HIV-related lymphomas in adults served in the public health network An observational study

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Abstract

Individuals infected with human immunodeficiency virus (HIV) have higher morbidity and mortality due to cancer, which is the third most common cause of death in this group, despite the high effectiveness of antiretroviral therapy (ART). We describe the clinical and laboratory characteristics, initial staging and outcome of HIV-related lymphoma.

We included 18 patients in the study, of whom 61.1% were male, mean age 41 years. Nine of the 18 patients (50%) had a diagnosis of HIV infection concurrent with the diagnosis of lymphoma.

The most common histological types were diffuse non-Hodgkin B-cell lymphoma, 8 patients (44.4%); and Burkitt lymphoma, 5 (27.8%) cases. The Cotswold revision of the Ann Arbor staging classification in 14 patients (77.7%) was between III and IV. B Symptoms were present in 11 patients (61.1%), bulky mass was observed in 11 cases (61.1%) and had extra-nodal involvement in 8 patients (44.4%).

Of the 18 cases analyzed, 8 followed on to second-line treatment, wherein the CODOX-M/IVAC scheme (cyclophosphamide, adriamycin, vincristine, methotrexate/ifosfamide, etoposide, and cytosine arabinoside) was used in 3 of the cases. The second most common scheme was etoposide, doxorubicin, vincristine and cyclophosphamide (EPOCH), used in 2 cases (25%), while in single cases (12.5% each) cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP), ifosfamide, etoposide, and carboplatin (ICE) and dexamethasone, cisplatin, and cytarabine (DHAP) were used.

In this series, we observed very high mortality, equivalent to 44.4%, and a complete response in only 11.1%, much lower than that observed by other authors.

We found that patients diagnosed with lymphoma associated with HIV had an advanced early clinical staging, and evolved with low response rates to chemotherapy.

Abbreviations: ART = antiretroviral therapy, CR = complete response, ECOG = Eastern Cooperative Oncology Group, EPOCH = etoposide, doxorubicin, vincristine, and cyclophosphamide, HIV = human immunodeficiency virus, LDH = lactate dehydrogenase.

Keywords: human immunodeficiency virus, Lymphoma, Neoplasia

1. Introduction

Individuals infected with human immunodeficiency virus (HIV) have higher morbidity and mortality due to cancer, which is the third most common cause of death in this group, despite the high effectiveness of antiretroviral therapy (ART).^[1] Since the beginning

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of the AIDS pandemic, the relationship between HIV and the appearance of certain cancers has been noted, notably Kaposi's sarcoma (KS) and lymphomas.^[2,3] Before the advent of ART, a 1000-fold increased risk was reported for the development of primary central nervous system lymphomas and Burkitt's lymphomas in HIV-infected patients, as well as 8 to 30-fold higher risk for Hodgkin's lymphoma and 60 to 200-fold higher risk for non-Hodgkin's lymphomas in this population.^[4,5] After the introduction of ART, there was a substantial decline in HIV-related morbidity and mortality, but the impact on the decline in the incidence of non-Hodgkin's lymphoma was lower than that observed for Kaposi's sarcomas and opportunistic infections.^[6]

Medicine

Regarding Hodgkin's lymphomas, some studies have hypothesized that the introduction of ART would be contrarily related to an increase in cases, since this group of lymphomas appears to be associated with more moderate degrees of immunodeficiency.^[7,8] There are few studies on AIDS-associated neoplasms in Brazil^[9], and there has been no report on the profile of these patients with lymphoma and their outcome in Pernambuco.

2. Methods

A retrospective, descriptive study, of a case series type, was carried out at 2 university hospitals and a reference hospital for

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Table 1

Histopathological characteristics of HIV-related lymphomas in adults served in the public.

Characteristics	Number, %
NHL-B	13 (72.2%)
Burkitt's lymphoma	5 (27.8%)
Diffuse B-cell non-Hodgkin's lymphoma	8 (44.4%)
NHL-T	2 (11.2%)
Anaplastic large cell lymphoma ALK-negative	1 (5.6%)
Peripheral T-cell lymphoma, without other specifications	1 (5.6%)
HL	3 (16.8%)
Hodgkin's lymphoma, lymphocyte-rich	1 (5.6%)
Hodgkin's lymphoma, mixed cellularity	1 (5.6%)
Hodgkin's lymphoma, nodular-lymphocyte predominant	1 (5.6%)

cancer treatment that attend patients of the public health network, from January 2010 to December 2015.

The medical records were analyzed of patients aged 18 years or more, diagnosed with lymphoma through histopathological and immunohistochemical examination and who had HIV or AIDS infection. The study was approved by the Research Ethics Committee involving Human Beings from each institution involved.

A specific form was used, containing the following variables: age, sex, histopathological diagnosis, immunohistochemical diagnosis, initial Ann Arbor staging, presence of bulky disease, presence of extra-nodal disease, presence of B symptoms, performance status at diagnosis by Eastern Cooperative Oncology Group (ECOG) hemoglobin dosage, platelet count, lactate dehydrogenase (LDH) dosage, use of ART, chemotherapeutic treatment used, opportunistic infections and infectious complications, treatment evolution and clinical outcome at the end of treatment or until the end of the study period. Microsoft Excel program was used for data collection and analysis according to absolute (n) and relative (%) frequency, and the evolution of the cases analyzed individually. The study received approval from Federal University of Pernambuco for this research and all data analyzed were anonymized.

3. Results

Data from 18 medical records of patients diagnosed with lymphoma and having HIV or AIDS infection were included, of which 11 (61.1%) were male, with a mean age of 41 years. Half of the cases had their HIV diagnosis concomitant with the diagnosis of lymphoma, 7 (38.8%) knew they had been infected with HIV for less than 1 year, and only 2 (11.1%) had been aware of HIV infection for more than 1 year before diagnosis of lymphoma. All patients used ART after HIV diagnosis.

3.1. Lymphoma status

Regarding laboratory tests, the value of LDH was above 300 IU/L in 12 patients (66.7%), between 150 and 300 IU/L in 3 (16%) and less than 150 IU/L in 2 patients (11.1%), in only 1 case (5.5%) was this data not recorded in medical records. Regarding the performance status by ECOG at diagnosis, 8 (44.4%) were fully active, being between 0 and 1 on the scale, and 3 (16.6%) presented some impairment of the general state receiving a score of 2 to 4, however, in 7 of the cases (38.8%) this data was not reported.

The histopathological study showed that the most frequent conditions were diffuse B-cell non-Hodgkin's lymphoma, present in 8 cases (44.4%) and Burkitt's lymphoma, found in 5 cases (27.8%). Non-Hodgkin's T lymphoma and Hodgkin's lymphoma totaled 2 cases (11.2%) and 3 cases (16.8%), respectively (Table 1).

Evaluating the initial Cotswolds-modified Ann Arbor staging, 9 of the patients (50%) were in stage IV, 5 (27.7%) in stage III, 3 (16.6%) in stage II and 1 (5.5%) in stage I. B symptoms were present in 11 patients (61.1%), and in 4 cases there was no report of this data, bulky disease was also observed in 11 patients

Table 2

Immunohistochemical profile of HIV-related lymphomas in adults served in the public health network.

		IMMUNOHISTOCHEMICAL MARKERS																					
ID	HIST0	CD20	CD10	CD45	CD30	CD3	CD5	CD15	CD4	CD8	CD7	ALK	CD23	EMA	BCL2	BCL6	CD68	EBV	KI67	KAPPA	LAMBDA	CICLINAD1	ALK
1	BL	+	+	NT	NT	_	NT	NT	NT	NT	NT	NT	NT	NT	_	NT	NT	NT	100%	NT	NT	NT	NT
2	BL	+	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	+	NT	NT	100%	NT	NT	NT	NT
3	BL	+	-	+	-	-	-	NT	NT	NT	NT	NT	-	NT	-	+	NT	+	95%	NT	NT	-	NT
4	BL	+	NT	NT	-	NT	NT	NT	NT	NT	NT	NT	-	NT	-	+	NT	+	100%	NT	NT	NT	NT
5	BL	+	+	NT	NT	-	NT	NT	NT	NT	NT	NT	NT	NT	-	+	NT	NT	100%	NT	NT	-	NT
6	DBCL	+	NT	NT	-	-	NT	NT	NT	NT	NT	NT	NT	NT	NT	+	NT	NT	90%	NT	NT	NT	NT
7	DBCL	+	NT	NT	+	-	NT	NT	NT	NT	NT	NT	NT	NT	+	+	NT	NT	80%	NT	NT	NT	NT
8	DBCL	+	NT	NT	NT	+	NT	NT	NT	NT	NT	NT	NT	NT	-	+	NT	NT	40%	NT	NT	NT	NT
9	DBCL	+	NT	NT	NT	-	NT	NT	NT	NT	NT	NT	NT	NT	-	NT		+	NI	NT	NT	NT	NT
10	DBCL	+	NT	+	NT	-	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
11	DBCL	+	-	NT	-	-	NT	NT	NT	NT	NT	NT	NT	NT	+	-	NT	NT	NT	NT	NT	NT	NT
12	DBCL	+	NT	+	NT	-	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NI	NT	NT	NT	NT
13	DBCL	+	NT	+	+	-	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	-	NI	+	-	NT	NT
14	TL	NT	NT	+		+	-	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	90%	NT	NT	NT	NT
15	TL	-	NT	+	+	-	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NI	-	-	NT	+
16	HL	-	NT	-	+	-	NT	+	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
17	HL	+	NT	-	+	-	NT	+	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NI	NT	NT	NT	NT
18	HL	+	NT	+	+	-	+	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT

BL=Burkitt's lymphoma, DBCL=Diffuse B-cell lymphoma, HISTO=Histopathology, HL=Hodgkin's lymphoma, ID=Identification, NI=not-informed, NT=not-tested, TL=T-cell lymphoma.

Ann Arbor staging with Cotswolds modification of HIV-related lymphomas in adults served in the public health network.

ID	Histo	Ann Arbor staging	Extra-nodal disease (E)	Presence of bulky mass (X)	B symptoms	Classification
1	BL	IV	Present	Present	Present	IV E X B
2	BL		Present	Present	Present	II E X B
3	BL	1	Absent	Present	Present	I X B
4	BL	11	Absent	Present	Absent	II X A
5	BL	IV	Present	Present	Present	IV E X B
6	DBCL	IV	Present	Absent	Present	IV E B
7	DBCL	III	Present	Absent	Present	III E B
8	DBCL		Absent	Present	Absent	II X A
9	DBCL		Notinformed	Present	Notinformed	III?X?
10	DBCL	IV	Present	Absent	Present	IV E B
11	DBCL		Notinformed	Present	Notinformed	III?X?
12	DBCL	IV	Absent	Present	Present	IV X B
13	DBCL	IV	Notinformed	Absent	Notinformed	IV??
14	TL	IV	Present	Present	Present	IV E X B
15	TL	IV	Present	Absent	Notinformed	IV E
16	HL		Absent	Present	Present	III X B
17	HL	III	Absent	Absent	Notinformed	?
18	HL	IV	Present	Absent	Present	IV E B

BL=Burkitt's lymphoma, DBCL=Diffuse B-cell lymphoma, Histo=Histopathology, HL=Hodgkin's lymphoma, ID=Identification, TL=T-cell lymphoma.

(61.1%). There was extra-lymph node involvement in 9 patients (50%) but in 3 cases this data was not available (Table 2).

3.2. Clinical management

In the case of patients with non-Hodgkin's lymphoma, first-line chemotherapy treatment (CT) in 8 patients (44.4%) was CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), while in only 1 case (5.5%) it was chosen to perform COP (cyclophosphamide, vincristine, and prednisone) due to the patient's general compromised state. In 5 patients (27.8%) etoposide, doxorubicin, vincristine, and cyclophosphamide (EPOCH) was used and 1 patient (5.5%) was treated with Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, methotrexate, ara-C, dexamethasone, and methylprednisolone). In only 1 case was

rituximab associated with CT. The 3 (16.7%) cases of Hodgkin's lymphoma were treated with ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) as the first-line treatment (Table 3).

Of the 18 cases analyzed, 8 followed on to second-line treatment, wherein the CODOX-M/IVAC scheme (cyclophosphamide, adriamycin, vincristine, methotrexate/ifosfamide, etoposide, and cytosine arabinoside) was used in 3 of the cases. The second most common scheme was EPOCH, used in 2 cases (25%), while in single cases (12.5% each) CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), ICE (ifosfamide, etoposide, and carboplatin) and DHAP (dexamethasone, cisplatin, and cytarabine) were used. For the third-line treatment, only 3 patients were followed using the CODOX-M/IVAC + radiotherapy and Hyper-CVAD regimens in 1 (33.6%) and 2 (66.7%) cases, respectively. Only 1 patient went

Table 4

Response to treatment of HIV-related lymphomas in adults treated in the public health system.

ID	Histo	Use of Rituximab	1st-line CT	Response to 1st-line CT	2nd-line CT	Response to 2nd-line CT	3rd-line CT	Response to 3rd-line CT	4th-line CT	Response to 4th-line CT
1	BL	No	HYPERCVAD	Partial response-in FU	-	-	-	-	-	-
2	BL	No	EPOCH (2 cycles)	Death	-	-	-	-	-	_
3	BL	No	CHOP	Refractory	EPOCH	Refractory	HYPERCVAD	Death	-	_
4	BL	No	EPOCH (6 cycles)	Complete response	-	-	-	-	-	-
5	BL	No	CHOP	Refractory	EPOCH	Refractory	CODOX-M/ IVAC+RT	Refractory	GDN	Death
6	DBCL	No	COP	Death	-	-	-	-	-	_
7	DBCL	No	EPOCH (8 cycles)	Refractory	CODOX-M/IVAC+RT	Death	-	-	-	_
8	DBCL	No	EPOCH (1 cycle)	Refractory	CODOX-M/IVAC+RT	In FU	-	-	-	-
9	DBCL	No	CHOP (2 cycles)	Partial response	CHOEP (2 cycles)	In FU	-	-	-	_
10	DBCL	No	CHOP	Loss of FU	-	-	-	-	-	_
11	DBCL	No	CHOP	Death	-	-	-	-	-	_
12	DBCL	Sim	CHOP	Partial response	DHAP	Refractory	HYPER-CVAD	Death	-	_
13	DBCL	No	CHOP (8 cycles)	Partial response-in FU	-	_	-	-	-	_
14	TL	No	EPOCH (3 cycles)	Partial response	CODOX-M/IVAC+RT	In FU	-		-	_
15	TL	No	CHOP (2 cycles)	Death	-	-	-	-	-	_
16	HL	Not applied	ABVD	Refractory	ICE	Complete response	-	-	-	_
17	HL	Not applied	ABVD	Loss of FU	-		-	-	-	_
18	HL	Not applied	ABVD (6 cycles)	Partial response-in FU	-	-	-	-	-	-

ABVD = doxorubicin, bleomycin, vinblastineanddacarbazine, BL = Burkitt'slymphoma, CHOEP = cyclophosphamide, doxorubicin, vincristine, etoposideandprednisone, CHOP = cyclophosphamide, doxorubicin, vincristineandprednisone, CODOX-M/IVAC = cyclophosphamide, adriamycin, vincristineemetotrexate/ifosfamide, etoposideandcytosinearabinoside, CT = chemotherapy, DBCL = Diffuse B-celllymphoma, DHAP = dexamethasone, cisplatinandcytarabine, FU = follow-up, GND = vinorelbine, gemcitabineanddoxorubicinaliposomal, Histo = Histopathology, HL = Hodgkin'slymphoma, Hyper-CVAD = cyclophosphamide, vincristine, doxorubicin, vincristineandcyclophosphamide, iCE = ifosfamide, etoposideandcarboplatin, ID = Identification, RT = radiotherapy, TL = T-celllymphoma.

	 (<u> </u>	1.0

Complications of treatment of HIV-related lymphomas in adults served in the public health network.

ID	Histo	Opportunistic infections related to HIV	Infectious complications
1	BL	Absent	NEUTROPENIC ENTEROCOLITIS
2	BL	Absent	FEBRILE NEUTROPENIA
3	BL	HERPES ZOSTER	RHINOSINUSITIS
4	BL	Absent	Absent
5	BL	Absent	SOFT-TISSUE INFECTION
6	DBCL	ORAL CANDIDIASIS	RESPIRATORY SEPSIS
7	DBCL	PULMONARY TUBERCULOSIS	FEBRILE NEUTROPENIA
8	DBCL	Absent	FEBRILE NEUTROPENIA
9	DBCL	Absent	Absent
10	DBCL	ORAL CANDIDIASIS	NEUTROPENIC ENTEROCOLITIS + RESPIRATORY SEPSIS
11	DBCL	ORAL CANDIDIASIS	SOFT-TISSUE INFECTION
12	DBCL	Absent	INFECTIVE ENDOCARDITIS IN MITRAL VALVE
13	DBCL	Notinformed	Notinformed
14	TL	Absent	FEBRILE NEUTROPENIA
15	TL	Notinformed	RESPIRATORY SEPSIS
16	HL	Absent	FEBRILE NEUTROPENIA + NEUTROPENIC ENTEROCOLITIS
17	HL	Absent	FEBRILE NEUTROPENIA
18	HL	ORAL CANDIDIASIS	RECURRING FEBRILE NEUTROPENIA

BL=Burkitt's lymphoma, DBCL=Diffuse B-cell lymphoma, Histo=Histopathology, HL=Hodgkin's lymphoma, ID=Identification, TL=T-cell lymphoma.

on to the fourth-line treatment, undergoing GND (vinorelbine, gemcitabine, and liposomal doxorubicin) (Table 4).

Regarding the evolution of treatment, 4 patients already died during first-line treatment and 5 were refractory. Partial responses (PR) were observed in 6 patients and only 1 presented a complete response (CR). In 2 cases, there was loss of follow-up after first-line treatment. Of the 8 patients who followed on to second-line treatment, 1 died and 1 presented a CR, 3 went on to the third-line due to refractory disease, and 3 were not reevaluated by the end of the study period. Among the 3 who continued on to the third-line treatment, 2 died, and the only patient who followed on to fourthline CT treatment also died (Table 5).

3.3. HIV disease complications

With regard to opportunistic infections related to HIV, 10 (55.5%) did not present this complication, while 4 (22.2%) had

Table 6

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ID	Viral Load copies/mL
1	more than 500,000 copies/mL
2	morethan 500,000 copies/mL
3	morethan 500,000 copies/mL
4	501–9999 copies/m
5	morethan 500,000 copies/mL
6	10 000–99,999 copies/mL
7	501-9999 copies/mL
8	less than 50 copies/mL
9	10,000–99,999 copies/mL
10	10,000–99,999 copies/mL
11	10,000–99,999 copies/mL
12	10,000–99,999 copies/mL
13	10,000–99,999 copies/mL
14	100,000-499,999 copies/mL
15	501–9999 copies/m
16	501-9999 copies/mL
17	501-9999 copies/mL
18	10 000-99,999 copies/mL

oral candidiasis, 1 (5.5%) had herpes zoster and 1 (5.5%), pulmonary tuberculosis. In terms of infectious complications, 2 patients (11.1%) presented no complications, 7 (38.9%) febrile neutropenia, 3 (16.6%) neutropenic enterocolitis, 3 (16.6%) respiratory sepsis, 2 (11.1%) soft-tissue infection, 1 (5.5%) rhinosinusitis, and 1 (5.5%) infective endocarditis. In 1 patient, an association of neutropenic enterocolitis and respiratory focus sepsis was reported. Furthermore, Viral Load of the patients is present in Table 6.

4. Discussion

In the study population, we observed a predominance of HIVrelated lymphomas in males, which has also been observed by other authors.^[10] This fact may be related to the prevalence of HIV infection in Brazil being higher in men than in women.^[11]

As for the time from diagnosis of HIV infection to the diagnosis of lymphoma, we observed that half of the cases had the diagnosis of HIV infection concomitant with that of lymphoma, as serology tests are performed as part of the initial protocol of examinations of cancer patients in public health services. This fact reveals the low rates of getting serological tests among the at-risk population, despite such tests being widely available nowadays in the public health system. Clearly, there is a need to educate the population about the risks and the need for a diagnosis in order to start treatment as soon as possible, which has been demonstrated to decrease HIV-related morbidity and mortality.^[6] In a UK study, it was observed that in only a small percentage of cases is lymphoma diagnosed simultaneously with HIV, evidencing good adherence to serological tests by this population with early start of treatment.^[12]

LDH values were elevated in 12 of the patients (66.7%), similar to a series performed by Cabrera^[1] with 55 patients, where LDH was more than 1.5 times greater than the normal value in 37 cases (75%), which confers a higher risk when evaluating the International Prognosis Index (IPI) for non-Hodgkin's lymphomas, a prognostic score that is also used for lymphomas related to HIV infection.^[13] On the other hand, the elevation of LDH is non-specific in patients with AIDS and may be elevated in several situations, such as *Pneumocystis jiroveci* infection, which may present a confounding bias when evaluating the IPI of this population under study.^[14] Although the value of LDH increased the IPI indices, shifting the patients to a classification of risk with a worse prognosis, the evaluation of status performance by ECOG at diagnosis found 8 patients (44.4%) had no impairment of their daily activities, with a score between 0 and 1, which may have been observed because of the low mean age of patients diagnosed with lymphoma.

The distribution of histological types was similar to that found in other studies¹⁵, predominating diffuse B-cell lymphoma and Burkitt's lymphoma. The immunohistochemical profile was similar to the general HIV-negative population, noting that in 7 cases (38.8%) Ki-67 antigen expression was greater than 90%, giving the disease a high rate of cell proliferation.^[16]

The Ann Arbor classification with Cotswolds modification was similar to that observed in other studies¹⁷, with more advanced stages predominating. Stages III and IV were observed in 14 patients (77.7%), associated with the presence of B symptoms, bulky disease and extra-lymph node involvement in more than 50% of the patients, which appears to be associated with the immunodeficiency status related to HIV infection.

When analyzing the treatments performed, we could observe a great variety of chemotherapeutic regimens, ranging from cytoreductive (COP) to intensive regimens with continuous infusion of drugs (EPOCH). As there is still no consensus on the best treatment for patients with HIV-related lymphomas^[17] and the fact that the study was conducted in more than 1 hospital, which is entirely independent, the choice was possibly related to the experience and availability of drugs in each service. However, we observed that in only 1 of the 15 cases in which CD20 was positive in the immunohistochemistry, rituximab was administered, although its effectiveness has already been demonstrated in some studies when used judiciously in patients with CD4 levels above 50 cells/mcL.^[18,19] This conduct is based on the Ordinance of the Ministry of Health of 2014, currently valid in Brazil, in which the use of the anti-CD20 monoclonal antibody is contraindicated in patients with serologies positive for HIV and Hepatitis B²⁰, which may have been 1 more factor that contributed to the unfavorable evolution of the patients studied.

In this series, we observed very high mortality, equivalent to 44.4%, and a complete response in only 11.1%, much lower than that observed by other authors.^[10] This high rate of treatment failure may be related to frequent treatment-related infectious complications, which occurred in 83.3% of cases, to the non-use of the anti-CD20 monoclonal antibody, to the delayed diagnosis of both lymphoma and HIV and to the precarious living conditions and the limited access to basic health care of the study population, reinforcing the need for better access to health care.

Due to the nature of the study, some limitations due to the small number of cases do not allow us to establish associations as well as extrapolate our findings to other populations, and prospective studies are necessary.

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All authors contributed in writing the manuscript. They read and approved the final manuscript.

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