0 (0.0)	7 (17.9)	12 (13.8)	0.682
Smokers at home	135/138	2 (22.2)	6 (15.4)	11 (12.6)	0.427
Cannabis use	134/138	0 (0.0)	2 (5.1)	0 (0.0)	0.185
Illicit drug use	134/138	0 (0.0)	1 (2.6)	0 (0.0)	0.35
Alcohol use	134/138	2 (22.2)	22 (56.4)	25 (29.1)	0.134
Hypertension	135/138	0 (0.0)	6 (15.4)	6 (6.9)	0.647
Asthma	135/138	0 (0.0)	3 (7.7)	7 (8.0)	0.515
Renal disease	135/138	0 (0.0)	3 (7.7)	4 (4.6)	0.978
Slow scarring	135/138	2 (22.2)	3 (7.7)	6 (6.9)	0.229
Metformin use	133/138	2 (22.2)	0 (0.0)	0 (0.0)	**< 0.01**
Consanguinity with index case	135/138	3 (33.3)	3 (7.7)	15 (17.2)	0.96
BMI (kg/m2) -median (IQR)	133/138	29.41 (26.9–31.7)	29.8 (28.1–33.4)	26.1 (2.9–29.4)	**< 0.01**
Waist circumference (cm) -median (IQR)	133/138	95 (93–105)	98 (94–107)	88 (79–94)	**< 0.01**
Hb (g/dL) -median (IQR)	138/138	13.2 (12.9–13.7)	13.6 (12.8–14.6)	13.1 (12.1–14.2)	0.151
Anemia	138/138	2 (22.2)	8 (20.0)	35 (39.3)	0.138
FPG (mg /dL) -median (IQR)	138/138	155.60 (134.3–218.3)	104.6 (102.0–107.9)	90.9 (87.5–94.2)	**< 0.01**
HbA1c (%)-median (IQR)	138/138	6.5 (5.9–10.0)	5.3 (4.8–5.50)	4.9 (4.6–5.2)	**< 0.01**
OGTT (mg/dL) -median (IQR)	124/138	91.6 (70.3–107.10)	107.8 (87.7–119.8)	91.6 (78.9–101.9)	**< 0.01**
Polyuria	138/138	5 (55.6)	7 (17.5)	19 (21.3)	0.187
Polydipsia	138/138	3 (33.3)	14 (35.0)	19 (21.3)	0.124
Malaise	138/138	2 (22.2)	10 (25.0)	24 (27.0)	0.721

Data represent no. (%); *IQR* Interquartile range, *BCG* Bacillus Calmette–Guérin, *BMI* Body Mass Index, *Hb* Hemoglobin, *FPG* Fasting Plasma Glucose, *HbA1c* Glycated Hemoglobin, *OGTT* Oral Glucose Tolerance Test. Hypertension, asthma, renal disease and anemia as defined by the World Health Organization as described in Methods

HbA1c or FPG tests to detect preDM in both TB patients and HHC (Fig. 6b).

Discussion

Estimating the prevalence of dysglycemia among TB cases is important to understand the real burden of TBDM and drive changes to optimize detection and treatment of this comorbidity. In the present study, high prevalence of DM and preDM was found in both TB patients (14%) and HHC (6.5%), which is unexpectedly higher than previous reports from the Peruvian Minister of Health (6.2%) [21], but similar to results from a recent report [22]. In the last years, low and middle income countries, such as Peru, have experienced a nutritional transition [23]. These populations historically affected by hunger and malnutrition now face additional problems of obesity and other non-communicable diseases, such as diabetes and hypertension [24]. Because DM is a known risk factor of TB [2, 25, 26], systematic screening should be performed in high-risk populations. Nevertheless, maybe due to high cost, many countries do not perform systematic screening and for this reason the dual burden of TB and DM is likely still underestimated. Findings from this study and others [27, 28] argue that,

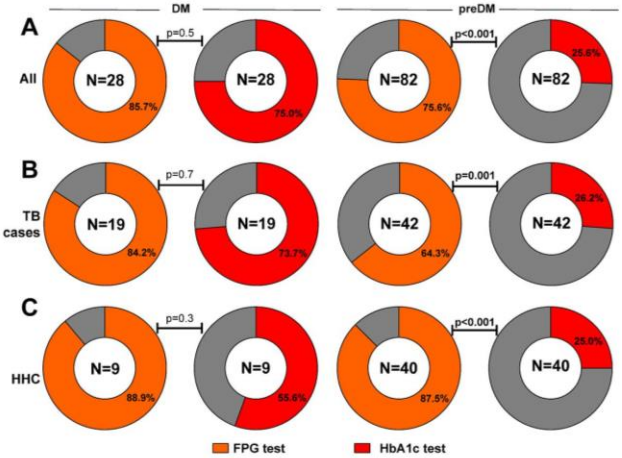

Fig. 5 Detection of diabetes and prediabetes using FPG or HbA1c. Frequency of individuals with diabetes (DM) or prediabetes (PDM) correctly diagnosed using either fasting plasma glucose (FPG) or HbA1c levels is shown for all participants (**a**) as well as for only TB patients (**b**) or household contacts (HHC) (**c**). Frequency of detection of DM or PDM between FPG and HbA1c was compared using the Fisher's exact test

[25]. In agreement with this idea, we have recently described in two distinct studies from Brazil that DM and also preDM were associated with increased frequency of clinical symptoms associated with TB [19]. Nevertheless, the association between DM and worse TB clinical and/or radiographic presentation has not been found by other investigations, including a recent study which examined Peruvian individuals [33]. It is possible that genetic or social differences between countries may influence the perception of the symptoms. Moreover, differences in timing from disease onset to admission at a TB clinical center may diminish the differences in clinical symptoms between normoglycemic and dysglycemic patients. Further studies are warranted to directly test these hypotheses. Interestingly, we found that TBDM patients exhibited increased AFB grades in sputum smears, which has been described by independent investigations worldwide [3, 19]. These findings reinforce the idea that DM may impact capability to restrain mycobacterial growth and thus may be associated with increased risk of transmission.

Anemia is a common clinical condition associated with TB [34]. It has been recently reported that chronic anemia is linked to a distinct systemic inflammatory profile that persists after 2 months of ATT in a Brazilian cohort [26]. In addition, hemoglobin levels have been described to affect detection of glycated hemoglobin, which brings potential challenges in DM diagnosis in patients with severe anemia [26]. Herein, all the TB-DM patients were anemic (median Hb level: 9.9 g/dL IQR: 7.6–13.4 g/dL). However, anemic status apparently did

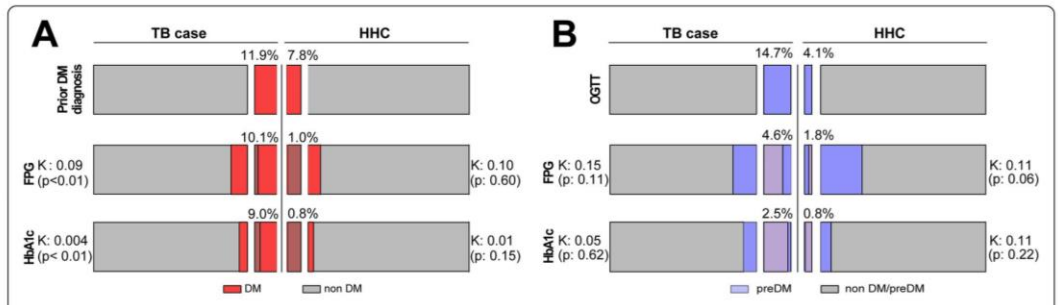

Fig. 6 Concordance Kappa (K) analysis between HbA1c, FPG and OGTT to detect diabetes or prediabetes in TB cases and HHC. **a** Results for TB cases (reference standard was prior DM diagnosis). **b** Results for HHC (reference value was OGGT). PD: Prior Diabetes Mellitus diagnosis; FPG: Fasting Plasma Glucose; HbA1c: Glycated Hemoglobin; OGTT: Oral Glucose Tolerance Test

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Publisher's Note

6.10 MANUSCRITO X

Severe pulmonary radiological manifestations are associated with a distinct biochemical profile in blood of tuberculosis patients with dysglycemia.

Acredita-se que a DM afeta a apresentação clínica TB e a resposta ao tratamento, porém poucos são os estudos acerca de como essa comorbidade afeta as manifestações radiológicas da TB pulmonar. Este estudo investigou o impacto do estado glicêmico nas manifestações radiológicas dos casos de TB pulmonar e sua relação com a concentração de parâmetros bioquímicos no sangue periférico.

Resumo dos resultados: A disglicemia (DM e pré-DM) afetou significativamente a apresentação das manifestações radiográficas e o número de lesões em pacientes com TB pulmonar, bem como o perfil bioquímico no sangue periférico. Pacientes com TB-DM/pré-DM apresentaram mais frequentemente infiltrados alveolares e tratos fibrosos do que aqueles com normoglicemia. Aqueles com maior número de lesões pulmonares exibiram um perfil laboratorial distinto, caracterizado por contagens de leucócitos e níveis circulantes de colesterol total, triglicerídeos e transaminases e, simultaneamente, níveis baixos de albumina e hemoglobina.

O resumo do manuscrito foi aceito no *50th Union World Conference on Lung Health*, 30 October to 02 November 2019

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Severe pulmonary radiological manifestations are associated with a distinct biochemical profile in blood of tuberculosis patients with dysglycemia

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Abstract

Background: Diabetes mellitus (DM) is thought to affect tuberculosis (TB) clinical presentation and treatment response. Whether DM impacts radiological manifestations of pulmonary TB is still not clear. This study investigated the impact of glycemic status on radiological manifestations of pulmonary TB cases and its relationship with concentration of biochemical parameters in peripheral blood.

Methods: A retrospective cross-sectional study used data from 132 microbiologically confirmed pulmonary TB patients from Lima, Peru, evaluated in a previous investigation performed between February and December 2017. Chest radiographs were analyzed by a radiologist and a pulmonologist. Radiographic lesions were identified as cavities, alveolar infiltrates and fibrous tracts. Hyperglycemia in TB patients was identified by use of fasting plasma glucose, HbA1c and oral glucose tolerance test. Clinical, biochemical and hematological parameters were also analyzed.

Results: TB patients with hyperglycemia presented more frequently with cavities, alveolar infiltrates and fibrous tracts than those with normoglycemia. Hierarchical clustering analysis indicated that patients with more diverse and higher number of lung lesions exhibited a distinct laboratorial profile characterized by heightened white blood cell counts and circulating levels of total cholesterol, triglycerides and transaminases and simultaneously low levels of albumin and hemoglobin. Multivariable regression analyses adjusted for age, sex, prior TB, hemoglobin levels and acid-fast bacilli ≥2+ in sputum smears, demonstrated that presence of prediabetes or diabetes in TB patients was associated with increased odds of having 3 pulmonary lesion types ($p = 0.003$ and $p < 0.01$ respectively) or ≥ 4 lesions ($p = 0.001$ and $p = 0.01$ respectively).

Conclusion: Hyperglycemia (both DM and prediabetes) significantly affected the presentation of radiographic manifestations and the number of lesions in pulmonary TB patients as well as the biochemical profile in peripheral blood.

Keywords: Chest x-ray, Hyperglycemia, Diabetes mellitus, Prediabetes, Pulmonary tuberculosis

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Background

The association between diabetes mellitus (DM) and tuberculosis (TB) has been re-called to attention in the 1980s, when the global prevalence of DM in adults increased by 20% in less than 30 years [1]. In recent years, hyperglycemia, which includes diabetes mellitus (DM) and prediabetes (PDM), has been reported to be very frequent in low and middle-income countries [2, 3] many of which are also endemic for TB [4, 5]. In Peru; this comorbidity has been recognized as an important issue since it challenges the success of TB control programs [6]. The Peruvian Ministry of Health has reported that the prevalence of DM in TB patients recently increased from 4 to 6.2% [7]. Conversely, in a recent study in Lima [8], we reported a much higher prevalence of DM (14%) and of PDM (31%) in TB patients. Both local and international agencies recommend both continuous screening for dysglycemia and tight glycemic control in people with active TB [9]. However, several factors limit the ability of individuals to properly monitor glycemic status/control [10, 11].

The mechanisms underlying the clinical outcomes of patients with TB-DM comorbidity are poorly understood. Poor glycemic control seems to exacerbate the clinical presentation of TB [12–14], increasing the frequency symptoms [11] and the radiographic manifestations of pulmonary TB [15]. Other studies, however, have failed to demonstrate that DM impacts radiographic signs of TB [16]. The radiology of thorax remains essential in the diagnosis of pulmonary TB. The clinical and radiological manifestations of pulmonary TB depend on the immune status of the infected host. Individuals with impaired immune responses, as observed in advanced HIV co-infection, commonly present with aberrant clinical and radiographic disease manifestations [17]. In different studies, DM has also been associated with a higher frequency of atypical radiological findings and cavitary tuberculosis [15], but there is still no consensus on whether TB-DM patients have worse radiographic disease. While some investigations have failed to demonstrate differences in frequency of lower lung lesions in TB-DM patients compared to those with normoglycemia [15], other studies have actually reported the opposite [18], suggesting that DM actually results in higher occurrence of typical cavitary lesions in TB patients [15, 18]. To better elucidate this question, we performed a study in which systematic radiographic evaluation was performed by both a radiologist and a pneumologist to describe the lung lesions in more details. We hypothesized that the radiographic manifestation of pulmonary TB is likely to be affected by dysglycemia (DM or PDM) in terms of types and number of lesions in patients from Peru.

Methods

Study design and settings

We performed a retrospective cross-sectional analysis of data collected originally from a larger prospective cohort study conducted between February and November 2017, which objective was to determine the prevalence of hyperglycemia in individuals with microbiologically confirmed pulmonary TB and their contacts [8]. For the present study, inclusion criteria were age ≥ 18 years of age, diagnosis performed by the National TB Program, patients who were not receiving anti-TB treatment or had started in no more than 5 days prior, and who had recorded chest X-rays analysis. The reason for excluding patients taking anti-TB treatment for more than 5 days was to minimize the exposure to the drugs, which has been shown to impact the glycemic status of patients after at least 2 weeks [19]. The study inclusion details of TB patients are outlined in Fig. 1. More information on patient evaluation, interviews and procedures have been published previously [8].

Laboratory and field procedures

All laboratory procedures were described in a previous publication [8]. All these tests were performed at the Socios En Salud (SES) Laboratory, located in Lima and graded following the standard recommendations [20–22]. Briefly, in all sputum samples, a direct examination (smear) was performed using the Ziehl-Neelsen staining and the semi-quantitative results were recorded. In parallel, a portion of the sputum samples was decontaminated with NAL-NaOH and then seeded in Lowenstein-Jensen medium or cultured using the BD MGIT 960 System (liquid culture). Confirmation of cultures which were positive for Mtb and drug sensitivity testing was then performed for the first line drugs rifampicin, isoniazid, ethambutol, streptomycin and pyrazinamide.

A panel composed by a pulmonologist and a radiologist analyzed and documented the readings from chest radiographs taken at the diagnosis. Cavities, infiltrates and fibrous tract were documented for the medical assessment in all study participants, based on Peruvian TB program guidelines [9]. Moreover, data on white blood cells count (WBC) as well as serum levels of hemoglobin (Hb), cholesterol (Chol), triglycerides (TG); alanine aminotransferase (ALT), aspartate aminotransferase (AST) and albumin were retrieved, reviewed and analyzed from the electronic medical records.

To determine the association of radiological manifestations with hyperglycemia, diagnosis of DM or prediabetes (PDM) was performed in agreement with American Diabetes Association (ADA) guidelines [4], and was based on fasting plasma glucose (FPG), glycated hemoglobin (HbA1c) and oral glucose tolerance test (OGTT) as previously described [8]. The measurement

Table 1 Characteristics of pulmonary TB cases stratified according to DM status in Lima, Peru, 2017

Characteristics	DM $n = 18$	PDM $n = 41$	Normoglycemia $n = 73$	*p*-value
Age (years)-median (IQR)	46.15 (36.64–58.28)	40 (26.67–53.89)	25.83 (21.05–30.92)	< 0.01
Sex				0.42
Male	8 (44.4)	28 (68.3)	45 (61.6)	
Female	10 (55.6)	13 (31.7)	28 (38.4)	
Education				< 0.01
Elementary and secondary school	17 (94.4)	36 (87.8)	45 (61.6)	
Higher education	1 (5.6)	5 (12.2)	28 (38.4)	
Prior TB	12 (66.7)	2 (4.9)	2 (2.7)	< 0.01
BCG vaccination	16 (88.9)	37 (92.5)	69 (94.5)	0.40
Smoking	4 (22.2)	9 (22.5)	15 (20.5)	0.82
Smoker at home	2 (11.1)	4 (10)	5 (6.8)	0.48
Cannabis use	1 (5.6)	6 (15)	13 (17.8)	0.23
Illicit drug use	1 (5.6)	7 (17.5)	8 (11)	0.92
Alcohol use	3 (16.7)	27 (67.5)	37 (50.7)	0.16
Hypertension	3 (16.7)	4 (10)	0 (0)	< 0.01
Asthma	0 (0)	3 (7.5)	4 (5.5)	0.57
Renal disease	1 (5.6)	0 (0)	1 (1.4)	0.41
Slow scarring	3 (16.7)	9 (22.5)	7 (9.6)	0.17
Metformin use	6 (33.3)	1 (2.7)	0 (0)	< 0.01
BMI (kg/m2)-median (IQR)	22.43 (21.41–26.36)	23.39 (21.53–25.04)	22.31 (20.25–25.39)	0.74
Waist circumference (cm) -median (IQR)	84 (80–89)	84 (77–90)	80 (74–86)	0.04
Hemoglobin (g/dL) -median (IQR)	10.55 (9.9–11.2)	11.8 (10.35–13.1)	12.6 (11.25–13.4)	< 0.01
FPG (mg /dL) -median (IQR)	259.55 (155.3–311.6)	100.4 (95.3–103.7)	89.9 (85.7–94.5)	< 0.01
HbA1c (%)- median (IQR)	11 (9.1–13.5)	5.3 (5–5.65)	5 (4.7–5.2)	< 0.01
OGTT (mg/dL) -median (IQR)	119.5 (119.5–119.5)	128.45 (110.3–157.05)	105 (83.3–122)	< 0.01
AFB smear				0.01
Negative	5 (27.8)	14 (34.1)	38 (52.8)	
1+	3 (16.7)	9 (22)	15 (20.8)	
2+	3 (16.7)	5 (12.2)	6 (8.3)	
3+	6 (33.3)	11 (26.8)	11 (15.3)	
Scanty	1 (5.6)	2 (4.9)	2 (2.8)	
L-J culture				1.00
Negative	4 (22.2)	8 (20.5)	24 (34.3)	
1+	11 (61.1)	18 (46.2)	32 (45.7)	
2+	2 (11.1)	4 (10.3)	3 (4.3)	
3+	0 (0)	4 (10.3)	3 (4.3)	
colonies	1 (5.6)	5 (12.8)	8 (11.4)	
BD MGIT™ 960 System				0.49
Positive	8 (80)	22 (81.5)	34 (87.2)	
Negative	2 (20)	5 (18.5)	5 (12.8)	
MDR	2 (18.2)	3 (12)	4 (10)	0.49
Isoniazid -resistant	2 (18.2)	5 (20)	7 (17.5)	0.89
Rifampicin -resistant	2 (18.2)	4 (16)	5 (12.5)	0.59

nual external quality assurance through competition panels of the College of American Pathologists (Northfield, Illinois) and other agencies.

Clinical data

Information on socio-demographic and clinical evaluation was retrieved from the medical records. Hypertension was

Characteristics of study participants were presented as median and interquartile range (IQR) values for continuous variables or frequency for categorical variables. Continuous variables were compared using the Mann-Whitney *U* test (between two groups) or the Kruskal-Wallis test with Dunn's multiple comparisons (between > 2 groups). Categorical variables were compared using

Table 1 Characteristics of pulmonary TB cases stratified according to DM status in Lima, Peru, 2017 *(Continued)*

Characteristics	DM $n = 18$	PDM $n = 41$	Normoglycemia $n = 73$	*p*-value
Cough for more than 4 weeks	17 (94.4)	38 (92.7)	65 (89)	0.40
Hemoptysis	8 (44.4)	13 (31.7)	34 (46.6)	0.45
Fever	6 (33.3)	20 (48.8)	35 (47.9)	0.39
Dyspnea	12 (66.7)	25 (61)	49 (67.1)	0.77
Night sweats	12 (66.7)	22 (53.7)	41 (56.2)	0.58
No appetite	12 (66.7)	28 (68.3)	40 (54.8)	0.19
Lost weight	15 (83.3)	35 (85.4)	47 (64.4)	< 0.01
Fatigue	15 (83.3)	33 (80.5)	55 (75.3)	0.40
Polyuria	8 (44.4)	17 (41.5)	26 (35.6)	0.42
Polydipsia	8 (44.4)	21 (51.2)	34 (46.6)	0.95
Type lesions				< 0.01
1	0 (0)	9 (22)	30 (41.1)	
2	4 (22.2)	12 (29.3)	24 (32.9)	
3	14 (77.8)	20 (48.8)	19 (26)	
Number of lesions - mean ± SD	6.1 ± 2.2	4.1 ± 1.8	2 ± 8	< 0.01
Number of lesions				< 0.01
≥ 4 lesions	17 (94.4)	27 (65.9)	24 (32.9)	
< 4 lesions	1 (5.6)	14 (34.1)	49 (67.1)	

Data represent no. (%); *IQR* Interquartile range. Except Number of lesions represented in mean ± SD (standard deviation). *BCG* Bacillus Calmette–Guérin, *BMI* Body Mass Index, *Hb* Hemoglobin, *FPG* Fasting Plasma Glucose, *HbA1c* Glycated Hemoglobin, *OGTT* Oral Glucose Tolerance Test, *AFB* Acid-Fast Bacilli, *L-J* Löwenstein-Jensen, *MDR* Multi Drug Resistant. Hypertension, asthma, renal disease and anemia as defined by the World Health Organization as described in Methods. Prior TB: diagnosis of active tuberculosis before of this

the Fisher's exact test (2 × 2 comparisons) or Pearson's chi square test. We also performed additional analyses employing dimension reduction approaches to define an overall biochemical profile associated with distinct radiographic lung lesions. Therefore, biochemical data were z-score normalized across the entire cohort and analyzed by hierarchical clustering (Ward's method, with 100X bootstrap). In this approach, dendrograms represented Euclidean distance, which infers similarity between the individuals and groups of study participants [23]. A multivariable regression model using variables with univariate *p*-value ≤0.2 was performed to assess the odds ratios (OR) and 95% confidence intervals (CIs) of the associations with 3 types lesion and the number of lung lesions ≥4 (defined here as outcomes). All analyses were pre-specified. Two-sided p value < 0.05 were considered statistically significant. Since our population composed by TB patients affected by hyperglycemia (59) and not affected by hyperglycemia (73), the study power was 95% (alpha risk of 0.05 in a bilateral contrast) to detect as statistically significant differences in worse radiological manifestations at ratios of 0.586 and 0.260 respectively. Statistical analyses were performed using SPSS 24.0 (IBM statistics), Graphpad Prism 7.0 (GraphPad Software, San Diego, CA) and JMP 13.0 (SAS, Cary, NC, USA).

Results

In this study, from 349 microbiologically confirmed TB cases initially screened at the primary health care centers (Fig. 1), 206 individuals were excluded for a number of reasons listed in Fig. 1, and 143 patients with active TB were further examined. At this stage, additional 14 persons were excluded due to HIV diagnosis ($n = 7$) and for non-existence of radiography records ($n = 7$), resulting in a population of 132 patients who were included in this cross-sectional study. Of note, 59 (44.7%) patients were diagnosed with hyperglycemia, and from those, 41 (31.1%) had PDM and 18 (13.6%) had DM.

Individuals with DM were on average older than those with PDM or normoglycemia (median age: 46.1 yrs. IQR: 36.6–58.3 vs. 40 yrs., IQR: 26.7–54.0 and 25.8 yrs. IQR: 21.0–30.9, respectively, $p < 0.01$) (Table 1). Lower level of education (elementary and secondary school years) was associated with presence of hyperglycemia (DM or PDM) ($p < 0.01$) (Table 1). The frequencies of both history of TB (66.7%) and hypertension (16.7%) were more frequent in DM patients than in PDM and normoglycemic individuals ($p < 0.01$). The DM, PDM and normoglycemic groups were similar with regard to a number of other characteristics including sex, BCG vaccination, history of asthma and renal disease, as well as life-style habits such as use of alcohol, illicit drugs or smoking.

Table 2 Characteristics of TB patients stratified according to types of lung lesions in Lima, Peru, 2017

Characteristics	1 Type lesion $n = 39$	2 Type lesions $n = 40$	3 Type lesions $n = 53$	*p*-value
Age (years)-median (IQR)	27.93 (22.75–31.92)	28.10 (22.04–49.06)	37.92 (24.58–47.64)	0.07
Sex				0.94
Male	23 (59.0)	25 (62.5)	33 (62.3)	
Female	16 (41.0)	15 (37.5)	20 (37.7)	
Education				0.12
Elementary and secondary school	25 (64.1)	29 (72.5)	44 (83.0)	
Higher education	14 (35.9)	11 (27.5)	9 (17.0)	
Prior TB	1 (2.6)	3 (7.5)	12 (22.6)	< 0.01
BCG vaccination	35 (89.7)	39 (97.5)	48 (92.3)	0.38
Smoking	7 (17.9)	13 (32.5)	8 (15.4)	0.12
Smoker at home	5 (12.8)	1 (2.5)	5 (9.6)	0.24
Cannabis use	6 (15.4)	8 (20.0)	6 (11.5)	0.54
Illicit drug use	3 (7.7)	7 (17.5)	6 (11.5)	0.41
Alcohol use	21 (53.8)	23 (57.5)	23 (44.2)	0.42
Hypertension	1 (2.6)	3 (7.5)	3 (5.8)	0.61
Asthma	4 (10.3)	1 (2.5)	2 (3.8)	0.26
Renal disease	0 (0.0)	1 (2.5)	1 (1.9)	0.64
Slow scarring	6 (15.4)	5 (12.5)	8 (15.4)	0.91
Metformin use	0 (0.0)	2 (5.3)	5 (9.8)	0.13
BMI (kg/m2)-median (IQR)	23.53 (21.22–25.08)	22.28 (20.08–25.39)	22.66 (20.19–25.68)	0.28
Waist circumference (cm) -median (IQR)	84 (76–90)	81 (75–86)	82 (77–89)	0.34
Hemoglobin (g/dL) -median (IQR)	12.60 (11.50–13.30)	12.15 (10.85–13.53)	11.25 (10.53–12.65)	0.03
FPG (mg /dL) -median (IQR)	91.5 (7.3)	100.4 (36.3)	140.9 (91.7)	< 0.01
HbA1c (%)- median (IQR)	4.9 (0.41)	5.2 (0.8)	6.9 (3.2)	< 0.01
OGTT (mg/dL) -median (IQR)	113.4 (29.9)	109.8 (26.7)	115.0 (28.6)	0.76
AFB smear				0.04
Negative	23 (59.0)	17 (43.6)	17 (32.1)	
1+	8 (20.5)	7 (17.9)	12 (22.6)	
2+	1 (2.6)	6 (15.4)	7 (13.2)	
3+	6 (15.4)	7 (17.9)	15 (28.3)	
Scanty	1 (2.6)	2 (5.1)	2 (3.8)	
L-J culture				< 0.01
Negative	14 (36.8)	16 (43.2)	6 (11.5)	
1+	18 (47.4)	14 (37.8)	29 (55.8)	
2+	1 (2.6)	4 (10.8)	4 (7.7)	
3+	1 (2.6)	2 (5.4)	4 (7.7)	
Colonies	4 (10.5)	1 (2.7)	9 (17.3)	
BD MGIT™ 960 System				0.43
Positive	18 (81.8)	13 (65.0)	33 (97.1)	
Negative	4 (18.2)	7 (35.0)	1 (2.9)	
MDR	3 (14.3)	2 (12.5)	4 (10.3)	0.90
Isoniazid -resistant	4 (19.0)	2 (12.5)	8 (20.5)	0.78
Rifampicin -resistant	4 (19.0)	3 (18.8)	4 (10.3)	0.57

Table 2 Characteristics of TB patients stratified according to types of lung lesions in Lima, Peru, 2017 *(Continued)*

Characteristics	1 Type lesion $n = 39$	2 Type lesions $n = 40$	3 Type lesions $n = 53$	*p*-value
Cough for more than 4 weeks	33 (84.6)	37 (92.5)	50 (94.3)	0.26
Hemoptysis	15 (38.5)	17 (42.5)	23 (43.4)	0.89
Fever	21 (53.8)	18 (45.0)	22 (41.5)	0.50
Dyspnea	29 (74.4)	27 (67.5)	30 (56.6)	0.20
Night sweats	20 (51.3)	22 (55.0)	33 (62.3)	0.56
No appetite	23 (59.0)	26 (65.0)	31 (58.5)	0.79
Lost weight	28 (71.8)	29 (72.5)	40 (75.5)	0.91
Fatigue	30 (76.9)	29 (72.5)	44 (83.0)	0.47
Polyuria	15 (38.5)	13 (32.5)	23 (43.4)	0.57
Polydipsia	16 (41.0)	21 (52.5)	26 (49.1)	0.58

Data represent no. (%); *IQR* Interquartile range. *BCG* Bacillus Calmette–Guérin, *BMI* Body Mass Index, *Hb* Hemoglobin, *FPG* Fasting Plasma Glucose, *HbA1c* Glycated Hemoglobin, *OGTT* Oral Glucose Tolerance Test, *AFB* Acid-Fast Bacilli, *L-J* Löwenstein-Jensen, *MDR* Multi Drug Resistant. Hypertension, asthma, renal disease and anemia as defined by the World Health Organization as described in Methods. Prior TB: diagnosis of active tuberculosis before of this

Furthermore, frequency of increased acid-fast bacilli grades in sputum smears was higher in the group of DM cases compared to the other groups ($p = 0.01$) (Table 1).

The statistical analysis of radiographic examination revealed that the absolute number of lung lesions as well as the frequency of different lesion types were both higher in the DM group compared to the groups of PDM and normoglycemic ($p < 0.01$) (Table 1). No differences were found between the characteristics of pulmonary TB cases stratified according to the presentation of the types of lung lesions or number of lesions, with the exception of previously treated TB (Tables 2 and 3, respectively). Simultaneous presence of the 3 different types of lung lesions (cavities, infiltrates and fibrous tracts), was significantly higher among hyperglycemic vs. normoglycemic TB patients (59 and 26% respectively, $p < 0.001$; Fig. 2a). Such frequency of the three lesion types was not different between DM (73.7%) and PDM (51.3%) TB patients (Fig. 2a).

Corroborating with the idea that dysglycemia is associated with worse radiographic presentation, the median values of FPG and HbA1c were significantly higher ($p < 0.01$) in TB patients affected with more lung lesion types (Fig. 2b). In addition, we found that 40.2% of TB patients had more than three lesions and 60% of those were simultaneously PDM or DM (Fig. 3a). Moreover, 52.3% of TB patients had more than 4 lesions; and > 70% of those also had hyperglycemia (Fig. 3a and b). TB patients with hyperglycemia more frequently exhibited bilateral lung lesions compared to those with normoglycemia (Fig. 3c).

Furthermore, we employed a hierarchical cluster analysis using a number of laboratory parameters measured in peripheral blood to test whether it was possible to identify a specific bio-signature that could characterize TB patients presenting with different types and numbers of radiographic lung lesions (Fig. 4a). This approach revealed that patients with 3 types of lung lesions and also with 4 or more lesions exhibited a distinct profile hallmarked by higher values of WBC counts, total cholesterol, triglycerides, liver transaminases as well as values of the DM screening tests (FPG, and HbA1c). The same subgroup of patients also exhibited lower levels of plasma albumin and hemoglobin compared to those from TB patients presenting with lower number and types of lesions (Fig. 4a). We next described in details the associations of biochemical and cellular parameters with number or types of lung lesions (Fig. 4b). We found that all parameters, except for the WBC counts in patients with> 4 lesions, were statistically different between the groups (Fig. 4b).

Having demonstrated that hyperglycemia significantly affected the biochemical profile in peripheral blood, we further investigated whether presence of PDM or DM directly associated with the radiographic presentation of pulmonary TB using multivariable logistic regression analyses (Fig. 5). We first observed that increases of 1 unit in HbA1c and of FPG values reflected increased odds of having 3 pulmonary lesion types (Fig. 5a) or ≥ 4 lung lesions in TB patients (Fig. 5b), except for FPG which lost significance with the latter parameter after adjustment for age, sex, prior TB, hemoglobin levels and acid-fast bacilli ≥2+ in sputum smears. Secondly, presence of PDM or DM was independently associated with increased odds of presenting with these worse radiographic manifestations of pulmonary TB (Fig. 5a and b), after the statistical adjustments.

Discussion

In this study, we demonstrated that hyperglycemia (DM and PDM) is strongly associated with worse radiographic manifestation of pulmonary TB in patients from Peru. The results showing association between DM and more

Table 3 Characteristics of pulmonary TB stratified according to number of lung lesions in Lima, Peru, 2017 *(Continued)*

Characteristics	≥ 4 lesions $n = 68$	< 4 lesions $n = 64$	*p*-value
Dyspnea	39 (56.5)	48 (73.8)	0.05
Night sweats	39 (56.5)	37 (56.9)	1.00
No appetite	39 (56.5)	42 (64.6)	0.38
Lost weight	48 (69.6)	49 (75.4)	0.56
Fatigue	55 (79.7)	49 (75.4)	0.68
Polyuria	27 (39.1)	25 (38.5)	1.00
Polydipsia	31 (44.9)	32 (49.2)	0.73
Hemoptysis	30 (43.5)	27 (41.5)	0.86
Fever	28 (40.6)	34 (52.3)	0.23

Data represent no. (%); *IQR* Interquartile range. *BCG* Bacillus Calmette–Guérin, *BMI* Body Mass Index, *Hb* Hemoglobin, *FPG* Fasting Plasma Glucose, *HbA1c* Glycated Hemoglobin, *OGTT* Oral Glucose Tolerance Test, *AFB* Acid-Fast Bacilli, *L-J* Löwenstein-Jensen, *MDR* Multi Drug Resistant. Hypertension, asthma, renal disease and anemia as defined by the World Health Organization as described in Methods. Prior TB: diagnosis of active tuberculosis before of this

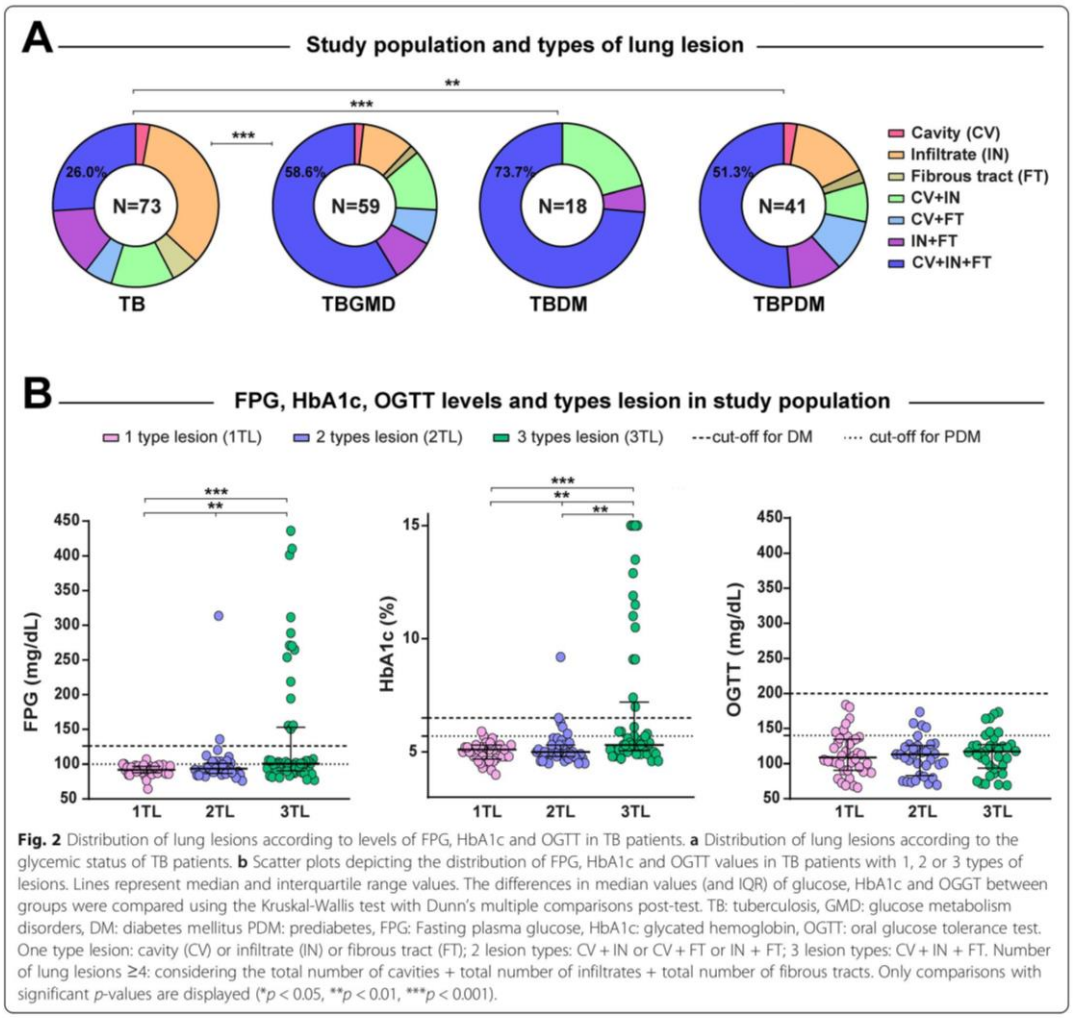

Fig. 2 Distribution of lung lesions according to levels of FPG, HbA1c and OGTT in TB patients. **a** Distribution of lung lesions according to the glycemic status of TB patients. **b** Scatter plots depicting the distribution of FPG, HbA1c and OGTT values in TB patients with 1, 2 or 3 types of lesions. Lines represent median and interquartile range values. The differences in median values (and IQR) of glucose, HbA1c and OGGT between groups were compared using the Kruskal-Wallis test with Dunn's multiple comparisons post-test. TB: tuberculosis, GMD: glucose metabolism disorders, DM: diabetes mellitus PDM: prediabetes, FPG: Fasting plasma glucose, HbA1c: glycated hemoglobin, OGTT: oral glucose tolerance test. One type lesion: cavity (CV) or infiltrate (IN) or fibrous tract (FT); 2 lesion types: CV + IN or CV + FT or IN + FT; 3 lesion types: CV + IN + FT. Number of lung lesions ≥4: considering the total number of cavities + total number of infiltrates + total number of fibrous tracts. Only comparisons with significant *p*-values are displayed (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

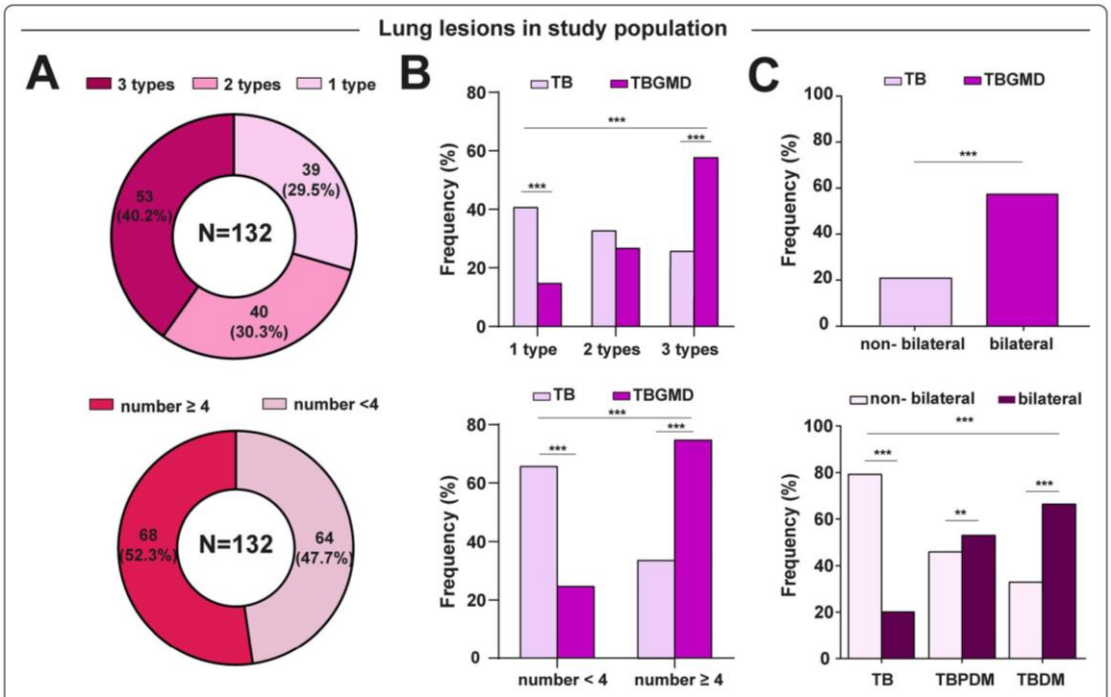

Fig. 3 Distribution and frequency of type and number of lung lesions in tuberculosis patients with dysglycemia. **a** Stratification of patients with 1, 2 and 3 types of lung lesions and patients with the number of lung lesions ≥4. **b** Distribution of types of lung lesions (upper panel) and number of lung lesions ≥4 (lower panel) between the TB and TBGMD groups **(C)** Frequency of bilateral lesions in patients classified in TB and TBGMD (upper panel) or in those classified in TBPDM and TB-DM (lower panel). In **b** and **c**, data were compared between the groups using the Fisher's exact test (2 × 2 comparisons) or the Pearson's chi-square test (> 2 groups). TB: tuberculosis, GMD: glucose metabolism disorders, DM: diabetes mellitus PDM: prediabetes, FPG: Fasting plasma glucose, HbA1c: glycated hemoglobin, OGTT: oral glucose tolerance test. One type lesion: cavity (CV) or infiltrate (IN) or fibrous tract (FT); 2 lesion types: CV + IN or CV + FT or IN + FT; 3 lesion types: CV + IN + FT. Number of lung lesions ≥4: considering the total number of cavities + total number of infiltrates + total number of fibrous tracts. Only comparisons with significant *p*-values are displayed (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$)

increased severity of radiographic TB disease are similar to previously reported findings [13, 24], but the findings on PDM have not been published before. Herein, a large proportion of the patients who presented with three types of lesions (cavities, infiltrates and fibrous tracts), or with more than 4 lesions, also had hyperglycemia. It is possible that dysglycemic patients presented with more advanced TB disease, which could have impacted the radiographic characteristics as indicated by others [25]. Regional differences in epidemiology of both TB and hyperglycemia may result in distinct impact of the glycemic control status on the radiographic presentation of pulmonary TB, reported by studies performed in different countries.

We have previously reported that patients with hyperglycemia more frequently present with multiple TB-related symptoms compared to those with normoglycemia [11]. In addition, TB-DM patients more commonly required transfer from a primary care center to hospitals in order to have access to more complex care [11]. These reported results were obtained in different patient populations from Brazil. Of note, we failed to demonstrate an association between hyperglycemia and TB-clinical presentation in the present study performed in Peru. Again, discrepancies driven by epidemiologic, clinical and even microbiologic factors may explain the conflicting findings. Despite the differences in clinical presentation, several studies reported similar results to those reported here, showing increased mycobacterial loads in sputum smears in hyperglycemic vs. normoglycemic patients [11, 13, 26–29]. A multinational, harmonized, clinical study is necessary to formally demonstrate the effect of DM and/or PDM on TB disease presentation and to test if such effect is independent on the bacterial loads in sputum.

Our findings indicate that hyperglycemia is associated with significant increases in the number tuberculoid lesions and in the diversity of the lesion types, as well as with occurrence of bilateral lung disease, in agreement

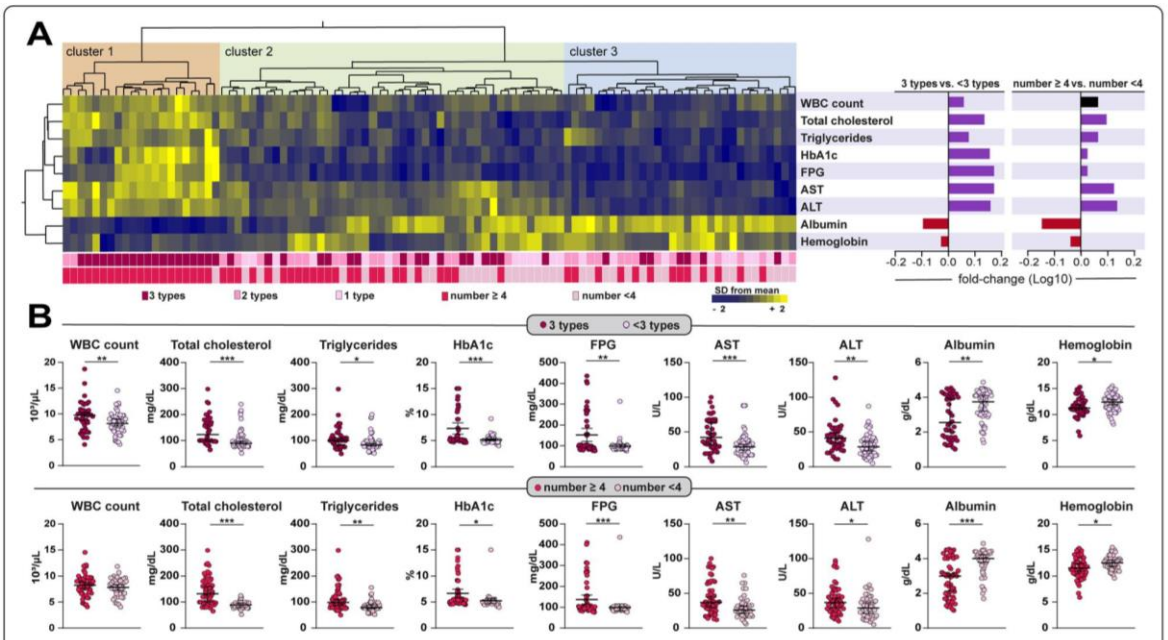

Fig. 4 Biochemical profiles of pulmonary TB patients stratified by type and number of lung lesions. **a** Value of each parameter was Log10 transformed. Mean values for each indicated clinical group were z-score normalized and a hierarchical cluster analysis (Ward's method with 100X bootstrap) was performed to illustrate the overall biochemical profiles. Fold differences (between the following groups: 3 types vs. < 3 types, and number ≥ 4 vs. number < 4) were calculated and statistically significant differences are highlighted in purple (positive) and red (negative). **b** Data represent median and interquartile ranges. The Mann-Whitney *U* test was employed to compare the values detected between the study subgroups. One type lesion: cavity (CV) or infiltrate (IN) or fibrous tract (FT); 2 lesion types: CV + IN or CV + FT or IN + FT; 3 lesion types: CV + IN + FT. Number of lung lesions ≥4: considering the total number of cavities + total number of infiltrates + total number of fibrous tracts. Only comparisons with significant p-values are displayed (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

with previous studies [12, 14]. This increased degree radiographic extension of TB disease may result in a possible acceleration of pulmonary dysfunction [30]. Some authors have reported that cavitary lesions in hyperglycemic patients are generally unilateral, affecting only one side of the lung [15], which stands contrary to our findings. The reason for this discrepancy deserved further investigation. The mechanism of more severe radiological manifestations could be related to hyperstimulation of leukocytes by both TB and the hyperglycemic state, resulting in a 'premature aging' of the lung [15] in patients with TB-DM comorbidity.

Our findings reveal that hyperglycemia was associated with a systemic pro-inflammatory state characterized by elevation of WBC counts and increased levels of liver transaminases, total cholesterol and triglycerides in serum, whereas albumin and hemoglobin levels were decreased, suggesting anemia. The hierarchical cluster analysis further demonstrated that the cellular and biochemical profile associated with hyperglycemia was also linked occurrence of increased number and diversity of lung lesions. We have recently described that TB-related anemia is associated with a distinct inflammatory profile that persists upon initiation of antitubercular therapy in a Brazilian cohort [23], but we have not previously tested the association between anemia and hyperglycemia in TB clinical or radiographic presentation. It is possible that progression of TB disease links these two apparently distinct pathophysiological conditions, hyperglycemia and anemia, through a mechanism that may involve chronic inflammation. Additional studies examining the intersection between TB, chronic inflammation, anemia and hyperglycemia are required to clarify this question.

Our study has some limitations. The analytical design did not allow us to investigate the temporary effect of TB infection on hyperglycemia, or vice-versa. Therefore, causal relationships cannot be established from this study. The cross-sectional design also prevented us to analyze the impact of TB treatment on the glycemic control or to answer whether diabetes therapy impacts TB treatment response. In addition, a different number of patients in each group of distinct glycemic status could have affected the accuracy of our findings in terms of confidence intervals. Nevertheless, the detailed

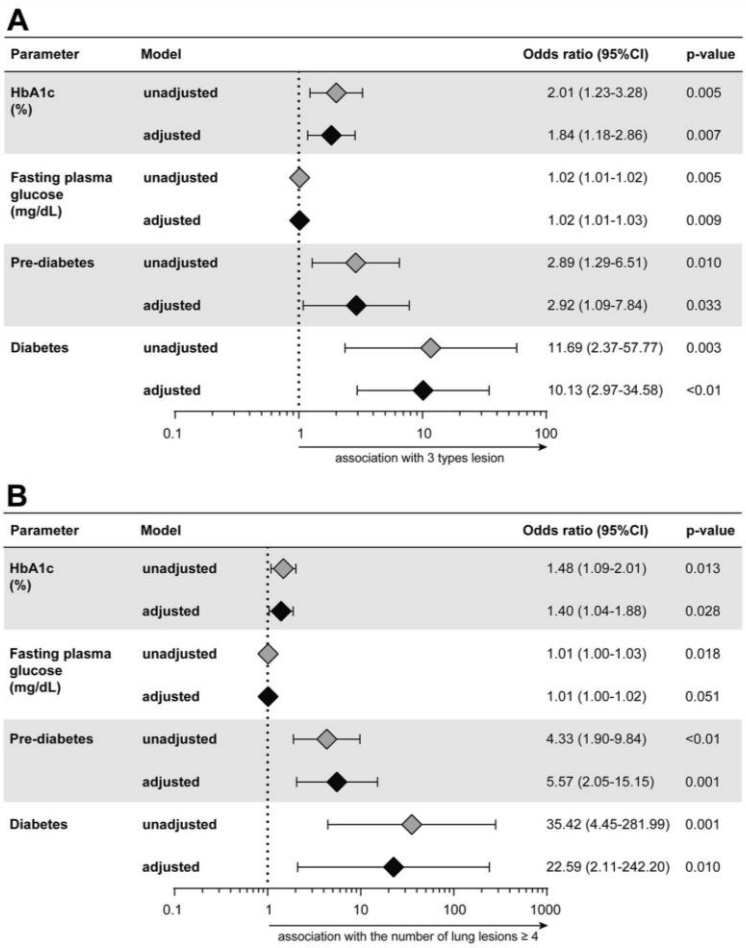

Fig. 5 Multivariable regression analysis to evaluate association between HbA1c, fasting plasma glucose, prediabetes, and diabetes with diversity and number of lung lesions in pulmonary TB patients. Multivariable logistic regression analysis was conducted to test association between indicated variables and odds of presenting with 3 types of lung lesions (**a**) and the number of lung lesions ≥4 (**b**) in radiographic evaluation of TB patients. In univariate model, each variable was tested individually. The adjusted model included all the variables shown in the graphs in addition to age, sex, prior TB, ≥2+ AFB smear and hemoglobin level. HbA1c: glycated hemoglobin

analyses merging clinical, laboratorial and radiographic investigations demonstrated a significant association between glycemic status and the presentation of pulmonary lesions in TB patients. If validated by other studies, the results presented here reinforce the importance of performing glycemic control in TB patients.

Conclusions

Hyperglycemia (both DM and PDM) was found to significantly increase the frequency and diversity of pulmonary lesions in patients with tuberculosis. Hyperglycemic TB patients were found to have significant alterations of the biochemical profile in peripheral blood, suggesting that there is a distinct metabolic state that likely contributes to the severity of pulmonary disease. These findings underscore the need for improved, accurate, screening and diagnosis of hyperglycemic conditions, and adequate glycemic control in patients with TB. Additional studies should be pursued to understand how the increased radiographic extension of TB observed in dysglycemic patients may affect pathogen transmission.

Abbreviations
ADA: American Diabetes Association; AFB: Acid-Fast Bacilli; ATT: Antitubercular treatment; BCG: Bacillus Calmette–Guérin; BMI: Body Mass Index; DM: Diabetes mellitus; FPG: Fasting plasma glucose; Hb: Hemoglobin; HbA1c: Glycated Hemoglobin; HHC: Household contact; IQR: Interquartile range; L-J: Löwenstein-Jensen; MDR: Multi Drug Resistant; Mtb: *Mycobacterium tuberculosis*; NTP: National TB Program; OGTT: Oral glucose tolerance test; PDM: Prediabetes; SEIS: Socios En Salud Informatic System; TB: Tuberculosis; TG: Triglycerides; WHO: World Health Organization

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Authors' contributions
NBP, MBA, BBA and RC conceived and designed the study, interpreted the data, and wrote the manuscript. NBP, MBA, JGA, KL, OMS, LL and RC implemented the lab study and collected the data. NBP, MBA, JFFN, TC, BBA and RC performed the data curation, analysis and performed data interpretation. All authors revised the manuscript critically for important intellectual content and gave final approval of the version to be published.

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Availability of data and materials
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the Institutional Committee of Ethics for Humans (CIEI, approval number: 158–22–16), an autonomous committee established by the Universidad Peruana Cayetano Heredia, with the authorization of National Institute of Health in Peru. Written informed consent was obtained from all participants or their legally responsible guardians, and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki and local and national Peruvian regulations.

Consent for publication
Not Applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

6.11 MANUSCRITO XI

Systems Nutrology of persons with tuberculosis identifies specific dietary profiles associated with dysglycemia.

A aderência de uma dieta adequada é um fator importante para o controle da disglicemia em pacientes com DM ou pré-DM. Além disso, o padrão alimentar de um paciente também pode estar associado a um maior ou menor risco de desenvolvimento de Tb ativa. Este trabalho teve como objetivo identificar padrões alimentares de pacientes com TB e disglicemia utilizando dados de uma coorte prospectiva de pacientes e seus contatos atendidos em Lima, Peru.

Resumo dos resultados: Três padrões alimentares foram identificados com base no perfil de ingestão alimentar dos participantes do estudo. A disglicemia em pacientes com TB foi associada principalmente ao aumento da ingestão de arroz e cereais, fast food e óleos. A identificação de padrões alimentares distintos envolvidos com TB e disglicemia pode ajudar a orientar intervenções nutricionais para otimizar o atendimento ao paciente.

Este trabalho está em revisão na *Nutrition Journal*, cujo Fator de Impacto (JCR 2021) foi igual a 3,27.

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Systems Nutrology of Persons with Tuberculosis Identifies Specific Dietary Profiles Associated with Dysglycemia

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Research Article

Keywords: tuberculosis, dysglycemia, dietary pattern, food group, systems nutrology, Peru, dietary intake, household contacts.

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treatment [10] and the underweight as a high risk factor for TB-specific and non-TB-specific mortality during anti-TB treatment [11]. There is also evidence that vitamin D [12] and vitamin A [13] concentrations in peripheral blood could affect the incidence and progression of TB. However, there is a gap in the literature about the evaluation of dietary patterns in the comorbid condition of TB and DM, and on whether such information may be useful to guide optimization of clinical management.

Following World Health Organization (WHO) guidelines, the Peruvian national TB program covers the full cost of TB treatment and offers psychological and nutritional counseling. Additionally, the program provides food baskets monthly to all patients in treatment through the Food and Nutrition Program for Outpatients with Tuberculosis and Family [14–16]. This provision of food baskets is offered to increase treatment adherence, improving weight gain and reduce mortality [14]. However, the increased frequency of patients with TB-DM comorbidity [15] raises the question of whether the current nutritional recommendations are appropriate. In a previous study, our group used big data and artificial intelligence analysis tools to develop the concept of Systems Nutrology, in order to identify dietary profiles of populations based on unsupervised analyses [16, 17]. Such knowledge and approach may be useful to define nuances in the dietary profiles that may be associated with dysglycemia in persons with TB. The present study employed our Systems Nutrology approach to characterize dietary patterns in individuals with TB and dysglycemia in a cohort of persons with TB enrolled in Lima, Peru.

Methods

Study design

This cross-sectional study is part of a prospective cohort study of pulmonary TB patients and their household contacts, conducted between February and November 2017 in Lima, Peru, which was main aimed to determinate the prevalence of DM and prediabetes (preDM) in persons with TB. The study was carried out in the Public Hospital Sergio Bernales and outpatient health centers of Carabayllo and Comas districts. Patients with pulmonary TB with ≥18 years of age diagnosed by the Peruvian National TB Program, who are not receiving anti-TB treatment or have started it in a period of no more than 5 days, were included. Exclusion criteria were patients or contacts diagnosed with HIV, pregnant women, who did not live permanently in the jurisdiction area of the study and patients who had infection or disease due to non-tuberculous mycobacteria. The follow-up of those patients and household contact was conducted up to 6 to 12 months after enrollment. 136 TB patients and 133 household contact were included in this study and classified in the investigated groups (dysglycemia, TB and TB-dysglycemia) and the control group, with healthy patients.

Furthermore, for this study we use the information from the TB patients and their contacts collected at the baseline visit (before the TB patient initiates anti-TB treatment). Clinical and epidemiological information (such as: age, sex, prior TB, among others) was used for analysis, in addition to the laboratorial results of hemoglobin (Hb), glycated hemoglobin (HbA1c), oral glucose tolerance test (OGTT) and fasting plasma glucose (FPG).

The recruitment details, laboratory and field procedures were described in the previous study of our group with the same cohort [15].

Definitions

TB patients were diagnosed according to definitions of the Peruvian National TB Program [18] in the health centers, by one or more of the following criteria: (a) clinical factors (presumptive diagnosis), (b) bacteriology (sputum smear positive) or positive culture (solid or liquid), (c) GeneXpert MTB RIF, and (d) chest radiography). Household contact was defined as a person who shared at least household where they sleep or take their meals (at least one of them per day) with a study TB patient.

DM was defined in agreement with American Diabetes Association (ADA) guidelines [19] as 2h OGTT≥200 mg/dL, HbA1c ≥6.5% or FPG ≥126 mg/dL. PreDM was also defined in agreement with ADA guidelines as 2h glucose 140 a 199 mg/dL, HbA1c 5.7 - 6.4% or fasting plasma glucose 100–125 mg/dL. Dysglycemia was defined as DM or PreDM.

Healthy controls were participants that did not have dysglycemia or TB diagnosis. Anemia was defined following WHO criteria as Hb levels below 12.5 g/dL and 13.5 g/dL for female and male patients, respectively. Hb measurement was performed in whole blood specimens stored at − 80 °C from patients approximately one year after the blood sample collection at the end of the enrollment. One 50 µL-aliquot of whole blood of each participant was thawed and separated in a new tube to be passed through the HumaCount 5D Hematology System (Wiesbaden, Germany). In our cohort, there are a good proportion of TB-dysglycemia people that are anemic. There is evidence supporting the idea that performance of HbA1c in detecting dysglycemia is affected by occurrence of anemia. Our previous study found no clear influence in the HbA1c test performance to diagnose DM and showed that FPG is indeed a good marker to be used for screening of DM or pre-DM in Peru.

Anthropometric status was defined according to the body mass index (BMI). The different anthropometric statuses were defined according to the conventional WHO classification: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) [20].

Food Consumption data collection

The food intake was obtained according to a food frequency questionnaire (FFQ), with 94 food items. FFQ was specifically developed for this study, to delineate the dietary patterns of TB patients and household contacts, with and without dysglycemia. In addition, the data retrieve and processing of variables were performed following standardized steps from a previous study from our group [16, 17]

The FFQ was applied to TB cases and their household contacts at the enrollment visit (before the patient initiated anti-TB treatment). The consults about the habitual diet were referred to consumption of food outside and inside the home in the last 6 months. The food frequency choices had the following response options: Never / rare; 1 to 3 times a month; 1 time per week; 2 to 4 times a week; ≥4 times a week. In addition, the number of times you consumed these foods was investigated. After data collection, through the use of food composition and nutrition tables, we standardized the amounts consumed of each food and / or preparation referred to units of weight (g) and / or volume (mL), which w[i]ere used for calculating the daily consumption of the food recorded in the FFQ. Industrialized foods and / or preparations that were not included in the tables were searched through the internet directly on the manufacturer's website or through recipes. Thus, it was possible to obtain an approximation of the total daily food consumption in grams through calculations based on weekly and monthly consumption.

The average of daily consumption in grams of these food items were provided by the self-report of participants. For the statistical analysis, the food items that composed the FFQ were categorized into 10 food groups according to the similarity in nutritional composition and food habits of the Peruvian population: Sugar and sweets, sweetened beverages, tubers, fast food, oils, milk and dairy, fruits and vegetables, rice and cereals, meat, and legumes. The approach used for creating these groups is described below (**Table 1**).

Statistical Analysis

Comparison between groups

Characteristics of study participants were presented as median and interquartile ranges (IQR) for continuous variables or frequency for categorical variables. Continuous variables were compared using the Mann-Whitney *U* test (between two groups) or Kruskal-Wallis test with Dunn's multiple comparisons. Categorical variables were compared using the Fisher's exact test (2 × 2 comparisons) or Pearson's chi square test. For comparisons of abundance of food consumption, the one-way ANOVA was used. Categorical variables were displayed as frequency (%) and compared using the Pearson's chi-square test.

Systems Nutrology Analysis

To analyze the potential association between food consumption profiles, anthropometric and dysglycemia status, we used an analytical approach denominated 'systems nutrology', created and detailed by our group in the article of Andrade et al. (2020), based on ecological analysis approach [21, 22].

Hierarchical cluster analysis

To evaluate the overall profile of consumption of the different food groups, we transformed data on total consumption of each food group (in grams) into abundance of consumption relative to total diet. This is

a common method used in ecological analysis and was used previously by our group evaluating food consumption of humans [16, 17]. After defining the proportion of consumption of each food group in the total ingestion we performed an unsupervised hierarchical cluster analysis to define the dietary patterns (Ward's method). Individuals were grouped based on similarity of abundance of food consumption. The different clusters were defined by overall similarity of food consumption, represented using dendrograms denoting the Euclidean distances. We also used bubble plots to illustrate the representativeness of consumption of each food group in each one of the food patterns calculated, using three measurements: low, middle, and high. Pie charts were used to illustrate frequency of individuals grouped by clinical group, sex, and anemia status in each dietary pattern.

Correlation between foodgroups and glucose levels

Correlations between total intake in grams of each food group and clinical variables associated to glucose levels (HbA1c and FPG) were evaluated by the Spearman rank test. We created correlation matrices stratifying the participants according to TB status. A correlation was considered to be weak with values below 0.45, moderately strong when the value of rho was between 0.45 and 0.75 and above 0.75 to be relatively strong.

Multinomial logistic Regression

To test the association between the clinical groups and the different dietary patterns identified (n=3) in the hierarchical cluster analysis, we performed a multinomial multivariate logistic regression analysis, adjusted for age, sex, hemoglobin and BMI. As in a previous study of our group [17], the outcome variable was the pattern of food consumption. The dietary pattern 2 was used as the baseline for estimation of odds of consumption of the other patterns, given that most patients in this cluster are healthy.

Prespecification and used software

All analyses and data visualization were pre-specified. Two-sided *P* value < 0.05 after adjustment for multiple comparisons (Bonferroni's method) were considered statistically significant. Statistical analyses were performed using R 3.4.2 (R Foundation) and SPSS 24.0 (IBM statistics). The R packages corresponding to each analysis are described in **Supplementary Table 1**.

Results

Study population and characteristics

vegetables, legumes, and meat, while DP3 presented the highest intakes of sweetened beverages, fast food and milk (**Figure 1B, Supplementary Table 2 and 3**).

Additional analyses tried to test associations between the dietary patterns and the clinical groups. All TB patients (with and without dysglycemia) were distributed in DP1 and DP3, while none of patients at DP2 presented this pathology ($p < 0.001$). In general, DP1 was predominantly composed by TB patients without dysglycemia (68.3%), with the youngest median age (26.4, IQR: 21-37, $p <0.001$), highest frequency of illiteracy (32.7%, $p = 0.002$), cannabis use (12.5%, $p = 0.008$) and anemia (59.6%, $p<0.001$). In contrast, the patients in this DP also presented lowest values of BMI (22.3, IQR: 20.2-24.5, $p < 0.001$), waist circumference (79.5, IQR: 74-87.2, $p < 0.001$) and HbA1c levels (5, IQR: 4.7-5.3, $p < 0.001$). DP3 was composed mainly for patients with dysglycemia with and without TB (94.5%, being 63.7% with TB, $p <0.001$), with the elderly median age (45.9, IQR: 30.5-54, $p <0.001$), highest illicit drug use (11%, $p <0.005$), fasting plasma glucose (104, IQR: 99-114, $p <0.001$) and glycated hemoglobin (5.3, IQR: 4.9-5.9, $p<0.001$). Finally, at DP2 are allocated almost all healthy patients (89.2%, $p <0.001$), with a small frequency of males (33.8%, $p = 0.002$), without illicit drug or cannabis use reported, highest BMI (27.4, IQR: 25.3-30.1, $p <0.001$), waist circumference (90, IQR: 83.2-98.8, $p <0.001$) and hemoglobin levels (13.1, IQR: 12.4-14.2, $p=0.014$) (**Figure 2 and Supplementary Table 3**).

To evaluate the influence of the intake of food groups on the glycemic status of the study participants (assessed here through FPG and HbA1c levels), we performed a Spearman correlation test between these two variables and each food group, stratifying the patients according to TB status. In our cohort, we observed that there was a higher correlation between some food groups and FPG in both groups (**Figure 3A, Supplementary Table 4**), but no statistically significant correlation was observed with glycated hemoglobin values (**Figure 3B, Supplementary Table 4**). In patients without TB, consumption of rice and cereals and sweet potato was positivity correlated with FPG levels while that of Legumes was negatively correlated. In TB patients, besides the consumption of rice and cereals, that of fast food and oils was also positively correlated with FPG levels (**Figure 3, Supplementary Table 4**).

Association between clinical characteristics and dietary patterns

To test for independent association between the DP identified and the clinical groups, we performed a multinomial multivariate logistic regression analysis, as described in Methods. We used DP2 as reference and tested the associations between clinical and epidemiologic characteristics and DP1 and DP3 (**Figure 4**). Using this approach, we found that obesity (adjusted Odds Ratio [aOR]: 1.02, 95%CI: 1.01-1.40, $p = 0.028$) and dysglycemia status (aOR: 1.88, 95%CI: 1.44-7.69, $p < 0.001$) were associated with DP1 independent of other tested factor. On the other hand, overweight (aOR: 1.70, 95%CI: 1.31-2.20, $p<0.001$), TB-Dysglycemia comorbidity (aOR: 4.92, 95%CI: 1.53-9.23, $p<0.001$) and dysglycemia condition (aOR: 1.16, 95%CI: 1.01-7.99, $p= 0.047$) were independently associated with the dietary pattern 3.

Discussion

It is common knowledge that there is a synergism between nutrition and the development of several human pathologies [23], which can be applied to diabetes [24] and tuberculosis [13]. In 2013, the guideline of Nutritional care and support for patients with tuberculosis was published [8]. TB and poor nutritional scenario are commonly recognized as associated because either of them can be a risk of the other [25]. It has been established that poor nutritional status is associated with limited cellular immunity (key for host defense against TB) and increased susceptibility to infections [26]. On the other hand, changes in eating behaviors and other factors have been related to the prevalence of diabetes in a scenario whose global trend towards obesity is widely distributed and documented in many regions of the world [27]. Moreover, the infection leads to nutritional stress and weight loss, thus weakening immune function and nutritional status [28] which could favor the development of other syndromic status.

In Peru, rice is the basis of the diet, and according to the Peruvian Ministry of Agriculture, rice consumption has grown by 25% between 2001 and 2009 [29]. That is why the consumption of rice in the study population, both in patients affected with TB and in those affected with the comorbidity TB-Dysglycemia, is high, as is the consumption of tubers (for example potatoes) and some other cereals. Potato intake was commonly associated with an increased risk of diabetes, through a mechanism related to increased glucose levels, although the glycemic index of the potato depends largely on the strain and the method used in preparation [30]. Because of this popular knowledge, may the population with dysglycemia avoid this type of food, justifying the lowest levels in DP3. On the other hand, as tuberculosis is often associated with worse nutritional status, it is expected that the intake of foods rich in carbohydrates such as potatoes will be stimulated in this population, as can be seen in DP1. It is remarkable to find that health directions recommend consuming foods rich in complex carbohydrates such as potatoes, sweet potatoes, rice, wheat and cereals [31]

In may setting such as that observed in Peru, malnutrition is due to excess to the consumption of foods with high energy content and low nutritional value, with the growing popularity of junk food, not expensive and ready to be eaten at any time. These new eating patterns have caused different health issues. Ultra-processed foods are really preferred in the Peruvian population and although various messages have appeared to avoid the use of some beverages, especially sodas or carbonated drinks, so-called fruit juices bottled together with sources of starch, are widely preferred and diverted by a bad message, little time for the preparation of better drinks and low economic possibility to avoid them [32]

Studying the patterns of food consumption is key to knowing the food system available as a manifestation of the functioning of food and in turn, they determine the nutritional status and especially the health of the population. Characterizing the composition and heterogeneity of the diet, especially in patients with the comorbidity TB-dysglycemia, will help us to understand the relationship with the low rates of therapeutic success in little-explored considerations and with this it will be possible to design policies aimed at promoting a healthy state of life. The eating patterns of Latin countries have traditionally been marked by a strong presence of foods based on cereals, roots and tubers. At the country level, a great heterogeneity is observed in the proportion of the availability of dietary energy derived from said foods and in Peru estimates indicate that they contribute half of the energy diet. New

eating patterns, together with less physical activity and unhealthy lifestyle habits, currently contribute to the accelerated increase in the levels of chronic non-communicable diseases such as dysglycemia or diabetes, obesity, among others; that affect an increased risk of Tuberculosis, among other infectious problems and death. The worst thing about this is that the treatment of comorbid conditions will have increasing impacts on the development of countries and on the sustainability of public health systems and national budgets [33].

With this systems nutrology analysis we found that aging was associated with DP3, mostly formed by individuals with TB-dysglycemia comorbidity. Previous studies have described how increasing age alters glucose metabolism [34]. In addition we identified that the highest BMI values were in DP2, where the consumption of fruits, vegetables, meat and legumes was higher than in the other two DPs, in addition to grouping more to healthy individuals and multinomial analysis confirms that the obesity condition was more associated with DP2, while overweight condition was associated with DP3, this is reported in previous findings in Singapore [35], where there were no differences between BMI and dysglycemia status among TB patients.

This study has limitations. In the first place, it has been difficult to have a wide range of socioeconomic data in enrolled patients to evaluate the relationship between economic power and dietary pattern. Certain disproportions have been assumed in the affected people, since normally the TB problem is as widespread in Lima as poverty, unemployment, malnutrition, and lack of access to an effective health system. On the other hand, the study could not use a specific form to evaluate eating patterns. Standardized surveys are not available to health professionals linked to the work of the TB prevention and control strategy, and this study has been carried out mainly under programmatic conditions. Finally, given that Lima concentrates more than two thirds of the TB and diabetes problem; the study was carried out only, in an urban population. Although the centralization in Lima and the consequent migration, allows an extrapolation of the customs still rooted in the population, it is possible that we can only represent a percentage of what happens in all of Lima or the country.

Conclusions

The new trends towards responsible consumption practices constitute an opportunity to promote public policies and multi-stakeholder agreements to promote transformations in current health systems. These changes should promote healthy lifestyles in the population; For this reason, it is necessary to innovate and implement policies in different areas, which are aimed especially at the most vulnerable population that, due to various socioeconomic factors, does not have access to food in sufficient quantity, quality, and variety.

Abbreviations

ADA	American Diabetes Association

ANOVA	Analysis of variance
BMI	Body Mass Index
DM	Diabetes mellitus
DP	Dietary patterns
FFQ	Food frequency questionnaire
FPG	Fasting Plasma Glucose
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HIV	Human immunodeficiency virus
IQR	Interquartile ranges
MDR-TB	Multi-drug resistance tuberculosis
OGTT	Oral glucose tolerance test
preDM	Prediabetes
TB	Tuberculosis
WHO	World Health Organization

Declarations

Ethics statement

The study was approved by the Institutional Committee of Ethics for Humans (CIEI, approval number: 158–22–16) of the Universidad Peruana Cayetano Heredia, with the authorization of National Institute of Health in Peru. Written informed consent was obtained from all participants or their legally responsible guardians, and all clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki and local and national Peruvian regulations.

Consent for publication

Not applicable.

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Pearson's chi-square test. P-values were adjusted for multiple measurements using the Holm-Bonferroni method.

TB: tuberculosis; TB TMG: tuberculosis and dysglycemia; BMI: body mass index; Hb: Hemoglobin; HbA1c: glycated hemoglobin.

Table 3. Food group consumption per grams according TB and dysglycemia status.

Food group (g/day)	Healthy	Dysglycemia	TB	TB Dysglycemia	p-value
	n=85	n=48	n=75	n=61	
Total consumption	1046 (963 - 1225)	1232 (1160-1350)	981 (885-1095)	1616 (1459-1733)	<0.001
Rice and cereals	490 (474 - 506)	574 (567 - 594)	559 (430 - 565)	645 (615 - 651)	<0.001
Tubers	187 (175 - 191)	237 (233 - 247)	233 (163 - 233)	275 (268 - 278)	<0.001
Milk and dairy	69.3 (34.7 - 107)	139 (69.3 - 213)	34.7 (34.7 - 61.3)	88.0 (42.7 - 213)	<0.001
Fruits and Vegetables	52.0 (34.7 - 78.0)	34.7 (26.0 - 62.8)	8.67 (8.67 - 13.0)	13.0 (13.0 - 21.7)	<0.001
Legumes	45.5 (31.5 - 49.0)	14.0 (14.0 - 17.5)	17.5 (10.5 - 21.0)	17.5 (10.5 - 21.0)	<0.001
Meat	50.3 (35.5 - 67.3)	56.6 (41.0 - 70.8)	33.0 (25.0 - 40.0)	42.2 (29.7 - 53.3)	<0.001
Fast Food	60.7 (28.3 - 74.7)	59.3 (51.3 - 108)	53.7 (18.7 - 74.7)	216 (123 - 427)	<0.001
Sweetened beverages	33.3 (33.3 - 83.3)	33.3 (6.25 - 133)	33.3 (8.33 - 83.3)	233 (100 - 267)	<0.001
Sugar and sweets	20.0 (20.0 - 20.0)	20.0 (10.0 - 25.0)	15.0 (10.0 - 20.0)	40.0 (20.0 - 45.0)	<0.001
Oils	5.33 (2.67 - 8.00)	10.7 (7.67 - 21.3)	2.67 (2.67 - 5.33)	10.7 (6.67 - 21.3)	<0.001

Figures

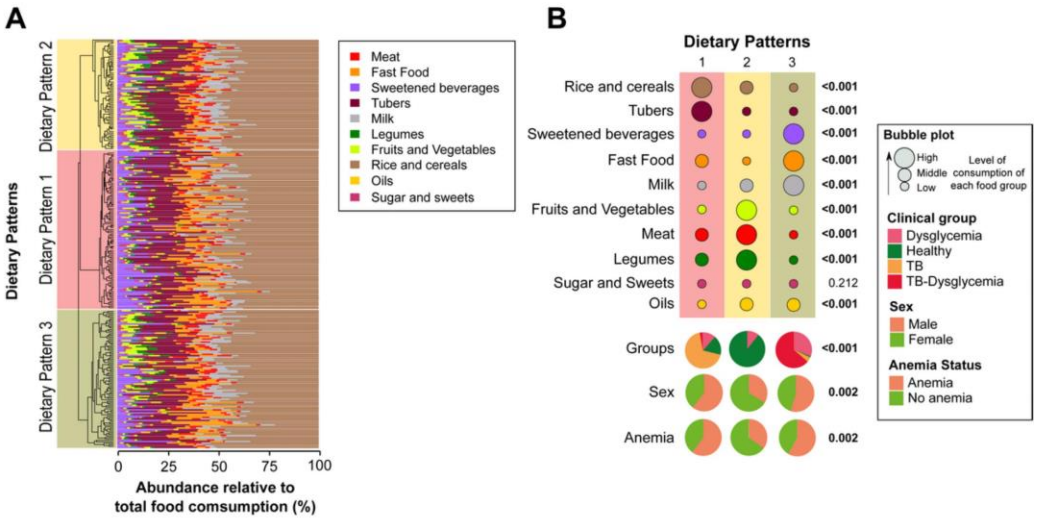

Figure 1

Dietary patterns of food groups using hierarchical clustering. The abundance of consumption of the indicated food groups in the diet was calculated for each one as described in Methods. (A) Hierarchical cluster analysis using Ward's unsupervised method. The dendrograms represent the Euclidean distance and was used to identify different consumption profiles. Using this approach, it was possible to identify three major dietary patterns. (B) Upper panel shows the abundance consumption stratified in high, middle and low, of each food group within each dietary pattern identified in the hierarchical cluster analysis. Lower panel shows frequencies individuals in each dietary pattern stratified by clinical groups, sex and anemia. To calculate the p-values, the average relative abundance of consumption of each food group was compared between the different dietary patterns using two-tailed one-way ANOVA. Proportions of clinical groups, sex and anemia were compared between the different dietary profiles using the Pearson's chi-square test. All p-values are indicated. The values of these analysis are detailed in Supplementary Table 2 and 3. Abbreviatures: TB: Tuberculosis.

Correlations between food consumption and values of FPG and HbA1c. A Spearman correlation test was performed between Fasting plasma glucose (A) or Glycate Hemoglobin (B) versus total consumption in grams of each food group. Significative correlations (|rho| > 0.45 and p < 0.05) for each glycemic test and group are highlighted in red bars. The values of these analysis are detailed in Supplementary Table 4. Abbreviatures: TB: tuberculosis.

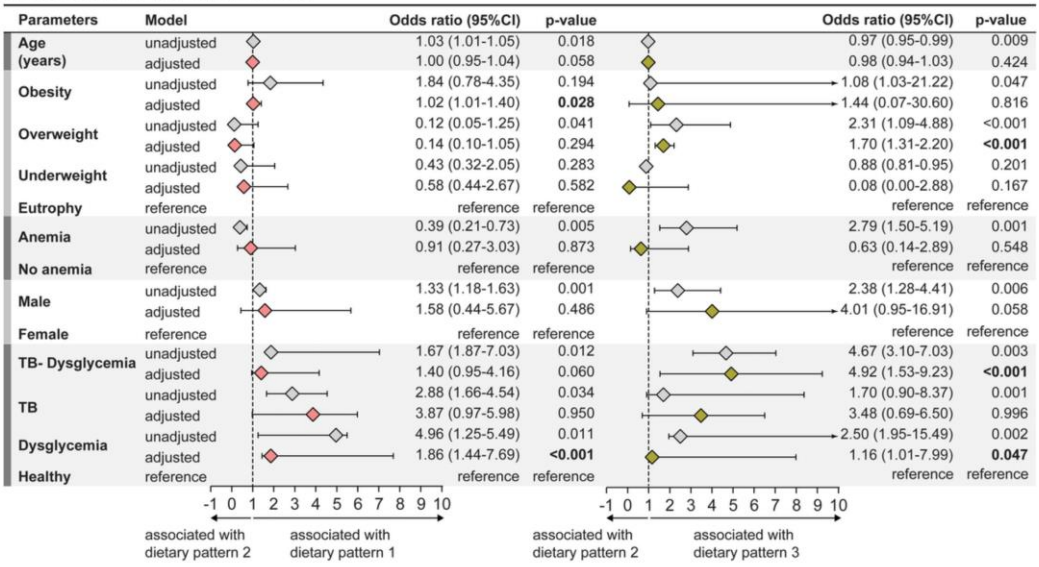

Figure 4

Multinomial logistic regression to test independent associations with the dietary patterns. Adjustment was performed for all variables presented in the figure. The dietary pattern 2 profile was used as reference to test associations between variables and dietary pattern 1 and 3. The statistical significance was estimated through a multinomial logistic regression model. The values of these analysis are detailed in Supplementary Table 2. Abbreviatures: TB: tuberculosis, CI: Confidence interval.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx

Supplementary Material

Supplementary Table 1. R packages used for analysis.

Package	Analysis
compareGroups v4.4.3	Comparison tests
ComplexHeatmap v2.2.0	Unsupervised hierarchical cluster analysis
Hmisc v4.4.1	Spearman rank test
ggplot2 v3.3.2	Data visualization

Table Note: The packages were used in Rstudio v 1.1.463, with R language v3.4.2.

Supplementary Table 2. Characteristics of the study population according dietary patterns.

Parameter	Dietary Pattern 1 n=104	Dietary Pattern 2 n=74	Dietary Pattern 3 n=91	P value
Clinical groups, n. (%)				**<0.001**
Healthy	18 (17.3)	66 (89.2)	1 (1.10)	
Dysglycemia	12 (11.5)	8 (10.8)	28 (30.8)	
TB	71 (68.3)	0 (0.00)	4 (4.40)	
TB Dysglycemia	3 (2.88)	0 (0.00)	58 (63.7)	
Age (years), median (IQR)	26.4 (21.0 - 37.0)	36.9 (23.5 - 48.8)	45.9 (30.5 - 54.0)	**<0.001**
Male, n. (%)	57 (54.8)	25 (33.8)	55 (60.4)	**0.002**
Illiteracy, n. (%)	34 (32.7)	14 (18.9)	11 (12.1)	**0.002**
Prior TB, n. (%)	14 (13.5)	8 (10.8)	15 (16.5)	0.571
Smoking, n. (%)	17 (16.3)	11 (14.9)	20 (22.2)	0.411
Passive smoking, n. (%)	9 (8.65)	10 (13.5)	11 (12.2)	0.557
Cannabis use, n. (%)	13 (12.5)	0 (0.00)	10 (11.1)	**0.008**
Illicit drug use, n. (%)	8 (7.69)	0 (0.00)	10 (11.1)	**0.005**
Alcohol use, n. (%)	40 (38.5)	26 (35.1)	52 (57.8)	**0.005**
Anemia, n. (%)	62 (59.6)	26 (35.1)	53 (58.24)	**<0.001**
BMI (kg/m^2), median (IQR)	22.3 (20.2 - 24.5)	27.4 (25.3 - 30.1)	25.4 (22.7 - 29.6)	**<0.001**
Waist (cm), median (IQR)	79.5 (74.0 - 87.2)	90.0 (83.2 - 98.8)	89.0 (82.0 - 98.0)	**<0.001**
Hb (g/dL), median (IQR)	12.6 (11.6 - 13.6)	13.1 (12.4 - 14.2)	12.5 (11.1 - 13.7)	**0.014**
FPG (g/dL), median (IQR)	91.8 (86.2 - 96.8)	91.8 (88.6 - 96.1)	104 (99.0 - 114)	**<0.001**
HbA1c (%), median (IQR)	5.00 (4.70 - 5.30)	5.05 (4.62 - 5.30)	5.30 (4.90 - 5.90)	**<0.001**

Table Note: The data presented in continuous variables (represented median and interquartile range [IQR]) between clinical groups were compared using the Kruskal-Wallis test with Dunn's multiple comparisons post-test. Qualitative variables were represented by number and frequency (%) and compared using the Pearson's chi-square test. p-values were adjusted for multiple measurements using the Holm-Bonferroni method.
TB: tuberculosis; TB TMG: tuberculosis and dysglycemia; BMI: body mass index; Hb: Hemoglobin; HbA1c: glycated hemoglobin.

Supplementary Table 3. Relative abundance of food group consumption according dietary pattern.

Relative abundance by food group (%)	Dietary Pattern 1 n=104	Dietary Pattern 2 n=74	Dietary Pattern 3 n=91	P value
Rice and cereals	0.52 (0.48 - 0.56)	0.47 (0.42 - 0.49)	0.41 (0.37 - 0.45)	**<0.001**
Tubers	0.21 (0.18 - 0.23)	0.18 (0.16 - 0.19)	0.18 (0.16 - 0.19)	**<0.001**
Milk and dairy	139 (69.3 - 213)	34.7 (34.7 - 61.3)	88.0 (42.7 - 213)	**<0.001**
Fruits and Vegetables	0.01 (0.01 - 0.03)	0.06 (0.03 - 0.08)	0.01 (0.01 - 0.02)	**<0.001**
Legumes	0.02 (0.01 - 0.02)	0.04 (0.03 - 0.05)	0.01 (0.01 - 0.01)	**<0.001**
Meat	0.03 (0.03 - 0.04)	0.05 (0.04 - 0.06)	0.03 (0.02 - 0.04)	**<0.001**
Fast Food	0.06 (0.03 - 0.09)	0.05 (0.03 - 0.07)	0.09 (0.05 - 0.21)	**<0.001**
Sweetened beverages	0.03 (0.01 - 0.07)	0.03 (0.00 - 0.08)	0.10 (0.04 - 0.15)	**<0.001**
Sugar and sweets	0.02 (0.01 - 0.02)	0.02 (0.01 - 0.02)	0.02 (0.01 - 0.03)	0.212
Oils	0.00 (0.00 - 0.01)	0.01 (0.00 - 0.01)	0.01 (0.00 - 0.01)	**<0.001**

Table Note: The data presented in continuous variables (represented median and interquartile range [IQR]) between food groups were compared using the Kruskal-Wallis test with Dunn's multiple comparisons post-test.

Supplementary Table 4. Spearman correlations coefficients

	Fasting Plasma Glucose (g/dL)				Glycated Hemoglobin (%)			
	Without TB (n=133)		With TB (n=136)		Without TB (n=133)		With TB (n=136)	
	Spearman rho	p value	Spearman rho	p value	Spearman rho	p value	Spearman rho	p value
Rice and Cereal	0.580	<0.001	0.478	<0.001	0.28	<0.001	0.376	<0.001
Tubers	0.682	<0.001	0.409	<0.001	0.31	<0.001	0.356	<0.001
Sweetened beverages	-0.035	0.688	0.364	<0.001	0.04	0.681	0.396	<0.001
Fast Food	0.225	0.009	0.523	<0.001	-0.01	0.911	0.325	<0.001
Milk	0.303	<0.001	0.236	0.005	0.09	0.323	-0.278	<0.001
Fruits and Vegetables	-0.281	0.001	0.407	<0.001	-0.05	0.595	0.301	<0.001
Meat	0.183	0.035	0.220	0.009	0.14	0.114	0.393	<0.001
Legumes	-0.556	<0.001	-0.300	<0.001	-0.23	0.007	0.268	<0.001
Sugar and Sweets	0.003	0.969	0.431	<0.001	-0.10	0.255	0.151	0.081
Oils	0.434	<0.001	0.501	<0.001	0.16	0.059	0.273	0.001

Table Note: The data correspond to Spearman rho coefficients between food groups and fasting plasma glucose (left) or glycated hemoglobin (right). To be considered significant, the correlation must have |rho| > 0.45 and p value < 0.05.

7 DISCUSSÃO

Este trabalho é um conjunto de estudos que apresentam diferentes abordagens da TB em duas coortes de pacientes com TB pulmonar e seus contatos no Brasil, e no Peru. Os onze manuscritos que compõem esta tese contribuem para o entendimento detalhado dos principais determinantes clínicos e epidemiológicos de susceptibilidade à TB, bem como fatores associados com desfecho desfavorável no tratamento de TB.

Para iniciar as análises da tese precisávamos testar se a coorte do RePORT- Brasil era representativa da população brasileira. O desafio era comparar os resultados de duas coortes, uma de 1060 indivíduos de 3 estados do Brasil versus uma coorte de 455.873 indivíduos de 26 estados do Brasil sem que as análises foram enviesadas pela diferencia numérica. Seguindo a linha de um dos pilares da Estratégia pelo Fim da TB, que é a intensificação da pesquisa é inovação, decidimos empregar no primeiro manuscrito um novo abordagem estatística para avaliar as características da coorte do RePORT-Brasil e comparamos com os resultados do banco de dados do SINAN (MINISTÉRIO DA SAÚDE DO BRASIL; SECRETARIA DE VIGILÂNCIA EM SAÚDE, 2007).

Um dos achados está relacionado com os desfechos do tratamento, as proporções de cura, óbito e abandono foram similares entre as cortes, mas os relatos de casos com falência no tratamento foram maiores e as transferências mais baixas na coorte de RePORT-Brasil. Isso pode ter acontecido pelas diferenças no acompanhamento dos pacientes em cada coorte. O RePORT-Brasil tem um acompanhamento ativo de até 24 meses após de iniciado o tratamento, enquanto nos centros de saúde na rotina, os pacientes não retornam após terminado o tratamento. Existe uma perda de seguimento nos pacientes transferidos ou que abandonaram o tratamento, tornando-se em subnotificações dos desfechos do tratamento. Esta limitação dos dados do SINAN foi relatada previamente (BALDEZ DO CANTO; BORGES NEDEL, 2020)

Na coorte do RePORT-Brasil, a DM e o uso de drogas ilícitas estiveram associadas independentemente aos desfechos não favoráveis no tratamento anti-TB, enquanto na coorte do SINAN foi a infecção por HIV, o uso de drogas e tratamento prévio de TB. Essas disparidades podem não necessariamente refletir diferenças na prevalência dessas condições na população do estudo, mas sim um diagnóstico e relato mais frequente no RePORT-Brasil porque os testes de HBA1c e HIV foram realizados uniformemente.

Outro achado foi o menor desempenho dos indicadores operacionais e epidemiológicos propostos pela OMS e reportados pelo SINAN, o que pode ser resultado pelo acesso limitado à testes de sensibilidade, à falta de solicitação de rotina para análises de cultura, escarro e HIV entre outros. Os indicadores operacionais do RePORT-Brasil com um desempeno melhor conseguiram identificar com mais precisão a presença de comorbidades e resistência medicamentosa.

Por meio do uso da inovadora ferramenta estatística *second generation-p* que é usada em casos em que os valores tradicionais do *p* são provavelmente afetados pelo tamanho da amostra em cada grupo analítico), observamos que a coorte do RePORT-Brasil é representativa da população brasileira descrita no SINAN. Esse resultado reafirma a importância de se manter a qualidade dos sistemas de notificação de doenças que são base para os relatos da OMS (WORLD HEALTH ORGANIZATION, 2020a). Os achados também fornecem suporte para o desenvolvimento de mais estudos translacionais e a generalização dos seus achados para guiar e implementar estratégias que controlem a TB.

Após de demostrar a representatividade da coorte do RePORT-Brasil, partimos explorar os dados dos contatos. A busca ativa de casos ILTB tem recebido maior atenção entre as estratégias de controle e eliminação da TB (WORLD HEALTH ORGANIZATION, 2018) devido ao seu potencial de expandir a detecção de casos em ambientes com alta carga de TB e reduzir os casos incidentes por transmissão interrompida (WORLD HEALTH ORGANIZATION, 2018). Portanto, deve-se prestar atenção a cada etapa do processo de detecção para minimizar as perdas.

Aplicamos uma análise em cascata usada também no cuidado das pessoas com HIV (NOSYK; MONTANER; COLLEY; LIMA *et al.*, 2014) e adaptado para o acompanhamento de pessoas com ILTB (ALSDURF; HILL; MATTEELLI; GETAHUN *et al.*, 2016) que considerou a etapa inicial como o *screening* dos contatos, seguido da aplicação do TST ou IGRA (e análise do radiograma torácico), recomendação de TPT, início de TPT e completar o TPT. No modelo da cascata foi quantificado o impacto da perda em cada etapa (ALSDURF; HILL; MATTEELLI; GETAHUN *et al.*, 2016) o que permite avaliar melhor as lacunas na condução de investigação do contato. A primeira vez que usamos essa abordagem foi no Manuscrito II, na população de um dos sites onde foi implementado o RePORT-Brasil, localizado em Salvador, Bahia.

Neste estudo identificou-se uma perda maior de acompanhamento na etapa inicial do s*creening* o que foi similar com outros estudos (ARMSTRONG-HOUGH; TURIMUMAHORO; MEYER; OCHOM *et al.*, 2017; SALAME; FERREIRA; BELO; TEIXEIRA *et al.*, 2017; WYSOCKI; VILLA; ARAKAWA; BRUNELLO *et al.*, 2016)

Na cascata também houve perda na aplicação do TST, ademais os contatos com TST positivo foram indicados para iniciar o tratamento preventivo da TB (TPT). A incidência de TB nos pacientes que não terminaram o TPT o foi maior que no grupo que terminou. O manejo sistemático dos contatos e a administração do TPT é eficaz na diminuição da incidência da TB (WYSOCKI; VILLA; ARAKAWA; BRUNELLO *et al.*, 2016; ZELNER; MURRAY; BECERRA; GALEA *et al.*, 2018). Também, cada ano de idade dos contatos estava associada a perdas na cascata, isso possivelmente relacionado ao número de participantes menores de 5 anos no estudo. Em uma pesquisa anterior realizada em nosso meio, observou-se que crianças contactantes de casos com TB têm pouco acesso ao sistema de saúde em diferentes níveis de atendimento (MENDONCA; KRITSKI; SANT'ANNA, 2015).

A limitação neste manuscrito inicial foi que o desenho do estudo era retrospectivo avaliando dados secundários. Portanto, com a experiência adquirida neste manuscrito decidimos usar a cascata de ILTB como abordagem para avaliar a coorte de contatos do RePORT-Brasil.

No Manuscrito III, avaliamos cada tipo de perda de acordo com cada etapa da cascata. Observamos que a maior parte de perdas totais na cascata foram na primeira etapa, o que é consistente com o Manuscrito II e com os artigos publicados que utilizaram esta abordagem. Numa revisão sistemática os motivos estão associados à baixa performance da avaliação de contatos foram: falta de interesse do contato e autopercepção de um baixo risco de infecção pela TB (ALSDURF; HILL; MATTEELLI; GETAHUN *et al.*, 2016).

Outro achado interessante neste estudo foi a associação entre as perdas em geral (não comparecer para o *screening*, não comparecer para a coleta de sangue para o IGRA, não iniciar tratamento quando indicado e não completar o TPT) e os fatores: ser iletrado, ter raça parda ou negra e infecção por HIV. Não há estudos prévios que relatem a relação entre raça ou ser ausência de escolaridade com não completar o TPT. Mas sim estão associados com a descontinuidade do tratamento da TB ativa (VIANA; GONCALVES; BASTA, 2016). Esses

fatores estão relacionados com um baixo status socioeconómico o que pode refletir a dinâmica social no Brasil. E preciso ter mais estudos para validar tais dados.

Os achados descritos nos Manuscrito II e III nos fornecem importantes e informações acerca das perdas gerais na cascata diagnóstica e terapêutica de cuidado de ILTB. Em conjunto nossos resultados reforçam a necessidade de otimizar o atendimento e acompanhamento dos contatos de pacientes com TB para conseguir um impacto no sistema de saúde pública com subsequente queda na incidência da TB.

Ao concluir as análises da coorte de contatos, decidimos explorar na coorte de casos com TB, a associação da DM com desfechos não favoráveis no tratamento anti-TB. A coorte do RePORT-Brasil tem os valores de HbA1c no baseline dos pacientes TB, o que permitiu explorar também o status glicêmico e corroborar os resultados com a coorte do SINAN, excluindo participantes com transferência e abandono no desfecho do tratamento anti-TB e não multirresistentes.

Nosso grupo tinha reportado anteriormente uma associação entre DM e apresentação clínica grave da TB (GIL-SANTANA; ALMEIDA-JUNIOR; OLIVEIRA; HICKSON *et al.*, 2016), incremento da carga bacteriana no escarro (ALMEIDA-JUNIOR; GIL-SANTANA; OLIVEIRA; CASTRO *et al.*, 2016), e o aumento da inflamação persistente na comorbidade TB-DM (MESQUITA; GIL-SANTANA; RAMALHO; TONOMURA *et al.*, 2016). Todos esses achados reforçam a evidência da relação entre a DM e desfechos não favoráveis no tratamento anti-TB. (SHEWADE; JEYASHREE; MAHAJAN; SHAH *et al.*, 2017; SIDDIQUI; KHAYYAM; SHARMA, 2016).

No Manuscrito IV investigamos a associação entre Hb1Ac, DM, pré-DM e disglicemia (DM ou pré-DM) com os desfechos não favoráveis (falência, recorrência e morte durante o tratamento) e apenas com a mortalidade.

Em nosso estudo não observamos associação entre disglicemia ou pré-DM e desfechos desfavoráveis ou mortalidade na coorte do RePORT-Brasil, mas sim com DM, quando ajustados com outros parâmetros clínicos. Os dados do SINAN foram semelhantes, a DM foi associada com desfechos desfavoráveis e com mortalidade. Estudos prévios reportaram que existe uma normalização dos valores glicêmicos durante o tratamento anti-TB em indivíduos com disglicemia que iniciaram o tratamento anti-TB (BOILLAT-BLANCO; RAMAIYA; MGANGA; MINJA *et al.*, 2016; MAGEE; SALINDRI; KYAW; AULD *et al.*, 2018).

Portanto, os efeitos negativos na resposta imune em pacientes com DM que é uma condição crónica, não é apresentado nos indivíduos com pré-DM (BOILLAT-BLANCO; RAMAIYA; MGANGA; MINJA *et al.*, 2016; MAGEE; SALINDRI; KYAW; AULD *et al.*, 2018). Infelizmente não conseguimos avaliar a hiperglicemia transitória porque não foi obtido o status glicêmico durante o tratamento.

Baseados nesses resultados iniciamos outro estudo na coorte prospectiva longitudinal peruana de pacientes com TB pulmonar e identificamos que a disglicemia (diabetes ou pré-diabetes) persistente estava associada com desfechos desfavoráveis no tratamento antituberculose. Esse achado corrobora o resultado do estudo descrito anteriormente. No Manuscrito V capturamos o fenômeno de níveis transitórios persistentes de glicemia elevada (EL-OSTA; BRASACCHIO; YAO; POCAI *et al.*, 2008; MAGEE; BLOSS; SHIN; CONTRERAS *et al.*, 2013) que poderiam impactar no resultado do tratamento da TB, avaliando periodicamente as alterações nos níveis de glicemia de jejum ou HbA1c, semelhante ao relatado em outros países (KORNFELD; WEST; KANE; KUMPATLA *et al.*, 2016; MAGEE; SALINDRI; KYAW; AULD *et al.*, 2018) .

Em nosso estudo, os níveis de HbA1c mudaram ligeiramente durante o tratamento com TB, enquanto a glicemia de jejum foi mais sensível em revelar qualquer efeito nos resultados do tratamento com TB. Isso pode ser explicado pelo fato de que níveis elevados de glicose no sangue causariam efeitos persistentes, apesar da normoglicêmia subsequente, por induzirem alterações epigenéticas ativadoras de longa duração, levando a algumas das variações no risco de complicações que não poderiam ser explicadas pela HbA1c. (EL-OSTA; BRASACCHIO; YAO; POCAI *et al.*, 2008).

Níveis elevados de glicose no sangue foram transitórios em um grupo PWTB, assim como em pacientes com outras doenças (DUNGAN; BRAITHWAITE; PREISER, 2009). Vários marcadores metabólicos foram observados alterados pela inflamação; mas observamos em nosso estudo que, apesar da quimioterapia anti-TB eficaz, o perfil hiper inflamatório poderia persistir durante a fase intensiva do tratamento, conforme relatado anteriormente (KUMAR; FUKUTANI; SHRUTHI; ALVES *et al.*, 2019). Como nosso estudo e outros estudos de nosso grupo demonstraram que não apenas a disglicemia está relacionada a um padrão inflamatório diferente, mas também a anemia (GIL-SANTANA; CRUZ; ARRIAGA; MIRANDA *et al.*, 2019) e neutrofilia (CARVALHO; AMORIM; MELO; SILVEIRA *et al.*,

2021), tem sido relatada como uma resposta hiper inflamatória persistente apesar do início do tratamento da TB.

Nos manuscritos IV e V, pudemos identificar o efeito da disglicemia no resultado do tratamento anti-TB. No Manuscrito IV também identificamos que a infecção pelo HIV é um fator relacionado a desfechos desfavoráveis, razão pela qual iniciamos uma nova investigação para explorar ainda mais a infecção pelo HIV na coorte RePORT-Brasil.

No Manuscrito VI descrevemos a prevalência de disglicemia e infecção pelo HIV em pessoas com TB pulmonar. Na coorte RePORT-Brasil, a prevalência de disglicemia entre os pacientes com TB no início do estudo foi de 61,5%. Essa prevalência foi maior do que a relatada recentemente em Gana (YORKE; BOIMA; DEY; AMISSAH-ARTHUR *et al.*, 2021) e no sul do Brasil (BERALDO; ANDRADE; PINTO; DA SILVA-SOBRINHO *et al.*, 2021). Nos dados do SINAN, observamos que a frequência de TB-DM no Brasil foi de apenas 9,2%, inferior à prevalência global de 15% e superior à prevalência sul-americana de 7,7%, calculada a partir de uma meta- análise de mais de 200 estudos recentes de todo o mundo (NOUBIAP; NANSSEU; NYAGA; NKECK *et al.*, 2019).

No RePORT-Brasil, a maioria dos pacientes com DM ou PDM era soronegativa para o HIV. Outros estudos mostraram essa baixa frequência de infecção pelo HIV associada ao DM no Brasil (ALMEIDA-JUNIOR; GIL-SANTANA; OLIVEIRA; CASTRO *et al.*, 2016). Os níveis de HbA1c também foram semelhantes em pacientes com TB estratificados por status sorológico. Há poucas evidências descrevendo a interação dos valores de HbA1c e HIV em pacientes com TB. No entanto, diferentemente do RePORT-Brasil, no SINAN, os pacientes com TB-DM tiveram uma frequência significativamente menor de infecção pelo HIV do que aqueles que não relataram DM. Essa diferença encontrada pode ser devido ao fato de que o controle glicêmico é realizado em todos os participantes do RePORT-Brasil com diagnóstico de disglicemia, enquanto os casos notificados no SINAN são apenas recomendados, e não obrigatórios, de acordo com as diretrizes brasileiras.

Na coorte do SINAN, a presença de infecção pelo HIV foi associada a maior probabilidade de normoglicêmia na população com TB pulmonar. Assim, os achados aqui apresentados das duas grandes coortes analisadas neste estudo argumentam que a infecção pelo HIV não parece ser um determinante da disglicemia em pacientes com TB pulmonar no Brasil.

A imunodeficiência e uma resposta inflamatória diminuída podem inibir a produção de escarro em pessoas com HIV; esses casos também tendem a ter menos achados radiográficos atípicos (ABAYE; ABEBE; WORKU; TOLESSA *et al.*, 2017), o que é consistente com a menor porcentagem geral de tosse e a menor frequência de radiografias anormais encontradas nos grupos TBDM-HIV, TBDM-HIV e TB-HIV. Entre os grupos de pessoas vivendo com HIV, o HIV-TBDM apresentou maior proporção de radiografias anormais e tosse autorreferida. Nossa hipótese é que a presença de DM pode potencializar mecanismos imunopatológicos que levam a danos teciduais e inflamação resultando em radiografias anormais e tosse.

Mostramos também que a maioria dos pacientes com DM-TB não tinha diagnóstico prévio de disglicemia, o que pode estar associado à subnotificação do DM no banco de dados do SINAN, e que a infecção pelo HIV não foi significativamente associada à disglicemia em pacientes com TB.

Os resultados reportados no Manuscrito IV e V como a implicação que têm a DM no curso clínico da TB e o impacto negativo no desfecho do tratamento anti-TB, somado às características descritas em outras pesquisas como maior extensão das cavidades pulmonares (PIZZOL; DI GENNARO; CHHAGANLAL; FABRIZIO *et al.*, 2016), persistência de tosse (GIL-SANTANA; ALMEIDA-JUNIOR; OLIVEIRA; HICKSON *et al.*, 2016), a negativação tardia do escarro e cultura (GIL-SANTANA; ALMEIDA-JUNIOR; OLIVEIRA; HICKSON *et al.*, 2016; SINGLA; KHAN; AL-SHARIF; AI-SAYEGH *et al.*, 2006), indicaram-nos que a comorbidade TB-DM talvez poderia influenciar na transmissão da Mtb. Para responder esse questionamento empregamos a coorte de pacientes com TB e a coorte dos contatos do RePORT-Brasil.

No Manuscrito VII observamos que dos 1573 contatos estudados, 1% foram diagnosticados com TB ativa no início do estudo e 42% foi diagnosticado com ILTB. Esses resultados foram consistentes com uma metanálise realizada de estudos conduzidos em países de baixa e média renda, incluindo o Brasil (FOX; BARRY; BRITTON; MARKS, 2013). Ademais só 5% dos contatos foram diagnosticados com DM, o que poderia ser uma subestimação porque não todos foram testados com HbA1c e a maioria deles deu uma resposta auto-reportada do diagnóstico de DM.

Identificamos que 609 indivíduos eram contatos de pacientes com TB-normoglicêmicos e 1186 eram contatos de casos de TB-disglicemia. Além disso nas análises multivariadas observamos que as características dos casos TB como ter pré-DM junto com BAAR positivo, cavitações pulmonares e ser tabagista passivo estavam independentemente associados com um resultado positivo no IGRA nos contatos. E os contatos de pacientes TB-DM tinham 1.21 mais chances de estar infetado com Mtb, quando ajustados com outras características dos casos TB como tose persistente, BAAR positivo e presença de cavitações pulmonares. Em estudos prévios foi relatada a relação da tose persistente, presença de cavitações e BAAR positivo e a transmissão de Mtb (GIL-SANTANA; ALMEIDA-JUNIOR; OLIVEIRA; HICKSON *et al.*, 2016; PIZZOL; DI GENNARO; CHHAGANLAL; FABRIZIO *et al.*, 2016) que respaldam nossos resultados.

Esses resultados confirmam a nossa hipótese, a condição de TB-DM influencia na transmissão de Mtb aos contatos. No Manuscrito VII é descrito um importante conhecimento na área que pode ser empregado em futuras estratégias no sistema de saúde na busca e seguimento adequado de contatos de pacientes com TB-DM e uma intervenção precoce com o objetivo de reduzir a incidência da TB.

Nos Manuscritos IV e V avaliamos os efeitos da disglicemia, diabetes e pré-DM no tratamento e na transmissão da Mtb, por causa da relevância achada da DM na tuberculose, acreditamos que é importante explorar os testes diagnósticos para DM, para isso empregamos dados do sítio de Salvador do Brasil e os dados da coorte do Peru, do grupo de *Socios en Salud*.

Com a implementação da Estratégia pelo Fim da TB houve uma diminuição da incidência global da TB. Entretanto nos últimos anos no Brasil e o Peru países com maior carga de TB nas Américas, ocorreu um aumento no número de casos diagnosticados de TB pulmonar e extrapulmonar (RANZANI; PESCARINI; MARTINEZ; GARCIA-BASTEIRO, 2021). Além disso, a carga de DM nesses países tem aumentado nos últimos anos (UGARTE-GIL; CURISINCHE; HERRERA-FLORES; HERNANDEZ *et al.*, 2021; WORLD HEALTH ORGANIZATION, 2020a). Os programas de controle da TB nos dois países recomendam a triagem para DM em pacientes com TB (MINISTÉRIO DA SAÚDE DO BRASIL; SECRETARIA DE VIGILÂNCIA EM SAÚDE, 2013; MINISTERIO DE SALUD- PERÚ, 2013), sendo que na rotina dos dois países utiliza-se a glicose plasmática em jejum (GPJ) e em alguns casos a HbA1c (MINISTÉRIO DA SAÚDE DO BRASIL; SECRETARIA DE

VIGILÂNCIA EM SAÚDE, 2013; MINISTERIO DE SALUD- PERÚ, 2013). No Manuscrito VIII avaliamos os testes diagnósticos para DM usados em pessoas com TB ativa.

Nossos resultados foram interessantes, pois observou-se uma diferente acurácia de HbA1c e glicose plasmática de jejum (GPJ) entre os países do Brasil e Peru. No Brasil houve melhor desempenho da HbA1c e no Peru da GPJ. Esses resultados reforçam os achados de estudos prévios, como na Índia, onde a HbA1c teve um melhor desempenho que o GPJ (KUMPATLA; ARAVINDALOCHANAN; RAJAN; VISWANATHAN *et al.*, 2013) ou outro estudo no Paquistão (AFTAB; AMBREEN; JAMIL; GARRED *et al.*, 2017) que identificou que o GPJ classificou mais falsos diabéticos. Nós elaboramos a hipótese de que esses resultados podem ser determinados pelos fatores genéticos ou ambientais de cada região. Em outros estudos observou-se que os valores de HbA1c variam de acordo com a etnicidade (CAVAGNOLLI; PIMENTEL; FREITAS; GROSS *et al.*, 2017; HERMAN; MA; UWAIFO; HAFFNER *et al.*, 2007) ou com abnormalidades nos eritrócitos atuando como confundidores para as análises de HbA1c (ENGLISH; IDRIS; SMITH; DHATARIYA *et al.*, 2015). Uma das limitações foi não analisar quais fatores são responsáveis da heterogeneidade dos países como raça ou variações genéticas na hemoglobina.

Os resultados obtidos reforçam a necessidade de rever a linha de cuidado na detecção de TB e DM. Deve ser lavado em conta as diferenças entre regiões e possíveis padrões genéticos. Com os resultados do Manuscrito VIII, iniciamos a caracterização dos pacientes TB-DM na coorte do Peru. No Manuscrito IX analisamos a prevalência da DM e pré-DM nos casos de TB e em seus contatos.

Apesar de que o Peru tem a segunda maior carga de TB e que é amplamente conhecido o risco de TB nos pacientes com DM (JEON; MURRAY, 2008) e o impacto negativo que tem a DM no curso clínico e do tratamento(GIL-SANTANA; ALMEIDA-JUNIOR; OLIVEIRA; HICKSON *et al.*, 2016; KREISEL; PASSANNANTE; LARDIZABAL, 2019), existem discrepâncias entres as publicações acerca da incidência de DM no Peru, ao ser utilizado apenas GPJ para triagem de DM. Nós elaboramos a hipótese de que existe uma maior frequência de DM o que significa é provável uma subnotificação dos casos TB-DM no Peru.

Foi inesperada a elevada prevalência de DM e pré-DM na coorte de pacientes com TB (14%) e nos contatos (6,5%), por conta dos dados que o Ministério de Saúde do Peru descritos de apenas 6,2%. A prevalência observada em nosso estudo foi similar ao descrito em outra

pesquisa prévia (UGARTE-GIL; ALISJAHBANA; RONACHER; RIZA *et al.*, 2019). A subnotificação dos casos TB-DM pode ser uma resposta à falta de seguimento sistemático e de uma padronização dos testes para diagnóstico de TB-DM.

Outro interessante e preocupante resultado foram os baixos níveis da hemoglobina nos pacientes TB-DM, todos os pacientes TB-DM tinham anemia. Em estudo realizado no Brasil observou-se que a anemia está relacionada a um perfil inflamatório sistêmico até dois meses após iniciado o tratamento anti-TB (GIL-SANTANA; CRUZ; ARRIAGA; MIRANDA *et al.*, 2019). Ademais, aparentemente a detecção de DM não foi afetada pelo estado anêmico dos pacientes em comparação de outros estudos que sim identificaram mudanças no diagnóstico da DM (GIL-SANTANA; CRUZ; ARRIAGA; MIRANDA *et al.*, 2019). Nosso estudo não foi elaborado para avaliar o status anêmico dos participantes, mas nossos achados podem servir de base para novas pesquisas de anemia e TB. Os resultados deste manuscrito indicam que a triagem de DM precisa ser padronizada como rotina nas intervenções clínicas para a detecção oportuna dos pacientes TB-disglicemia no sistema de saúde do Peru.

Os resultados de uma elevada prevalência de DM nos casos TB e baixos níveis de hemoglobina nas pessoas com TB-DM na coorte de Peru, impulsionou a explorar mais as características dessa população. O Manuscrito X descreve a associação entre a condição TB-DM e as manifestações radiográfica.

A radiografia (Rx) de tórax é um suporte importe no diagnóstico e seguimento da TB. Diferentes pesquisas tem relatado achados anormais graves na Rx de tórax de pessoas com TB-DM, mas outros estudos demostraram não ter diferenças entre as apresentações de lesões pulmonares no Rx. Para esclarecer essas contradições, neste estudo avaliamos com mais detalhe a associação de TB-DM e as manifestações radiográficas.

Três tipos de lesões foram achados neste estudo, as cavitações, infiltrados e tratos fibrosos e mais de 4 lesões no pulmão, as duas condições associadas a disglicemia, o que coincide com outros reportes prévios (GIL-SANTANA; CRUZ; ARRIAGA; MIRANDA *et al.*, 2019). É possível que pacientes disglicêmicos apresentassem TB mais avançada, o que poderia ter impactado as características radiográficas indicadas por outros(GIL-SANTANA; CRUZ; ARRIAGA; MIRANDA *et al.*, 2019). Nossos achados também indicam que a disglicemia está associada a aumentos significativos na quantidade, diversidade e localização de lesões tuberculóides, (CHIANG; BAI; LIN; CHIEN *et al.*, 2015). Nossos achados revelam

que a hiperglicemia foi associada a processos inflamatórios caracterizados por elevação dos níveis de leucócitos e aumento dos níveis de transaminases, colesterol total e triglicerídeos no soro, enquanto os níveis de albumina e hemoglobina diminuíram, sugerindo anemia. Na análise de agrupamento hierárquico observamos ainda que o perfil celular e bioquímico associado à hiperglicemia também estava relacionado à ocorrência de aumento no número e diversidade de lesões pulmonares. Em um estudo anterior descrevemos que a anemia estava relacionada à TB e a um perfil inflamatório distinto que persiste após o início da terapia antituberculár em uma coorte brasileira, (GIL-SANTANA; CRUZ; ARRIAGA; MIRANDA *et al.*, 2019) mas não testamos anteriormente a associação entre anemia e hiperglicemia na apresentação clínica ou radiográfica da TB. É possível que a progressão da TB vincule essas duas condições fisiopatológicas aparentemente distintas, por meio de um mecanismo que pode envolver inflamação crônica. Esses achados advertem da necessidade de melhorar o rastreamento e diagnóstico para o controle glicêmico adequado em pacientes com TB. Estudos adicionais devem ser realizados para entender como o aumento da extensão da lesão pulmonar da TB observada em pacientes disglicêmicos pode afetar a transmissão da Mtb.

No manuscrito IX, além de achar uma alta prevalência de DM entre as pessoas com TB, os indivíduos com TB-DM tiveram todos baixos níveis de hemoglobina. Esse último achado nos levou a questionar o estado nutricional dessa população. Antes nosso grupo já tinha avaliado o estado nutricional de adolescentes empregando uma abordagem com padrões nutricionais e ferramentas de *Big Data* e Biologia de Sistemas Multidimensional, que chamamos de *systems nutrology* (ANDRADE; DE SANTANA; FUKUTANI; QUEIROZ et al., 2019; ANDRADE; SANTANA; FUKUTANI; QUEIROZ et al., 2020). No manuscrito X descrevemos o padrão dietético associado à disglicemia em pacientes com TB.

Em vários estudos foi avaliada a relação da ingestão alimentar com o risco de tuberculose (KRAWINKEL, 2012) e, separadamente, com o diabetes. Além disso, em outros estudos foi relatada a variação do IMC entre pacientes com TB, antes, durante e ao final do tratamento da TB (BHARGAVA; CHATTERJEE; JAIN; CHATTERJEE *et al.*, 2013) e o baixo peso como um fator de alto risco para TB específico e não TB -mortalidade específica durante o tratamento anti-TB (YEN; CHUANG; YEN; LIN *et al.*, 2016). No entanto, existe uma lacuna na literatura sobre a avaliação dos padrões alimentares na comorbidade de TB e DM e se tais informações podem ser úteis para orientar a otimização do manejo clínico.

No Manuscrito XI empregamos nossa abordagem de *systems nutrology* para caracterizar os padrões alimentares em indivíduos com TB e disglicemia em uma coorte de pessoas com TB de Lima, Peru.

Ao analisar os padrões alimentares (DP) de acordo com a abundância relativa dos grupos alimentares consumidos, foi possível observar que o arroz e os cereais foram o grupo alimentar mais representativo nos três aglomerados, seguido pela batata-doce. Através do análises de agrupamento, identificamos três padrões alimentares. Em geral, o DP1 foi predominantemente composto por pacientes com TB sem disglicemia, e menor frequência de pessoas com anemia. Em contrapartida, a DP2, que apresentou a maior frequência do sexo feminino, apresentou maior consumo de frutas e hortaliças, leguminosas e carne, enquanto a DP3, com a maioria de pacientes TB-disglicêmicos e maior frequência de anemia, apresentou as maiores ingestão de bebidas adoçadas, fast food e leite.

No Peru, o arroz é a base da dieta e, de acordo com o Ministério da Agricultura do Peru, o consumo de arroz cresceu 25% entre 2001 e 2009 (MINISTERIO DE AGRICULTURA-PERÚ, 2010) É provável que o consumo de arroz na comorbidade TB-Disglicemia, fosse alto, assim como o consumo de tubérculos (por exemplo, batata) e alguns outros cereais. A ingestão de batata foi comumente associada a um risco aumentado de diabetes, por meio de um mecanismo relacionado ao aumento dos níveis de glicose, embora o índice glicêmico da batata dependa em grande parte da cepa e do método usado na preparação (FOSTER-POWELL; HOLT; BRAND-MILLER, 2002). Devido a esse conhecimento popular, que a população com disglicemia evite esse tipo de alimentação, justificando os níveis mais baixos no DP3. Por outro lado, como a tuberculose costuma estar associada a pior estado nutricional, espera-se que a ingestão de alimentos ricos em carboidratos, como a batata, seja estimulada nessa população, como pode ser verificado no DP1. É notável descobrir que as orientações de saúde recomendam o consumo de alimentos ricos em carboidratos complexos, como batata, batata doce, arroz, trigo e cereais (LEE; PAZ-SOLDAN; RILEY-POWELL; GOMEZ *et al.*, 2020). Esses novos padrões alimentares têm causado diversos problemas de saúde. Alimentos ultra processados são realmente preferidos pela população peruana e, embora várias mensagens tenham aparecido para evitar o uso de algumas bebidas, especialmente refrigerantes ou refrigerantes, os chamados sucos de frutas engarrafados junto com fontes de amido são amplamente preferidos e desviados por uma mensagem ruim, pouco tempo para o

preparo de bebidas melhores e baixa possibilidade econômica de evitá-las (LÁZARO SERRANO; DOMÍNGUEZ CURI, 2019).

Uma limitação nesse estudo foi que não estudamos a dieta e a inflamação, estudos anteriores de nosso grupo mostraram que a dieta influencia no estado inflamatório, mas em nossas pesquisas a futuro esse campo será investigado. Outra limitação foi que não exploramos a interação da dieta e outras comorbidades. Caracterizar a composição e heterogeneidade da dieta alimentar, principalmente em pacientes com a comorbidade TB-disglicemia, nos ajudará a traçar políticas voltadas para promover um estado de vida saudável, além de atualizar as guias nutricionais com essa comorbidade.

Os onze manuscritos apresentados e discutidos aqui, em conjunto dão luz a determinantes importantes para susceptibilidade da Mtb e para a resposta terapêutica também são base para a implementação de estratégias com intervenções mais específicas como o objetivo de controlar a TB no Brasil. O uso de ferramentas e abordagens inovadoras permitiram aperfeiçoar a conduzir a uma melhora no nível de qualidade da pesquisa para dar resposta ao desafio da saúde pública, que é reduzir até erradicar a TB no mundo.

8 **CONCLUSÕES**

Os resultados dos manuscritos descritos na tese proporcionaram as seguintes conclusões:

- Com as análises do valor p de segunda geração demostramos que as coortes do RePORT-Brasil e do SINAN-TB eram similares, sendo que a coorte de RePORT-Brasil é representativa da população brasileira com TB. Adicionalmente, RePORT-Brasil mostrou uma significativa maior capacidade diagnóstica.

- Identificamos perdas em todos os estágios da cascata diagnóstica e terapêutica de ILTB, principalmente nas etapas iniciais de triagem. Contatos próximos com a idade avançada, baixo nível socioeconômico e vivendo com HIV estavam em maior risco de não completar a cascata de cuidados de ILTB no Brasil.

- Observamos que a DM é uma doença com prevalência crescente e um importante fator de risco para desfechos desfavoráveis no tratamento anti-TB, incluindo morte durante o tratamento, junto com a infecção por HIV e o uso de substâncias.

- Identificamos que a disglicemia persistente também está significativamente associada a maiores chances de resultados desfavoráveis do tratamento da TB.

- Descrevemos uma alta prevalência de disglicemia em pacientes com TB pulmonar no Brasil, independentemente do status de HIV.

- Identificamos que a presença de HIV não afeta substancialmente a apresentação clínica em pessoas com TBDM, embora esteja associada ao uso mais frequente de drogas recreativas e amostras de escarro negativas durante a triagem de TB.

- Confirmamos que os contatos de casos de TB com disglicêmia têm maior risco de ter um resultado de QuantiFERON positivo no baseline ou no mês 6 o que evidencia que os participantes com TB-disglicêmicos podem transmitir mais Mtb para contatos.

- Nas análises apresentadas no estudo de DM em pacientes com TB atendidos no Brasil e Peru, observamos resultados discriminativos diferentes para o diagnóstico de

disglicêmia, destacando-se pelo desempenho superior da HbA1c no Brasil, enquanto a glicemia em jejum apresentou melhor acurácia entre os casos TB do Peru.

- Os resultados revelaram uma elevada prevalência de DM e pré-DM previamente subnotificada em pacientes com TB do Peru. Assim, usar apenas HbA1c pode levar a um erro de subnotificação de pré-DM nos pacientes TB.

- A disglicemia (DM ou pré-DM) incrementa significativamente a frequência e os tipos de lesões pulmonares no radiograma torácico em pessoas com TB. Nesses pacientes também se observou alterações significativas nos perfis bioquímicos, sugerindo estados metabólicos distintos que provavelmente contribuem para o aumento da gravidade da doença pulmonar.

- O uso da abordagem analítica multidimensional em nutrologia (*Systems Nutrology*) identificou o padrão alimentar associado ao grupo de pacientes com TB e disglicêmia, caracterizado pelo ao aumento da ingestão de arroz e cereais, *fast food* e óleos.

Em conjunto, os diversos trabalhos expostos nesta presente tese, adicionam conhecimento relevante para melhor entendimento sobre os determinantes da TB. Os resultados aqui discutidos fornecem uma base sólida para fundamentar e direcionar políticas de saúde pública no Brasil, e em outros países com semelhantes perfis epidemiológicos, com foco na otimização do controle da TB. A **Tabela 4** delineia um paralelo entre os resultados de cada manuscrito e as possíveis recomendações direcionadas para o Ministério da Saúde do Brasil. As perspectivas de uso dos conhecimentos gerados pela tese têm grande potencial para auxiliar a gestão do SUS para que o Brasil consiga progredir de maneira mais substancial no plano global de erradicação da TB estabelecido pela OMS.

Tabela 4 - Conclusões dos manuscritos da tese e recomendações

Conclusões	Recomendações
· Com as análises do valor p de segunda geração demostramos que as coortes do RePORT-Brasil e do SINAN-TB eram similares, sendo que a coorte de RePORT-Brasil é representativa da população brasileira com TB. Adicionalmente, RePORT-Brasil mostrou uma significativa. maior capacidade diagnóstica.	• Como parte dos esforços para atender aos objetivos da iniciativa ENDTB, o programa de controle de TB deve continuar com o caminho da inovação em todas as áreas, tomando modelos aplicados em estudos com outras doenças que permitam uma avaliação adequada das coortes de pacientes e consequentemente melhores decisões clínicas para alcançar a erradicação da doença. • A atualização da base de dados do SINAN, bem como o monitoramento dos dados e as bases de dados nacionais interligadas, ajudaria a obter melhores indicadores de qualidade, o que permitiria uma avaliação adequada das coortes de pacientes e, consequentemente, melhores decisões clínicas. Recomendamos a prática de avaliar a representatividade das coortes, pois permite identificar viés de seleção e se as estimativas derivadas da coorte estão corretas.
· Identificamos perdas em todos os estágios da cascata diagnóstica e terapêutica de ILTB, principalmente nas etapas iniciais de triagem. Contatos próximos com a idade avançada, baixo nível socioeconômico e vivendo com HIV estavam em maior risco de não completar a cascata de cuidados de ILTB no Brasil.	• A maior parte das perdas de seguimento dos contatos de pessoas com TB, foram nas duas primeiras fases da cascata (1ª comunicação com o contacto para identificação e a 2da etapa para avaliação), pelo que consideramos que a melhora da a abordagem dos contatos deve se tornar prioridade dentro do atendimento e acompanhamento dos contatos de pacientes com TB.

Conclusões	Recomendações
· Observamos que a DM é uma doença com prevalência crescente e um importante fator de risco para desfechos desfavoráveis no tratamento anti-TB, incluindo morte durante o tratamento, junto com a infecção por HIV e o uso de substâncias.	• Para pessoas com a comorbidade TB-DM, recomenda-se manter o acompanhamento que garanta o controle glicêmico do paciente, reduzindo assim as chances de um desfecho não favorável no tratamento da TB.
• Identificamos que a disglicemia persistente também está significativamente associada a maiores chances de resultados desfavoráveis do tratamento da TB.	
· Descrevemos uma alta prevalência de disglicemia em pacientes com TB pulmonar no Brasil, independentemente do status de HIV.	• Para melhorar a detecção precoce e melhorar o manejo do DM e HIV entre os pacientes com TB, recomenda-se a triagem de rotina, estabelecida e recomendada pelo programa de controle da TB, mas com uma melhor estrutura colaborativa nos ambientes de saúde existentes.
· Identificamos que a presença de HIV não afeta substancialmente a apresentação clínica em pessoas com TBDM, embora esteja associada ao uso mais frequente de drogas recreativas e amostras de escarro negativas durante a triagem de TB.	
· Confirmamos que os contatos de casos de TB com disglicemia têm maior risco de ter um resultado de QuantiFERON positivo no baseline ou no mês 6 o que evidencia que os participantes com TB-disglicêmicos podem transmitir mais Mtb para contatos.	• Mais pesquisas são necessárias para abordar as limitações de nosso artigo (por exemplo o uso de só um teste diagnostico de DM), além de reiterar a importância do diagnóstico oportuno da TB em pacientes com DM e vice-versa para o controle da transmissão da TB.

Conclusões	Recomendações
· Nas análises apresentadas no estudo de DM em pacientes com TB atendidos no Brasil e Peru, observamos resultados discriminativos diferentes para o diagnóstico de disglicemia, destacando-se pelo desempenho superior da HbA1c no Brasil, enquanto a glicemia em jejum apresentou melhor acurácia entre os casos TB do Peru.	• O papel dos testes diagnósticos para DM em pessoas com TB deve ser avaliado em diferentes populações e durante o seguimento do tratamento anti-TB.
· Os resultados revelaram uma elevada prevalência de DM e pré-DM previamente subnotificada em pacientes com TB do Peru. Assim, usar apenas HbA1c pode levar a um erro de subnotificação de pré-DM nos pacientes TB.	
· A disglicemia (DM ou pré-DM) incrementa significativamente a frequência e os tipos de lesões pulmonares no radiograma torácico em pessoas com TB. Nesses pacientes também foi observado alterações significativas nos perfis bioquímicos, sugerindo estados metabólicos distintos que provavelmente contribuem para o aumento da gravidade da doença pulmonar.	• É necessário dar mais atenção aos exames de rotina no atendimento de pacientes com TB, como a radiografia de tórax em pacientes com TB-disglicemia que ajuda a identificar e priorizar pacientes de alto risco para uma apresentação clínica desfavorável da doença ou com resultado desfavorável no tratamento anti-TB
· O uso da abordagem analítica multidimensional em nutrologia (*Systems Nutrology*) identificou o padrão alimentar associado ao grupo de pacientes com TB e disglicemia, caracterizado pelo ao aumento da ingestão de arroz e cereais, *fast food* e óleos.	• A implementação de novas abordagens na avaliação nutricional como o padrão alimentar dos pacientes com TB pode contribuir na melhora do estado nutricional e assim encontrar o ponto de equilíbrio do controle glicêmico que seria a chave para prevenir complicações da TB e disglicemia ao mesmo tempo

Fonte: Elaborado pela autora

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ZELNER, J.; MURRAY, M.; BECERRA, M.; GALEA, J. *et al.* Protective effects of household-based TB interventions are robust to neighbourhood-level variation in exposure risk in Lima, Peru: a model-based analysis. **Int J Epidemiol**, 47, n. 1, p. 185-192, Feb 1 2018.

Anexo A - Produção científica

María Arriaga iniciou o doutorado como bolsista de Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB). Durante o período do doutorado, publicou 51 artigos, deles, em 5 teve a primeira autora, em 12 compartilhou a primeira autoria, em 1 compartilhou a autoria sênior e em 33 artigos teve função de colaboradora. Além disso, nesse mesmo período apresentou abstracts em 3 congressos, 1 webinar e em 4 reuniões/seminários internacionais. Quatro artigos estão em revisão e cinco artigos estão em etapa final da escrita.

A **Figura Anexo 1** detalha os dados publicados e em seguida os artigos publicados estão listados por ano de trabalho

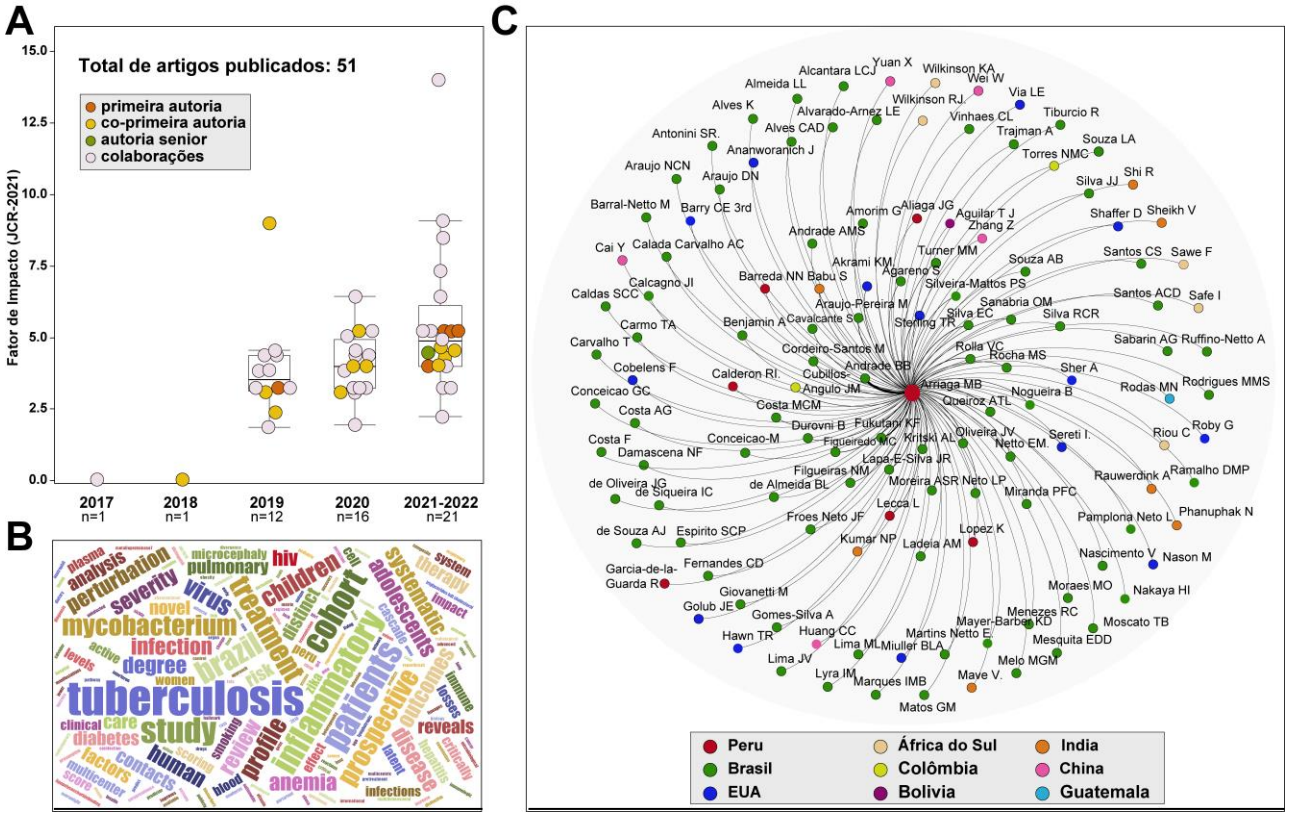

Figura Anexo 1. Artigos publicados no período do doutorado (2017-2021). (A) Frequência de artigos publicados no período do doutorado entre os anos 2017-2022 e o fator de impacto (JCR 2021) das revistas onde foram publicados os artigos, classificados pelo tipo de participação, no período do doutorado. Entre os anos 2017 e 2018 foi realizado o planejamento dos projetos. **(B)** Desenho de rede "World Cloud**"** mostrando as palavras mais frequentes nos títulos dos artigos publicados durante o período do doutorado. A palavra mais frequente foi "tuberculose". **(C)** Análises de redes mostram cada co-autor dos artigos publicados durante o período do doutorado. As circunferências são os autores e a cor o país do co-autor. A espessura de cada linha é proporcional ao número de colaborações em conjunto. Abreviaturas**:** JRC: Journal Citation Reports.

Anexo B - Lista de artigos publicados durante o período do doutorado

Ano 2017

1 AGUILAR, J, **ARRIAGA MB**, ZEBALLOS DR, CHAVES TORRES NF, Entendiendo la Odds Ratio, Scientifica. Jun 2017

Ano 2018

1 CALDERON RI, **ARRIAGA MB**, LOPEZ KT, BARREDA ND, MITNICK C, DAVIES G, COLEMAN D, Fosfomycin to Control Contamination in M. tuberculosis Culture in BACTEC MGIT 960 System European Journal of Clinical and Biomedical Sciences 4(3):51, January 2018

Ano 2019

1 AGUILAR, J. P.; **ARRIAGA, M. B**.; RODAS, M. N.; MARTINS NETTO, E. Smoking and pulmonary tuberculosis treatment failure: a case-control study. J Bras Pneumol, 45, n. 2, p. e20180359, Apr 25 2019.

2 ALBUQUERQUE, V. V. S.; KUMAR, N. P.; FUKUTANI, K. F.; VASCONCELOS, B.; **ARRIAGA, M. B.;** SILVEIRA-MATTOS, P. S.; BABU, S.; ANDRADE, B. B. Plasma levels of C-reactive protein, matrix metalloproteinase-7 and lipopolysaccharide-binding protein distinguish active pulmonary or extrapulmonary tuberculosis from uninfected controls in children. Cytokine, 123, p. 154773, Nov 2019.

3 ANDRADE, V. M. B.; DE SANTANA, M. L. P.; FUKUTANI, K. F.; QUEIROZ, A. T. L.; **ARRIAGA, M. B.;** CONCEIÇÃO-MACHADO, M. E. P.; SILVA, R. C. R.; ANDRADE, B. B. Multidimensional Analysis of Food Consumption Reveals a Unique Dietary Profile Associated with Overweight and Obesity in Adolescents. Nutrients, 11, n. 8, Aug 19 2019.

4 **ARRIAGA, M. B**.; TORRES, N. M. C.; ARAUJO, N. C. N.; CALDAS, S. C. C.; ANDRADE, B. B.; NETTO, E. M. Impact of the change in the antitubercular regimen from three to four drugs on cure and frequency of adverse reactions in tuberculosis patients from Brazil: A retrospective cohort study. PLoS One, 14, n. 12, p. e0227101, 2019.

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6 CHAVES TORRES, N. M.; QUIJANO RODRÍGUEZ, J. J.; PORRAS ANDRADE, P. S.; **ARRIAGA, M. B**.; NETTO, E. M. Factors predictive of the success of tuberculosis treatment: A systematic review with meta-analysis. PLoS One, 14, n. 12, p. e0226507, 2019.

7 CUBILLOS-ANGULO, J. M.; **ARRIAGA, M. B**.; SILVA, E. C.; MÜLLER, B. L. A.; RAMALHO, D. M. P.; FUKUTANI, K. F.; MIRANDA, P. F. C.; MOREIRA, A. S. R.; RUFFINO-NETTO, A.; LAPA, E. S. J. R.; STERLING, T. R.; KRITSKI, A. L.; OLIVEIRA,

M. M.; ANDRADE, B. B. Polymorphisms in TLR4 and TNFA and Risk of Mycobacterium tuberculosis Infection and Development of Active Disease in Contacts of Tuberculosis Cases in Brazil: A Prospective Cohort Study. Clin Infect Dis, 69, n. 6, p. 1027-1035, Aug 30 2019.

8 DEMITTO, F. O.; SCHMALTZ, C. A. S.; SANT'ANNA, F. M.; **ARRIAGA, M. B**.; ANDRADE, B. B.; ROLLA, V. C. Predictors of early mortality and effectiveness of antiretroviral therapy in TB-HIV patients from Brazil. PLoS One, 14, n. 6, p. e0217014, 2019.

9 FERNANDES, C. D.; **ARRIAGA, M. B**.; COSTA, M. C. M.; COSTA, M. C. M.; COSTA, M. H. M.; VINHAES, C. L.; SILVEIRA-MATTOS, P. S.; FUKUTANI, K. F.; ANDRADE, B. B. Host Inflammatory Biomarkers of Disease Severity in Pediatric Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. Open Forum Infect Dis, 6, n. 12, p. ofz520, Dec 2019.

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Anexo C - Lista dos Artigos

Esta tese é baseada nos seguintes manuscritos numerados

Manuscrito I
Novel stepwise approach to assess representativeness of a large multicenter observational cohort of tuberculosis patients: The example of RePORT Brazil.
Int J Infect Dis 2021, 103:110-118.

Manuscrito II
Determinants of losses in the latent tuberculosis cascade of care in Brazil: A retrospective cohort study
Int J Infect Dis 2020, 93:277-283.

Manuscrito III
Determinants of losses in the latent tuberculosis infection cascade of care in Brazil.
BMJ Glob Health 2021

Manuscrito IV
The Effect of Diabetes and Prediabetes on Anti-tuberculosis Treatment Outcomes: A Multicentric Prospective Cohort Study
J Infect Dis. 2021

Manuscrito V
Persistent dysglycemia is associated with unfavorable treatment outcomes in patients with pulmonary tuberculosis from Peru
Int J Infect Dis 2022

Manuscrito VI
Prevalence and Clinical Profiling of Dysglycemia and HIV infection in Persons with Pulmonary Tuberculosis in Brazil
Front Med 2022, fmed.2021.804173

Manuscrito VII
The Effect of Diabetes and Prediabetes on *Mycobacterium tuberculosis* Transmission to Close Contacts.
J Infect Dis. 2021, jiab264

Manuscrito VIII
Divergence in Accuracy of Diabetes Screening Methods in Tuberculosis Patients: A Cross-Sectional Study from Brazil and Peru
Plos One (submetido). Pré-print na plataforma *Research Square* 2021

Manuscrito IX
High prevalence and heterogeneity of Dysglycemia in patients with tuberculosis from Peru: a prospective cohort study
BMC Infect Dis. 2019, 11;19:799.

Manuscrito X
Severe pulmonary radiological manifestations are associated with a distinct biochemical profile in blood of tuberculosis patients with dysglycemia.
BMC Infect Dis. 2020, 14;20:139.

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