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Risk assessment and rationalization of health resource allocation: Lessons from the Brazilian COVID-19 cohort in 2020

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1. Introduction

On December 31st, 2019, the World Health Organization (WHO) was alerted to several cases of pneumonia in China (PAHO, 2021). The coronavirus spread rapidly throughout China, and subsequently infected patients were identified in other countries in Europe, the United States, Canada, and Brazil. On March 11, 2020, the WHO declared the disease a global pandemic (Boletim Epidemiológico Especial - Doenca pelo Coronavírus COVID-19., 2021). Initial reports suggested that the severity of illness was associated with advanced age and the presence of underlying health conditions (Boletim Epidemiológico Especial - Doenca pelo Coronavírus COVID-19., 2021).

In 2020, Brazil recorded 6·5 million cases of SARS-CoV-2, of which 104,000 were either severe or critical infections that required hospitalization, ventilatory support (VS), or intensive care (IBGE, 2021). By May 22nd, 2021, Brazil has accumulated 15,732,836 cases and had 439,050 deaths confirmed, (PAHO, 2021) with an expressive increase in the number of cases and deaths attributed, both to difficulties in imposing social distancing policies on the population, (Gelfand, 2021) and to the emergence of new, more virulent SARS-CoV-2 variants (Brazilian, 2021). So far, almost all states have experienced, for some period, greater demand than supply from their health systems. The overloaded health systems have generated queues for hospital beds and medical care and depleted stocks of hospital oxygen and medications used for orotracheal intubation of patients in intensive care units (ICU) (Peet, 2021).

Interrupting virus circulation is even more challenging for the health system if we consider the impact of pre-existing health conditions and the increasing exposure of the population to SARS-CoV-2 due to the aggravated economic crisis. Insufficient spending on emergency programs on vulnerable populations at greater risk of falling below the poverty line has led a growing segment of the population to not adhere to social isolation policies and consequently increase their exposure to COVID-19 to find an occupation and survive.

While the interruption of the virus circulation in Brazil is ongoing, healthcare providers will need to rationalize the limited resources demanded by overloaded health units. Patients' symptoms presented at hospital admission may lead to an erroneous assessment of the real clinical condition and its risk of worsening. Efficient implementation of in-hospital triage in individuals of different ages with diverse clinical presentations of COVID-19 will be of great help. A previous study has considered age, symptoms, and comorbidities as independent clinical risk factors to provide patients' risk profiles (Pietre et al., 2021). This study aimed to bring new clinical evidence to assessing relative risk and to establish a better flow of care in a setting of limited healthcare resources, focusing on the interactions between age (age strata), symptoms, and comorbidities and their association with healthcare resource demand, such as VS and ICU admission, and COVID-19-related death.

2. Methods

2.1. Data

In this retrospective cross-sectional observational study, we analyzed the dataset SIVEP-Gripe, launched on January 11th, 2021, downloaded from https://opendatasus.saude.gov.br/dataset/ae90fa8f-3e94-467e-a33f-94adbb66edf8. This database, maintained by the Brazilian Ministry of Health (MoH), is the primary source of information on COVID-19 hospital admissions and deaths, containing sociodemographic and clinical information of those patients. Only symptomatic patients with positive laboratory samples or clinical diagnosis of COVID-19, admitted and discharged from February 20 to December 31, were included in the analyses.

2.1.1. Groups of symptoms

For categorizing the patients' symptoms at hospital admission, we

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employed a hierarchical ordinal search from the possibly highest-risk group (group 6) to the possibly lowest-risk group (group 1), adapted from Sudre et al. (2021): (1) Flu-like without fever, characterized by headache, loss of smell, cough, sore throat, without fever; (2) Flu-like with fever, characterized by headache, loss of smell, cough, sore throat, and fever; (3) Gastrointestinal, characterized by diarrhea, abdominal pain, vomit, and absence of cough; (4) Severe level one (fatigue), characterized by difficulty breathing, dyspnea, fatigue, myalgia, and fever; (5) Severe level two (mental confusion), characterized by difficulty breathing, dyspnea, headache, mental confusion, and fever; and, (6) Severe level three (abdominal and respiratory), characterized by oxygen saturation lower than 95%, difficulty breathing, dyspnea, diarrhea, abdominal pain, vomit, and fever (Sudre et al., 2021). The combination of symptoms characterizing each group needed to be adapted to the specificity of our data and population. Some of these symptoms and comorbidities were recorded in mandatory fields of the SIVEP-Gripe/MoH, while additional information was recorded in complementary fields. Symptoms and comorbidities recorded in mandatory fields were probably registered with higher accuracy, despite being self-reported at the time of hospital triage. These variables contain three levels: yes, no, and unknown; the last one indicating that the field was not filled in. On the other hand, for those recorded in complementary fields, the "unknown" proportion is significantly higher as we cannot precise if the absence of data implies that the patient really did not have that condition or the information was just not registered.

2.2. Statistical analyses

For a clinical-sociology-demographic description of patients who were admitted to intensive care units or not, used VS or not, and survived or died due to COVID-19, for continuous numerical variables we used medians, while for nominal variables we used absolute and relative frequencies. To determine factors associated with risk of death, use of VS, and ICU admission, we used logistic models adjusted for sex, ethnicity, education, age, and days between database registration and first COVID-19 symptoms. Measures of association were presented as adjusted odds-ratios (aOR) and their 95% confidence intervals. The p-values were corrected for the number of comparisons with the reference level by the Holm-Sidak method. In determining comorbidities associated with in/decreasing risk in symptom groups within fixed age strata, logistic models with the interaction between the effects of interest adjusted for ethnicity, education, and days between database registration and first symptoms of COVID-19 were fitted, and mean marginal and their 95% confidence intervals obtained by keeping all other variables in the model either at their mean values (continuous numeric variables) or in equal proportion among their levels (nominal variables). The confounding variables (baseline information) used in the models containing symptom groups, age strata, and comorbidities as leading factors were selected by fitting bi- and multivariate binomial models when associated with each outcome of interest. All statistical analyses were performed in R v.4.0.5, the 'emmeans' library, and its dependencies.

3. Results

3.1. Population

Of the 1,136,681 records in the SIVEP-Gripe/MoH, 2992 were eliminated due to lack of information on the state of residence or invalid age (greater than 105 years or negative). Out of these 1,133,689 records, 606,554 (53·5%) had SARS-CoV-2 infection confirmed by different criteria, such as laboratory (94·1%), clinical (1·8%), clinical-epidemiological (0·7%), or clinical-imaging (lung X-ray/CT scan) (3·26%) and were either cured or died probably related to COVID-19. Demographic and clinical factors of COVID-19 hospitalized patients by healthcare resource demand may be seen in Supplementary Tables 1–3. The majority, 250,505 (60·0%) required VS, and 123,634 (29·6%) required intensive care. The latter, with a median time of ICU use of 8 days (IQR = 12). 105,654 (25·3%) had death confirmed as a result of COVID-19, but the evolution of 48,150 (11·5%) was unknown. Regarding symptom groups at the time of COVID-19 notification, 115,766 (27·7%) belonged to Group 1 (flu-like), 182,301 (43·7%) belonged to Group 2 (flu-like with fever), 18,836 (4·5%) belonged to Group 3 (gastrointestinal), 40,351 (9·7%) belonged to Group 4 (severe with fatigue), 21,385 (5·1%) belonged to Group 5 (severe with mental confusion), and 38,695 (9·7%) belonged to Group 6 (severe with abdominal and respiratory symptoms).

3.2. Demographic and clinical risk factors for health resource demand

Considering the risk factors associated with healthcare resource demands (Table 1), men used more VS (aOR = 1·19 [1·16-1·22]) and were admitted more often to ICU (aOR = 1·21 [1·18-1·23]) than women. Individuals self-declared as black/brown used less VS (aOR = 0·88 [0·86–0·9]) and were less admitted to ICU (aOR = 0·91 [0·89–0·93]) than self-declared white individuals. Groups 2 and 3 were less associated to VS (aOR = 0·92 [0·89–0·94] and aOR = 0·61 [0·57–0·64]; respectively), while Groups 4, 5 and 6 used more VS (aOR = 1·57 [1·5–1·64], aOR = 1·28 [1·21–1·36], and aOR = 2·34 [2·24–2·46], respectively); and, with the exception of Group 5, were also more admitted to ICU (aOR = 1·18 [1·13–1·23], and aOR = 1·16 [1·12–1·21], respectively for Groups 4 and 6) than Group 1. In general, individuals with comorbidities used more VS and were admitted to ICU more often (Table 1). Among these, obesity, as well as smoking, almost doubled the risks of both VS (aOR = 1·9 [1·8–1·99] and aOR = 1·95 [1·76–2·15]) and ICU admission (aOR = 1·91 [1·84–1·99] and aOR = 2 [1·86–2·15]).

Consistent with health resource requirements, men died more as a result of COVID-19 (aOR = 1·31 [1·28–1·35]) than women (Table 1). Self-reported black/brown individuals died more (aOR = 1·51 [1·48–1·55]) than white individuals. This pattern was even more evident in indigenous (aOR = 1·72 [1·43–2·06]) but did not replicate among Asiatics. The same trend of decreasing risk from individuals with up to 5 years of schooling to graduate individuals to those with up to 12 years of schooling was observed for COVID-19-related death (aOR = 0·83 [0·79–0·88], aOR = 0·85 [0·81–0·9], aOR = 0·73 [0·69–0·77], and aOR = 0·54 [0·5–0·57]; respectively for up to 5, 9, 12 years of schooling, and graduates) relative to illiterate individuals. Although obesity and smoking were also associated with increased death due to COVID-19 (aOR = 1·7 [1·63-1·78], and aOR = 1·52 [1·4-1·64]), chronic liver disease (aOR = 2·08 [1·86-2·33]), immunodepression (aOR = 2·04 [1·91-2·18]), renal disease (aOR = 2·36 [2·22-2·5]), and neoplasia (aOR = 2·94 [2·68-3·23]), had much higher mean risk increments than the former. Only for Group 6 we did observe an increased risk of COVID-19-related death (aOR = 1·21 [1·16-1·27]).

3.3. Comorbidities and symptom risk factors for health resource demand by age strata

Tables 2–4 replicate the analyses in Table 1, focusing on the risk increments associated with different comorbidities across age strata and symptom groups. Complete results of the adjusted logistic models are presented in Supplementary Tables 4–6. Absolute frequencies of each comorbidity within each age stratum and symptom group for each study outcome are presented in Supplementary Tables 7–9.

Overall, diabetes, cardiovascular disease, obesity, and smoking were associated with an increased risk of VS use (Table 2). Diabetes on average increased the chance of VS use by 17–65%, cardiovascular disease by 20–38%, obesity by 53–129%, and smoking by 68–130%. Considering individuals aged 21–40 years, in Group 1, there were increases in the use of VS of 122% (neoplasia), 284% (chronic obstructive pulmonary disease (COPD)), and 130% (smoking). Among individuals aged 41–60 years, pneumopathy (aORs 1·46 and 1·48), neurological

Table 1
Adjusted Logistic Models to Estimate Health Resources Demand and Clinical Outcome Risks by Demographic and Clinical Factors in COVID-19 hospitalized Patients. Brazil, February 16th to December 31st, 2020.

Feature	Level	(1)[1]	(2)[1]	(3)[1]
Sex	F	Reference	Reference	Reference
	M	1.19 (1.16–1.22)	1.21 (1.18–1.23)	1.31 (1.28–1.35)
Colour Skin	white	Reference	Reference	Reference
	black/brown	0.88 (0.86–0.9)	0.91 (0.89–0.93)	1.51 (1.48–1.55)
	yellow	0.71 (0.64–0.78)	0.87 (0.78–0.97)	1.06 (0.94–1.19)
	red	0.77 (0.64–0.92)	0.5 (0.41–0.62)	1.72 (1.43–2.06)
Schooling	0y	Reference	Reference	Reference
	5y	1.02 (0.96–1.08)	1.1 (1.04–1.16)	0.83 (0.79–0.88)
	9y	1.11 (1.05–1.18)	1.25 (1.18–1.32)	0.85 (0.81–0.9)
	12y	0.84 (0.79–0.89)	1.2 (1.14–1.27)	0.73 (0.69–0.77)
	graduated	0.67 (0.63–0.71)	1.34 (1.26–1.42)	0.54 (0.5–0.57)
Age	(21,40]	Reference	Reference	Reference
	(41,60]	1.73 (1.69–1.76)	1.34 (1.31–1.37)	1.34 (1.31–1.37)
	(61,80]	2.65 (2.59–2.7)	2.03 (1.98–2.07)	2.03 (1.98–2.07)
Symp Days[3]		1.3 (1.27–1.32)	1.19 (1.16–1.21)	0.93 (0.91–0.95)
Symp Group	flu-like	Reference	Reference	Reference
	flu-like with fever	0.92 (0.89–0.94)	0.98 (0.95–1.01)	1.12 (1.09–1.16)
	gastrointestinal	0.61 (0.57–0.64)	0.96 (0.9–1.02)	1.05 (0.99–1.12)
	severe with fatigue	1.57 (1.5–1.64)	1.18 (1.13–1.23)	1.04 (0.99–1.08)
	severe with mental confusion	1.28 (1.21–1.36)	1.03 (0.98–1.09)	0.9 (0.85–0.96)
	severe with abdominal and respiratory symptoms	2.34 (2.24–2.46)	1.16 (1.12–1.21)	1.21 (1.16–1.27)
Nosocomial transmission	yes	1.06 (0.97–1.15)	1.81 (1.67–1.96)	2.57 (2.36–2.81)
Cardiovascular disease	yes	1.32 (1.28–1.37)	1.24 (1.2–1.28)	1.12 (1.08–1.15)
Hematological disease	yes	0.95 (0.83–1.08)	1.27 (1.13–1.43)	1.67 (1.48–1.9)
Chronic liver disease	yes	0.91 (0.81–1.03)	1.4 (1.26–1.56)	2.08 (1.86–2.33)
Asthma	yes	1.06 (0.99–1.14)	0.96 (0.9–1.03)	0.9 (0.83–0.97)
Diabetes	yes	1.21 (1.17–1.25)	1.21 (1.18–1.25)	1.28 (1.24–1.32)
Neurologic disease	yes	1.22 (1.13–1.33)	1.22 (1.14–1.31)	1.67 (1.55–1.79)
Pneumopathy	yes	1.61 (1.49–1.74)	1.5 (1.42–1.59)	1.76 (1.65–1.87)
Immunosuppression	yes	0.93 (0.87–1)	1.3 (1.22–1.39)	2.04 (1.91–2.18)
Renal disease	yes	1.04 (0.97–1.11)	1.73 (1.64–1.83)	2.36 (2.22–2.5)
Obesity	yes	1.9 (1.8–1.99)	1.91 (1.84–1.99)	1.7 (1.63–1.78)
Arterial hypertension	yes	1.08 (1.04–1.12)	1.15 (1.12–1.19)	1.2 (1.16–1.24)
Smoking	yes/ex	1.95 (1.76–2.15)	2 (1.86–2.15)	1.52 (1.4–1.64)
COPD	yes	1.61 (1.32–1.95)	1.56 (1.36–1.8)	1.49 (1.28–1.73)
Neoplasia	yes	1.14 (1.03–1.26)	1.21 (1.1–1.32)	2.94 (2.68–3.23)
Hypothyroidism	yes	1.33 (1.2–1.47)	1.36 (1.25–1.49)	0.92 (0.83–1.02)

[2] All adjusted logistic models included age, sex, education, and days of symptoms as confounders.
[1] (1) = Respiratory Support Requirement, (2) = ICU Admission, and (3) = COVID-19 Related Death.
[3] Median [Quartil range].

diseases (aORs 1·35 and 1·56), asthma (aOR = 1·25), and hypothyroidism (aOR = 1·64) were associated with the use of VS in individuals from Groups 1 and/or 2. Among individuals aged 61–80 years, pneumopathy was associated with increased use of VS, particularly among individuals from Groups 1 to 3 (aOR = 1·69), but also among individuals from Group 6 (aOR = 1·58). In addition, increments in VS use of 13–24% and 66–77% were associated with arterial hypertension and COPD, respectively, for Groups 1 and/or 2 and/or 3 in this same age group.

Regarding ICU admission (Table 3), obesity was a risk factor for all age ranges, increasing the demand for ICU by 45–124% depending on the age and symptoms group. Individuals aged 21–40 years, presenting mild symptoms (Groups 1 and/or 2 and/or 3) associated with renal disease, smoking, or arterial hypertension had a risk 57–69%, 97–251%, and 46–47% higher of ICU admission, respectively. Among individuals aged 41–60 years, renal disease (aOR = 1·67-1·93), smoking (aOR = 1·57-2·05), diabetes (aOR = 1·2-1·47), nosocomial transmission (aOR = 1·54-2·75), and arterial hypertension (aOR = 1·23-1·38) were associated with a higher risk of ICU admission for almost all patients' symptoms. Considering individuals aged 61–80 years, renal disease and pneumopathy increased the risk of ICU admission in 63–90% and 39–72%, respectively, independently of the patients' symptoms. Other comorbidities were identified as risk factors for ICU admission, such as COPD (Groups 1, 2, 3, and 4, aOR = 1·49-2·36), immunosuppression (Groups 1, 2, 4, and 6, aOR = 1·27-1·4), diabetes (Groups 1, 2, 3, and 6, aOR = 1·14-1·27), arterial hypertension (Groups 1, 2, and 4, aOR = 1·17-1·21), cardiovascular disease (Groups 1, 2, and 5, aOR = 1·2-1·37), chronic liver disease (Groups 1 and 6, aOR = 1·41-1·68), and neurological diseases (Groups 1 and 4, aOR = 1·2-1·3), as well as nosocomial transmission (Groups 1, 2, 3, and 6, aOR = 1·47-2·17).

In addition to assessing the demand for healthcare resources, we also assessed the risk associated with COVID-19-related death among symptom groups in the different age strata (Table 4). Overall, immunosuppression (54–235%), renal disease (89–189%), and obesity (26–85%) were the comorbidities most associated with the increment of COVID-19-related deaths. These included renal disease, which nearly doubled the risk of COVID-19-related death across all symptom groups in 41–60 and 61–80 age strata, and more than doubled this risk in the 21–40 age stratum for the Groups 1 to 3. Neoplasia was the most prevalent comorbidity in 41–60 and 61–80 age strata, with even higher risk increments (74–352%) associated with COVID-19-related death for the different symptom groups. Individuals aged 21–40 years from Groups 1 and/or 2, and/or 3 and, nosocomial transmission, neurological disease, smoking, or chronic liver disease had extremely high mean risks of death (75–183%, 107–122%, 121–136%, and 117–355%, respectively). Considering the 41–60 age stratum, several comorbidities increased the risk associated with COVID-19-related death in at least 4 of the 6 symptom groups. In this age stratum for Group 5, neurological disease, pneumopathy, immunosuppression, and nosocomially transmitted SARS-CoV-2 infection were not associated with increased COVID-19-related death. In the 61–80 age stratum, nosocomial transmission (71–178%), neurological disease (65–93%), pneumopathy (52–96%), diabetes (15–35%), and neoplasia (74–121%) substantially increased COVID-19-related deaths, regardless of symptoms; often except for Group 5.

Table 2
Adjusted Logistic Models to Estimate the Risk of Use of Ventilatory Support by Comorbidities, according to Age Strata and Symptom Groups (N = 354,921). Brazil, February 16th to December 31st, 2020.

Age	Symp. Group	(1)[1]	(2)[1]	(3)[1]	(4)[1]	(5)[1]	(6)[1]	(7)[1]	(8)[1]	(9)[1]	(10)[1]	(11)[1]	(12)[1]	(13)[1]	(14)[1]	(15)[1]	(16)[1]
(20,40]	flu-like		1.37				1.52					**2.29**	1.68	**2.3**	**3.84**	**2.22**	1.81
(20,40]	flu-like with fever	0.74	1.38				1.39					**2.01**	1.47	1.68			
(20,40]	gastrointestinal						1.65					1.85					
(20,40]	severe with fatigue											**2.18**			–		
(20,40]	severe with mental confusion											1.9					
(20,40]	severe with abdominal and respiratory symptoms											**2.03**			–		
(40,60]	flu-like		1.29				1.27	1.56	1.48			1.81	1.23	1.88			1.64
(40,60]	flu-like with fever		1.24			1.25	1.37	1.35	1.46	0.84		1.7	1.2	1.85			
(40,60]	gastrointestinal						1.35					1.56		2			
(40,60]	severe with fatigue		1.26									1.78	1.2	1.73			
(40,60]	severe with mental confusion		1.35				1.32					1.78		1.85			
(40,60]	severe with abdominal and respiratory symptoms		1.24									1.53					
(60,80]	flu-like		1.28				1.17	1.27	1.69		1.19	1.6	1.13	1.9	1.66		
(60,80]	flu-like with fever		1.33				1.22	1.29	1.69			1.66		1.74	1.77		
(60,80]	gastrointestinal		1.32						1.69				1.24	**2.22**			
(60,80]	severe with fatigue		1.2									1.65		1.94			
(60,80]	severe with mental confusion		1.32				1.31					1.62					
(60,80]	severe with abdominal and respiratory symptoms								1.58			1.62					

Cells with values indicate statistical significance (p-value < 0.05). Values in bold indicate large effect sizes (aOR). All adjusted logistic models used age, sex, education and days of symptoms as confounders.

[1] (1) = Nosocomial transmission, (2) = Cardiovascular disease, (3) = Hematological disease, (4) = Chronic liver disease, (5) = Asthma, (6) = Diabetes, (7) = Neurologic disease, (8) = Pneumopathy, (9) = Immunosuppression, (10) = Renal disease, (11) = Obesity, (12) = Arterial hypertension, (13) = Smoking, (14) = COPD, (15) = Neoplasia, and (16) = Hypothyroidism.

Table 3
Adjusted Logistic Models to Estimate the Risk of Intensive Care Unit Admission by Comorbidities, according to Age Strata and Symptom Groups (N = 357,404). Brazil, February 16th to December 31st, 2020.

Age	Symp. Group	(1)[1]	(2)[1]	(3)[1]	(4)[1]	(5)[1]	(6)[1]	(7)[1]	(8)[1]	(9)[1]	(10)[1]	(11)[1]	(12)[1]	(13)[1]	(14)[1]	(15)[1]	(16)[1]
(20,40]	flu-like	1.7	1.38				1.32			1.63	1.69	1.86	1.46		1.03	**2.17**	
(20,40]	flu-like with fever						1.34				1.57	1.81	1.47	1.97			**2.17**
(20,40]	gastrointestinal						1.92					1.67		**3.51**			
(20,40]	severe with fatigue						1.43					1.76			–		
(20,40]	severe with mental confusion											1.76					
(20,40]	severe with abdominal and respiratory symptoms	**2.27**										1.45			–		
(40,60]	flu-like	1.54	1.25		1.51		1.21	1.62	1.33		1.83	1.77	1.23	1.7	**2.31**		1.37
(40,60]	flu-like with fever	1.59	1.16				1.25	1.28	1.48		1.67	1.93	1.25	1.86	1.85		1.46
(40,60]	gastrointestinal	**2.38**			1.74		1.47				1.93	1.81	1.38	1.73			
(40,60]	severe with fatigue	1.84					1.2				1.77	1.98	1.23	1.77			
(40,60]	severe with mental confusion											1.78	1.38	1.57			
(40,60]	severe with abdominal and respiratory symptoms	**2.75**								1.48	1.93	1.63	1.29	**2.05**			
(60,80]	flu-like	1.58	1.2		1.41		1.16	1.2	1.39	1.27	1.75	1.76	1.21	1.76	1.49		1.24
(60,80]	flu-like with fever	1.47	1.21				1.18		1.61	1.27	1.66	**2.03**	1.17	1.71	1.79		1.46
(60,80]	gastrointestinal	**2.17**					1.27		1.71		1.9	1.84		1.52	**2.36**		
(60,80]	severe with fatigue							1.3	1.45	1.4	1.63	1.72	1.19	1.48	1.84		
(60,80]	severe with mental confusion		1.37						1.72		1.7	**2.24**					
(60,80]	severe with abdominal and respiratory symptoms	**2.08**			1.68		1.14		1.51	1.38	1.81	1.59		1.84			

Cells with values indicate statistical significance (p-value < 0.05). Values in bold indicate large effect sizes (aOR). All adjusted logistic models used age, sex, education and days of symptoms as confounders.

[1] (1) = Nosocomial transmission, (2) = Cardiovascular disease, (3) = Hematological disease, (4) = Chronic liver disease, (5) = Asthma, (6) = Diabetes, (7) = Neurologic disease, (8) = Pneumopathy, (9) = Immunosuppression, (10) = Renal disease, (11) = Obesity, (12) = Arterial hypertension, (13) = Smoking, (14) = COPD, (15) = Neoplasia, and (16) = Hypothyroidism.

4. Discussion

In this study, we examined the association between groups of symptoms and comorbidities frequently associated with COVID-19, the demand for healthcare resources, and the increment of COVID-19-related deaths for different age strata of the population. We believe that the results presented here will contribute to the expansion of current knowledge about the epidemic in Brazil, revealing the complex distribution of risks and assist healthcare providers.

This work showed counter-intuitive results. Within age-strata, mild symptoms groups were often more associated with an increased risk of an unfavorable clinical outcome when presenting any comorbidity than other groups considered more severe. The evidence suggests that among young patients, mild symptoms (Groups 1 to 3), when associated with

Table 4
Adjusted Logistic Models to Estimate the Risk of Death by Comorbidity, according Age and Symptoms Groups (N = 369,125). Brazil, February 16th to December 31st, 2020.

Age	Symp. Group	(1)[1]	(2)[1]	(3)[1]	(4)[1]	(5)[1]	(6)[1]	(7)[1]	(8)[1]	(9)[1]	(10)[1]	(11)[1]	(12)[1]	(13)[1]	(14)[1]	(15)[1]	(16)[1]
(20,40]	flu-like	**2.76**			**2.81**	0.54	1.34	**2.22**		**2.46**	**2.69**	1.51	1.61	**2.36**		**14.3**	
(20,40]	flu-like with fever	1.75		1.78	**2.17**	0.6	1.46	**2.07**		1.97	**2.01**	1.5	1.92	**2.21**			
(20,40]	gastrointestinal	**2.83**			**4.55**		1.79			**3.35**	**2.3**						
(20,40]	severe with fatigue									**2.53**		1.46			–		
(20,40]	severe with mental confusion											1.85	**2.31**			**13.1**	
(20,40]	severe with abdominal and respiratory symptoms	**3.36**								**2.77**	**2.32**		1.79		–		
(40,60]	flu-like	**2.99**		1.72	**2.31**		1.32	1.74	1.77	**2.33**	**2.58**	1.49	1.32	1.62	**2.47**	**4.52**	
(40,60]	flu-like with fever	**2.21**		1.64	1.82		1.44	1.7	1.89	1.7	**2.39**	1.64	1.43	1.82	**2.91**	**3.12**	
(40,60]	gastrointestinal	**3.3**			**3.53**	0.38	1.41	1.9	**2.01**	**2.13**	**2.69**			**2.82**		**3.76**	
(40,60]	severe with fatigue	**2.66**			**2.08**		1.3	1.96	1.93	**2.09**	**2.16**	1.73	1.59	1.87	**3.07**	**2.53**	
(40,60]	severe with mental confusion						1.69				**2.62**	1.61	1.55	**2.07**		**2.61**	
(40,60]	severe with abdominal and respiratory symptoms	**3.3**			**2.4**		1.43		1.79	1.81	**2.89**	1.41	1.37	1.75		**3.53**	
(60,80]	flu-like	**2.49**	1.11	1.4	1.82		1.15	1.7	1.64	1.93	**2.13**	1.42	1.14	1.36	1.48	**2.18**	
(60,80]	flu-like with fever	1.71	1.09	1.37	1.75		1.21	1.65	1.62	1.56	1.89	1.5	1.11	1.29	1.65	1.74	
(60,80]	gastrointestinal	**2.78**			**2.59**		1.26	1.93	1.88	1.57	**2.32**	1.46		1.52		**2.21**	
(60,80]	severe with fatigue	1.94		1.94			1.23	1.88	1.52	1.54	**2.21**	1.36	1.21			**2.06**	
(60,80]	severe with mental confusion						1.35		1.96		**2.56**	1.37					
(60,80]	severe with abdominal and respiratory symptoms	**2.06**			1.63		1.28	1.72	1.7	1.77	**2.04**	1.26		1.4		**2.14**	

(8) = Pneumopathy, (9) = Immunosuppression, (10) = Renal disease, (11) = Obesity, (12) = Arterial hypertension, (13) = Smoking, (14) = COPD, (15) = Neoplasia, and
(16) = Hypothyroidism.
Cells with values indicate statistical significance (p-value < 0.05). Values in bold indicate large effect sizes (aOR). All adjusted logistic models used age, sex, education and days of symptoms as confounders.
[1] (1) = Nosocomial transmission, (2) = Cardiovascular disease, (3) = Hematological disease, (4) = Chronic liver disease, (5) = Asthma, (6) = Diabetes, (7) = Neurologic disease,

any comorbidities often required more healthcare resources, and also progressed more frequently to death than those without comorbidities. A similar pattern also manifested itself among the older patients, but less pronouncedly, possibly due to the prevalent accumulation of comorbidities among individuals in these strata. Our results confirmed the association of aging with the demand for healthcare resources and COVID-19-related deaths reported in different Brazilian states, (Sousa et al., 2020; Macedo et al., 2020; Cobre et al., 2020; Escosteguy et al., 2020; Moura et al., 2020; Leal et al., 2021; Policarpo et al., 2021; Bastos et al., 2020) in population restricted to a clinical condition or not, or even in national population studies, (Santos et al., 2021; de Souza et al., 2020; Nascimento et al., 2020; Marcolino et al., 2021; Castro et al., 2021) but also reported in studies in Latin America, (Escalera-Antezana et al., 2020; Araujo et al., 2020; Elizondo et al., 2021; Galindo et al., 2021; Yacobitti et al., 2021; Ortiz-Prado et al., 2021) and in international cohorts (Pepe et al., 2021). Overall, frailty and the high prevalence of comorbidities made the elderly more susceptible to severe infection by COVID-19. In high-income countries, where the population is typically older, and sometimes living in nursing homes, the relative incidence of severe infections, and even deaths, was higher among the elderly, even though they were more likely to have lower exposure to the virus (O'Driscoll et al., 2021). In Brazil, as in other low- and middle-income countries, the population is younger, however, even young adults have at least one comorbidity reflecting poor preexisting health conditions (Silva and Ribeiro-Alves, 2021). Adults aged 21–50 have already been reported to be crucial in maintaining the spread of SARS-CoV-2 due to their greater mobility and consequent exposure to the virus (Monod et al., 2021). Moreover, the scenario of socioeconomic inequalities and limited access to health facilities may further contribute to the rejuvenation of the pandemic in Brazil; when compared to Italy and the UK, countries with a different demographic distribution.

Taking into consideration the influence of comorbidities on clinical evolution, some aspects are worth mentioning. Considering the comorbidities associated with COVID-19-related death, nosocomial transmission, diabetes, immunosuppression, kidney disease, and obesity were important risk factors, regardless of age strata. Concordant results were reported for one or more of these comorbidities (Moura et al., 2020; de Souza et al., 2020; Marcolino et al., 2021; Yacobitti et al., 2021; Pepe et al., 2021; Ceballos et al., 2021; Olivas-Martínez et al., 2021; Rocha et al., 2021; Escalera-Antezana et al., 2020; Marques et al., 2021). Also, some comorbidities were associated with some, but not all, of the observed outcomes. Some of the comorbidities that increase risk the most are not either considered or directly related to respiratory disease. Pneumopathy increased risk to a lesser extent than non-respiratory comorbidities, and only among older people, while asthma not only did not increase risk but was, for some combinations of age strata and symptom groups, unexpectedly a risk-carrying factor. Other authors also found asthma associated with lower ICU admission, COVID-19-related death, or both (Santos et al., 2021; Castro et al., 2021; Álvarez-Maldonado et al., 2021). Conversely, smoking increased risks for all outcomes evaluated, as expected. Finally, we found evidence of inequality in the distribution of health resources and COVID-19-related death in the year 2020. Individuals who self-declared black/brown and/or had lower education simultaneously had a higher risk of death and lower demand for health resources when compared to self-declared white and highly educated individuals; a frequent finding in population studies with Brazilians (Santos et al., 2021; de Andrade et al., 2020). Either this shows racism in the health system, which prioritizes resources in the care of white individuals to the detriment of black individuals or, because an imbalance of resources between the private and public health networks. A more detailed examination of this association will be necessary to explain this apparently unfair situation.

This study has limitations both methodological and related to the database analyzed. The lack of individualized longitudinal symptom data prevents us from constructing causal relationships, so we only present associations between symptoms, comorbidities, and outcomes. While in

Sudre et al. (2021) were analyzed longitudinal symptoms self-registered in an app by patients themselves, we adapted the COVID-19 symptoms recorded at the healthcare unit admission (Sudre et al., 2021). Also, the interval between the first symptoms and the notification may have influenced the reported symptoms and outcomes. This bias was partially overcome by including in the models the days since first symptoms. We considered symptoms and comorbidities recorded in mandatory fields and from the complementary fields. Then, the "unknown" proportion observed in the data does not necessarily mean that the patient did not have that condition, since the information may simply not have been registered. This lack of information or even the lack of information on outcomes, VS, ICU admission, and death related to COVID-19, may have incorporated bias into our results; even though we are using the national compulsory registry data (SIVEP-Gripe/MoH). On the other hand, we believe that the adaptations we made to symptom group were adequate to fit the characteristics of our registries and allowed us to make inferences about our local scenario. Despite we have included several clinical and socio-demographic information about patients in models, we cannot rule out the possibility of biased estimation due to potential unobserved confounders. Another limitation of our estimates was that we considered the marginal effects of comorbidities in isolation, disregarding the possibilities of interaction between them. However, it is already known that the accumulation of any comorbidities increases the risk of death especially among young people (Pietre et al., 2021; Maciel et al., 2020). Finally, the present study evaluated only symptomatic cases, possibly medium to severe. SIVEP-Gripe/MoH is a national, official database used to count all COVID-19-related admissions and deaths, so no significant reporting bias was expected. However, there was a very low testing of cases in Brazil. Epidemiological surveillance studies of national relevance point out that for every reported case there were at least five other unknown cases (Hallal et al., 2020). During the period that we analyzed, the SARS-CoV-2 strains circulating in Brazil were B.1.128, B.1.1.33, P.2, and B.1.1.7, (Faria et al., 2021) and no vaccine was yet available. The effects of the new SARS-CoV-2 strains and vaccination on the risk profile of infected individuals are still uncertain. There is, however, no evidence that the increased risk associated with comorbidities in different age strata with distinct symptoms presented at outpatient/hospital screening is altered by vaccination. Also, we cannot rule out that more severe cases may emerge from patients with milder symptoms as more adapted, i.e., more infectious, variants that convalesce less their hosts, such as the Omicron variant. This is the case in Latin American countries, where the Omicron variant is spreading and which the symptom profile has evolved to those of a "severe cold", i.e., headache, sore throat, runny nose, fever, and cough, with even worse outcomes among non-immunized young persons.

5. Conclusion

The eradication of SARS-CoV-2 is still a distant reality in Brazil. Before proven effective protocols are fully accepted and implemented, and we reach this reality, healthcare providers will continue to need to rationalize the limited resources of the health units. The contributions of this study show how imperative it is to interactively consider age, comorbidities, and symptoms to obtain a more accurate patient risk profile at screening and consequently better allocate health resources.

6. Data sharing

The data used in this study are public and are available on the website of the Brazilian Ministry of Health. The analysis code for the paper will be made available on Arca, the Institutional Repository of the Oswaldo Cruz Foundation (Fiocruz/Brazil).

CRediT authorship contribution statement

Vitória Berg Cattani: Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Thaís Araujo dos Santos:** Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Julio Castro-Alves:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Marcelo Ribeiro-Alves:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2022.101724.

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