Mortality Trend of Hematological Cancers in Sergipe and its Geospatial Distribution from 1980 to 2021

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Tendência de Mortalidade por Cânceres Hematológicos em Sergipe e sua Distribuição Geoespacial de 1980 a 2021

Tendencia de la Mortalidade por Cánceres Hematológicos en Sergipe y su Distribución Geoespacial de 1980 a 2021

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ABSTRACT

Introduction: Cancer is the leading cause of non-metabolic death worldwide. Blood cancers originate in the hematopoietic system and are classified as lymphomas, leukemias, plasma cell neoplasms, and myelodysplastic syndromes. **Objective:** To describe the mortality trend of the main hematologic neoplasms in the State of Sergipe between 1980 and 2021 and their spatial distribution. **Method:** The mortality rates from the State's Mortality Information System were investigated through longitudinal and geospatial analysis software and analyzed by age group, sex, type of neoplasm, and municipality. Time trend graphs were constructed and their annual and average percentage variations analyzed, and geodistribution maps of the rates were created, with areas of contiguity, and statistical significance analysis by the Moran and LISA methods. **Results:** The mortality rates were continuously increasing in the period for all statistically significant neoplasms and groups. The highest number of deaths occurred in males, with annual increase of 3% (95% CI 2.5-3.5). Leukemias accounted for 48.78% of total deaths. The descending order of mortality was leukemia, non-Hodgkin lymphoma and multiple myeloma. The age group of 65+ represented 35.76% of total deaths. The risk areas were the *Leste* and *Agreste* Mesoregions and the *Grande Aracaju* Region. **Conclusion:** The trend of mortality due to hematologic cancers in Sergipe is a topic little analyzed. Mortality rates have increased in the State, with emphasis on leukemias, males, older adults, and municipalities with great inequality and agricultural production.

Key words: Hematologic Neoplasms; Mortality/trends; Spatio-Temporal Analysis.

RESUMO

Introdução: O câncer é a principal causa de morte de origem não metabólica no mundo. Os cânceres sanguíneos têm origem no sistema hematopoiético e são classificados em linfomas, leucemias, neoplasias de plasmócitos e síndromes mielodisplásicas. **Objetivo:** Descrever a tendência de mortalidade das principais neoplasias hematológicas no Estado de Sergipe entre 1980 e 2021 e sua distribuição espacial. **Método:** Foram estudadas, por meio de *softwares* de análise longitudinal e geoespacial, as taxas de mortalidade do Sistema de Informação sobre Mortalidade para o Estado e analisadas por grupo etário, sexo, tipo de neoplasia e município. Foram construídos gráficos de tendência temporal e analisadas suas variações percentuais anuais e médias, e confeccionados mapas de geodistribuição das taxas, com áreas de contiguidade, e análise de significância estatística pelos métodos Moran e LISA. **Resultados:** As taxas de mortalidade apresentaram-se constantemente crescentes no período em todas as neoplasias e grupos em que houve significância estatística. O maior número de óbitos ocorreu em homens com crescimento anual de 3% (IC 95%; 2,5-3,5). As leucemias corresponderam a 48,78% do total de óbitos. A ordem decrescente de mortalidade foi leucemias, linfoma não Hodgkin e mieloma múltiplo. O grupo etário de 65+ representou 35,76% do total de óbitos. As áreas de risco foram as Mesorregiões Leste e Agreste e a Região Grande Aracaju. **Conclusão:** A tendência de mortalidade por cânceres hematológicos em Sergipe é um tema pouco analisado. As taxas de mortalidade têm crescido no Estado, destacando-se leucemias, sexo masculino, idosos, e municípios com maior desigualdade e produção agrária.

Palavras-chave: Neoplasias Hematológicas; Mortalidade/tendências; Análise Espaço-Temporal.

RESUMEN

Introducción: El cáncer es la principal causa de muerte no metabólica en el mundo. Los cánceres de sangre se originan en el sistema hematopoyético y se clasifican en linfomas, leucemias, neoplasias de células plasmáticas y síndromes mielodisplásicos. **Objetivo:** Describir la tendencia de la mortalidad de las principales neoplasias hematológicas en el estado de Sergipe entre 1980 y 2021 y su distribución espacial. **Método:** Mediante *softwares* de análisis longitudinal y geoespacial se estudiaron las tasas de mortalidad del Sistema de Información sobre Mortalidad para el Estado y analizadas por edad, sexo, tipo de neoplasia y municipio. Se construyeron gráficos de tendencias temporales y se analizaron sus variaciones porcentuales anuales y promedio, y se crearon mapas de geodistribución de tarifas, con áreas de contigüidad y análisis de significación estadística mediante los métodos de Moran y LISA. **Resultados:** Las tasas de mortalidad aumentaron constantemente durante el período en todas las neoplasias y grupos en los que hubo significación estadística. En los hombres, que tuvieron el mayor número de muertes, hubo un aumento del 3% por año (IC 95% 2,5-3,5). La leucemia correspondió al 48,78% del total de muertes. Las causas en orden decreciente de mortalidad fueron leucemias, linfoma no Hodgkin y mieloma múltiple. El grupo de edad de 65+ representó el 35,76% del total de muertes. Las áreas de riesgo fueron las mesorregiones Este y Agreste y la región del Gran Aracaju. **Conclusión:** La tendencia de mortalidad por cánceres hematológicos en Sergipe es un tema poco analizado. Las tasas de mortalidad han crecido en el estado, con énfasis en leucemia, varones, adultos mayores y municipios con mayor desigualdad y producción agrícola.

Palabras clave: Neoplasias Hematológicas; Mortalidad/tendencias; Análisis Espacio-Temporal.

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INTRODUCTION

Cancer is the main cause of non-metabolic death worlwide[1]. The cumulative risk of developing cancer before 75 years was 20% for both sexes according to the Global Cancer Observatory (Globocan) in 2022. On its turn, the cumulative risk of death by cancer before 75 years was 9.6% for both sexes[2]. In Brazil, between 1997 and 2016, 213,750 deaths by leukemia, lymphomas, myelodysplastic syndromes, multiple myeloma and other plasma cells neoplasms occurred, with 39,731 registered on the Northeast Region alone and 1,460 on the State of Sergipe[3].

Hematological malignancies (HM), or blood cancers originate from precursor cells of blood cells and of the immune system. They result from alterations of hematopoiesis, leading to the uncontrolled growth of cells in various stages of maturation, depositing on bone marrow, lymph nodes, immune organs system and peripheral blood. Can be classified as Hodgkin and non-Hodgkin lymphomas (multiple myeloma and plasmacytoma) and myelodysplastic syndromes[4].

Chemotherapy is the most common treatment for hematologic cancers increasing the global survival of the patients, in addition to other options as immune therapy, radiotherapy and bone marrow transplantation (BMT) depending on the disease. Patients' survival can be impacted by disparities of access to the treatment[5].

Sergipe, the smallest Federative State has undergone significant structural populational, economical and quality of life changes in the last decades. To what extent these changes have impacted the mortality rates by hematological cancers needs to be evaluated[6].

The objective of the study is to investigate whether mortality by HM increased in Sergipe in the last years, the identification of the respective main hematological neoplasms and the spatial distribution by age-range, sex and municipalities or health regions. Few studies addressed the spatiotemporal analysis of mortality by hematological cancers in Sergipe due to its relevance within urban and social transformations. It is expected that the study can contribute to stimulate new investigations that elucidate the relation among mortality by HM and Human Development Index (HDI), disparities of health access and comorbidities.

METHOD

Spatial analysis-based time series ecological study of deaths by HM in Sergipe, from 1980 to 2021, with data of the State's Mortality Information System (SIM)[7] to calculate the mortality rates.

Mortality rates were calculated from deaths occurred across every age-range for both sexes according to the inclusion criteria: death by hematological cancers pursuant to the International Classification of Diseases and Related Health Problems (ICD-10)[8], in Sergipe registered by SIM in the period.

Deaths were categorized according to ICD-9 (utilized until 1992) and ICD-10. The classification per ICD-10 is: C81 – Hodgkin disease; C82 – non-Hodgkin lymphoma, follicular; C83 – non-Hodgkin lymphoma, diffuse; C84 – peripheral and cutaneous T-cell lymphomas; C85 – other specified and unspecified types of non-Hodgkin lymphoma; C90 – multiple myeloma and malignant plasma cells; C91 – lymphoid leukemia ; C92 – myeloid leukemia; C93 – monocytic leukemia; C94 – other leukemias of specified cell type; C95 – leukemia of unspecified cell type, and D46 – myelodysplastic syndrome.

The variables analyzed were: type of neoplasm, age at death, sex, and year of death. The deidentified data were collected from Sergipe's SIM.

SIM database under the purview of Sergipe Health Secretary was utilized to analyze mortality by cancer with registries since 1980 for the whole State. Deaths by cancer were considered when the cause was filled in as basal cause and consequential or immediate causes pursuant to Part 1 of field 49 of the death certificate. Data were grouped by sex, age-range (0-19; 20-44; 45-64 and 65+), type of blood, malignant disease and municipality of residence.

The rates utilized in the trend curves were calculated in Excel, version 2010 with p and standard deviation (SD) for the data, with confidence interval (CI) of 95%.

The Census of 1991, 2000 and 2010 have been adopted as populational references for the calculation of age standardized and specific rates, in addition to inter-census estimates provided by "*Instituto Brasileiro de Geografia e Estatística (IBGE)*"[9]. Age-specific rate was calculated dividing the total number of deaths per age-range and sex in the age considered by the population of reference per age-range and sex of the same year, per million. Age-standardized rate was calculated by the sum of the product of specific rates and number of individuals per each age-range, divided by the standard world population according to the model of Segi & Doll[10].

CI 95% were calculated for the rates with the formula: CI 95% = R ± (1.96 x SE), where R is the rate, 1.96 is the constant z and SE is the standard error. SE was calculated as SE = R x $\sqrt{N}$, being R the rate and N, the number of annual deaths.

Excel spreadsheets were elaborated with the total number of deaths by hematologic cancers and specific neoplasms, selecting those with higher mortality at

the database: leukemias, non-Hodgkin lymphoma and multiple myeloma. The spreadsheets have also included the number of deaths by age-ranges (0-19; 20-44; 45-64 and 65+), crude and standardized rates annually between 1980 and 2021 for both sexes.

Temporal trends in mortality were calculated by the US National Cancer Institute Joinpoint Regression Program[11], version 5.0.2, which identifies changes in the trend curves through joinpoints and determines the annual percent change and average (APC and AAPC).

Next, charts with the respective temporal trend curves were created to analyze the growth or decline of the mortality rates.

The coefficient million was utilized for the temporal trend because of very small mortality rates for some specific neoplasms the software was unable to read. Years with null mortality were excluded from the analysis with upper exclusionary limit of 20% of the years. Therefore, temporal analysis was performed for the whole State.

Spatial analysis for Sergipe utilized the software TerraView 4.2.2[12], based on Local Bayes Empirical smoothing method of the rates and Moran Global index to evaluate the spatial autocorrelation. The maps were exported to QGIS[13], version 3.10.7, for time series presentation.

Excel spreadsheets were created with the geographical code of the municipality, name, population according to the IBGE census, age-standardized rates for hematological cancers, number of deaths by specific neoplasms and health area. Each spreadsheet was divided in ten-year periods (1990-1999, 2000-2009 and 2010-2019), excluding the years before 1990 due to geographical changes.

The spreadsheets were exported to QGIS[13], which matched the grids of the State to create maps containing geographic and mortality information. TerraView[12] calculated the Bayesian rates and Moran index utilized in the final maps by QGIS[13].

The mortality rate of the neoplasms investigated portrayed in the maps was analyzed per 100 thousand inhabitants, different from TerraView temporal analysis by convenience.

The analysis of the Moran index[14] considered the autocorrelation of contiguous areas to characterize the mortality per regions classified as:

– High mortality region (Q1): high mortality municipalities near other high mortality municipalities.

– Low mortality region (Q4): low mortality region near other low mortality municipalities.

– Variable mortality region R (Q2 and Q3): high mortality municipalities near other low mortality municipalities and vice-versa.

The LISA[14] method confirmed the statistical significance of areas of higher or lower populational risk in the period analyzed, considering the likelihood of the data represented by CI (95%, 99% and 99.9%).

Bayesian rates, Moran index analysis and LISA's significance analysis were considered for the maps. Each map was displayed side-by-side in a time series in three periods, scale 1:3,000,000, and geographic scale referenced in km. The software Photoscape was utilized to gather the maps in one image with the caption and other indicative figures (scale and arrow for direction).

The study was approved by the Institutional Review Board of "*Universidade Federal de Sergipe*", report number 5,875,491 (CAAE (submission for ethical review): 66896523.2.0000.5546) in compliance with Directive 466/12[15] of the National Health Council. Secondary mortality data by cancer of deidentified individuals in Sergipe collected from SIM and available at the State Health Secretary have been utilized.

The authors were granted access to SIM consolidated database by the assigned authorities and the data were collected upon signature of the Data Use Agreement (DUA), waiving the Informed Consent Form.

RESULTS

Mortality by leukemias, non-Hodgkin lymphoma and multiple myeloma corresponded to 91.52% (2,966) of the total deaths by HM while 8.48% (275) were caused by other HM. The age range of 65 + accounted for 35.76% (1,159) of the total deaths registered in the series (Supplementary Material 1 and 2).

Mortality by leukemias in the period corresponded to 48.78% (1,581) of the total deaths by HM, men's standardized ratio were 42% higher than women's. Mortality by non-Hodgkin lymphoma corresponded to 28% (908) of the total with mean standardized rates 54% higher in men than in women. Multiple myeloma responded to 14.71% (477) of the total deaths, standardized mean ratio for men were 4% higher than women. Comparatively, standardized mortality ratio for men were 39% in average higher than in women. The absolute number of deaths were 19.8% higher in men than in women.

The Joinpoint trend graphs for men showed increase without inflection in mortality per million for all HM and age-ranges with more significant annual increase in the age range of 65 years + (APC = 4.7, CI 95%; 3.7 – 5.8), followed by young adults (20-44 years), APC = 2.1 (CI 95%; 1.0 – 3.2). Another expressive APC occurred in all ages (APC = 3.0, CI 95%; 2.5 – 3.5) (Figure 1 and Table 1).

Captions: A and B: All HMN. A: male. **B:** female. **C and D: Leukemias. C:** male. **D:** female. **E and F: non-Hodgkin's lymphoma. E:** male. **F:** female. **G and F: multiple myeloma. G:** male. **H:** female.

Figure 1. Trends of mortality per million for all HM and their main groups for both sexes, considering the age standardized rates for the age-ranges 0 to 19; 20 to 44; 45 to 64; 65+ and all ages (ASR)

Women's mortality trend for all HM increased between 1992 and 2019 (APC = 2.1, CI 95%; 1.3 – 3.0). For older than 65 years, growth without inflection points, considering statistical significance (APC = 5.1, CI 95%; 4.2 – 6.0) until 2018.

For all age-ranges in men, leukemia grew without inflection points, except for 20 to 44 and 45 to 64 years where no statistical significance was found, standing out the 65+ group, APC = 3.5 (CI 95%; 2.2 – 4.7). For women, rising mortality trend by leukemias without inflections was found for the age-standardized rate and 65+ group. The most expressive APC was in the age-range of 65+ years, APC = 3.2 (CI 95%; 1.9 – 4.6).

Age standardized rate (ASR) for non-Hodgkin lymphoma in men increased without inflection points in the period (APC = 2.2, CI 95%; 1.4 – 3.0). The 65+ years group stood out with APC = 2.8 (CI 95%; 1.5 – 4.1). For women, the age standardized rate increased without inflection points (APC = 1.8, CI 95%; 0.7 – 2.9).

Time series analysis for multiple myeloma in men revealed rising ASR between 1985 and 2021, APC = 5.9 (CI 95%; -4.4 – 7.4). For females, it increased without inflection points for the age range of 65 +, APC = 3.0 (CI 95%; 1.0 – 5.0).

According to the spatial analysis, mortality data geoprocessing was statistically significant for Bayesian rates based maps whereas the heterogeneity of the territory and populational distribution, which ensures reliability and applicability to the reality. The period 2010-2019 is the closest to the reality, making the analysis more robust for research purposes and evaluation of the risk areas for the neoplasms investigated (Supplementary Material 3).

Bayesian rates maps for men revealed important variations in the spatial distribution of mortality during the periods analyzed. Deaths concentrated in the regions of *Grande Aracaju*, *Leste*, *Agreste Central* and *Sul* between 1990 and 1999. Between 2000 and 2009, the rates increased in all regions, with new concentrations in *Baixo São Francisco* and *Médio Sertão*. Between 2010 and 2019, the concentration occurred on the Mesoregions *Agreste* and *Leste* (Figure 2C), with increased rates in the rural area.

Moran's maps showed clusters of significant autocorrelation (Figures 2D, 2E and 2F). In the period 1990-1999 (Figure 2D), part of *Grande Aracaju* was considered with high risk of mortality by HM for men. Between 2000 and 2009, the high risk cluster occurred in *Grande Aracaju* and in the municipality of *Aquidabã* (Figure 2E). In the period 2010-2019, the high risk cluster was again *Grande Aracaju* and *Aquidabã* (Figure 2F). The low risk regions for mortality by HM between 1990 and 1999 were the regions *Centro-Sul* and some municipalities of *Alto* and *Médio Sertão.* Between 2000 and 2009, low risk regions were *Centro-Sul, Sul*, and the municipalities of *Poço Redondo*. Between 2010 and 2019, some low risk municipalities were detected in the regions of *Alto Sertão* and *Agreste Central*.

Bayesian rates maps for females presented variations in the spatial distribution of mortality. Deaths concentrated in *Grande Aracaju* between 1990 and 1999 (Figure 3A). Between 2000 and 2009, rates increased for all regions, except *Alto Sertão* and part of *Sul* (Figure 3B). Between 2010 and 2019, great concentration occurred in *Alto Sertão*, *Grande Aracaju* and *Centro-Sul* of the State (Figure 3C).

Moran maps for females have also shown clusters of significant correlation (Figures 3D, 3E and 3F). Between 1990 and 1999 (Figure 3D), part of *Grande Aracaju* presented high risk. Between 2000 and 2009 (Figure 3E), high-risk regions were *Grande Aracaju* and the municipality of *Aquidabã*. The high risk cluster in the period 2010-2019 was *Grande Aracaju* and the municipality of *Lagarto*, with low risk cluster in *Alto Sertão* (Figure 3F). Low risk regions between 1990 and

Table 1. Trends of mortality for total HM and their main groups for both sexes, considering the ASR for the age ranges 0 to 19; 20 to 44; 45 to 64; 65 + years and all ages

All HM							
Female							
ASR	**JP**	**APC**	**CI 95%**	***p***	**AAPC**	**CI 95%**	***p***
	3	(1980-1988) -8.6	-16.3; -0.3	0.044	0.7	-3.4; 5.0	0.732
		(1988-1992) 21.4	-15.4; 74.2	0.282	0.7	-3.4; 5.0	0.732
		(1992-2019) 2.1	1.3; 3.0	<0.001	0.7	-3.4; 5.0	0.732
		(2019-2021) -15.1	-39.9; 19.9	0.341	0.7	-3.4; 5.0	0.732
0-19 years	0	1.5	0.2; 2.7	0.022	1.5	0.2; 2.7	0.022
20-44 years	0	0.8	-0.4; 2.0	0.205	0.8	-0.4; 2.0	0.205
45-64 years	0	1.3	0.3; 2.3	0.009	1.3	0.3; 2.3	0.009
65 years or more	1	(1980-2019) 5.1	4.2; 6.0	< 0.001	3.4	1.2; 5.6	0.002
		(2019-2021) -24.9	-50.6; 14.1	0.174	3.4	1.2; 5.6	0.002
Male							
	JP	**APC**	**CI 95%**	***p***	**AAPC**	**CI 95%**	***p***
ASR	0	3.0	2.5; 3.5	< 0.001	3.0	2.5; 3.5	< 0.001
0-19 years	0	2.0	0.9; 3.1	< 0.001	2.0	0.9; 3.1	< 0.001
20-44 years	0	2.1	1.0; 3.2	< 0.001	2.1	1.0; 3.2	< 0.001
45-64 years	0	1.7	0.6; 2.7	0.002	1.7	0.6; 2.7	0.002
65 years or more	0	4.7	3.7; 5.8	< 0.001	4.7	3.7; 5.8	< 0.001
Leukemias							
Female							
	JP	**APC**	**CI 95%**	***p***	**AAPC**	**CI 95%**	***p***
ASR	0	1.6	0.8; 2.4	< 0.001	1.6	0.8; 2.4	< 0.001
0-19 years	0	2.0	0.7; 3.2	0.003	2.0	0.7; 3.2	0.003
20-44 years	0	0.4	-0.8; 1.7	0.478	0.4	-0.8; 1.7	0.478
45-64 years	0	0	-1.6; 1.5	0.953	0	-1.6; 1.5	0.953
65 years or more	0	3.2	1.9; 4.6	< 0.001	3.2	1.9; 4.6	< 0.001
Male							
	JP	**APC**	**CI 95%**	***p***	**AAPC**	**CI 95%**	***p***
ASR	0	2.4	1.6; 3.1	< 0.001	2.4	1.6; 3.1	< 0.001
0-19 years	0	2.5	1.3; 3.8	< 0.001	2.5	1.3; 3.8	< 0.001
20-44 years	0	1.0	-0.3; 2.3	0.133	1.0	-0.3; 2.3	0.133
45-64 years	0	-0.4	-1.9; 1.2	0.614	-0.4	-1.9; 1.2	0.614
65 years or more	0	3.5	2.2; 4.7	< 0.001	3.5	2.2; 4.7	< 0.001
Non-Hodgkin Lymphoma							
Female							
	JP	**APC**	**CI 95%**	***p***	**AAPC**	**CI 95%**	***p***
ASR	0	1.8	0.7; 2.9	0.002	1.8	0.7; 2.9	0.002
0-19 years	0	-1.4	-3.5; 0.8	0.195	-1.4	-3.5; 0.8	0.195
20-44 years	0	-0.1	-2.3; 2.1	0.912	-0.1	-2.3; 2.1	0.912
45-64 years	0	0.9	-0.6; 2.3	0.225	0.9	-0.6; 2.3	0.225
65 years or more	0	2.7	0.8; 4.6	0.006	2.7	0.8; 4.6	0.006

to be continued

Table 1. continuation

Male							
	JP	**APC**	**CI 95%**	***p***	**AAPC**	**CI 95%**	***p***
ASR	0	2.2	1.4; 3.0	< 0.001	2.2	1.4; 3.0	< 0.001
	4	(1981-1983) -51.5	-88.7; 107.9	0.314	-2.6	-13.6; 9.8	0.664
		(1983-2005) 5.5	1.2; 10.0	0.014	-2.6	-13.6; 9.8	0.664
		(2005-2009) -33.6	-69.2; 43.1	0.282	-2.6	-13.6; 9.8	0.664
		(2009-2014) 44.3	-7.5; 125.1	0.101	-2.6	-13.6; 9.8	0.664
0-19 years		(2014-2021) -13.1	-28.9; 6.1	0.160	-2.6	-13.6; 9.8	0.664
20-44 years	0	0.8	-1.0; 2.6	0.398	0.8	-1.0; 2.6	0.398
45-64 years	0	0.9	-0.5; 2.3	0.192	0.9	-0.5; 2.3	0.192
65 years or more	0	2.8	1.5; 4.1	< 0.001	2.8	1.5; 4.1	< 0.001
Multiple Myeloma							
Female							
	JP	**APC**	**CI 95%**	***p***	**AAPC**	**CI 95%**	***p***
ASR	0	1.2	-0.7; 3.1	0.199	1.2	-0.7; 3.1	0.199
45-64 years	0	0.9	-1.2; 3.0	0.401	0.9	-1.2; 3.0	0.401
65 years or more	0	3.0	1.0; 5.0	0.004	3.0	1.0; 5.0	0.004
Male							
	JP	**APC**	**CI 95%**	***p***	**AAPC**	**CI 95%**	***p***
ASR	1	(1981-1985) -37.9	-65.8; 12.6	0.112	0.4	-5.3; 6.4	0.901
		(1985-2021) 5.9	-4.4; 7.4	< 0.001	0.4	-5.3; 6.4	0.901
45-64 years	0	2.0	0.1; 3.8	0.036	2.0	0.1; 3.8	0.036
65 years or more	1	(1981-2008) 0.3	-3.5; 4.2	0.867	3.9	1.0; 6.8	0.007
		(2008-2021) 11.7	6.8; 16.8	< 0.001	3.9	1.0; 6.8	0.007

Caption: ASR = Age standardized rate; JP = number of Joinpoints; APC = annual percent change; AAPC = average annual percent change; CI 95% = confidence interval 95%.

1999 were some municipalities of the *Sul*, *Médio Sertão*, *Médio Agreste* and *Médio São Francisco*. Low risk regions between 2000 and 2009 were the municipality of *Poço Redondo* and some municipalities of the *Centro-Sul* and *Sul*. Between 2010 and 2019, the low risk region was *Alto Sertão*, in addition to some municipalities of the region of *Baixo São Francisco* and the municipality of *Ribeirópolis*.

DISCUSSION

Age standardized rates and Bayesian mortality rates by hematological neoplasms investigated in Sergipe increased between 1980 and 2021, indicating mortality rise by these neoplasms in the State. Leukemias presented the highest mortality rates followed by non-Hodgkin lymphoma and multiple myeloma. The age group with highest mortality was 65+. The mesoregions *Leste* and *Agreste* had the highest mortality rates, standing out *Grande Aracaju* according to the spatial distribution.

Similar trend was noticed in Bahia between 2008 and 2018, with mortality increase on all health macro-regions for the age ranges analyzed (0-60 years and 60+)[16]. That scenario matches the study by Barbosa, et al.[17], with rising estimates of mortality by cancer until 2030 in the Northeast Region contrary to declining estimates in the South, Southeast and Mid-West regions of the country in the same year.

In developed countries as the USA, mortality rates by HM have been declining since the 1990s, reflecting improvement of the therapeutic protocols and efforts of prevention, early diagnosis and treatment. However, in developing countries as Brazil, mortality by these neoplasms is high yet due to poor specific policies and reduced therapeutic resources available[18-21].

In Sergipe, mortality by HM in descending order is due to leukemias, non-Hodgkin lymphoma, multiple myeloma and other HM, similar to Globocan[2] world scenario, where leukemias cause highest mortality. Mortality by leukemia has been associated with occupational exposure to benzene and formaldehyde in developing countries according to some studies, while in developed countries, it is related to high body mass index (BMI)[18].

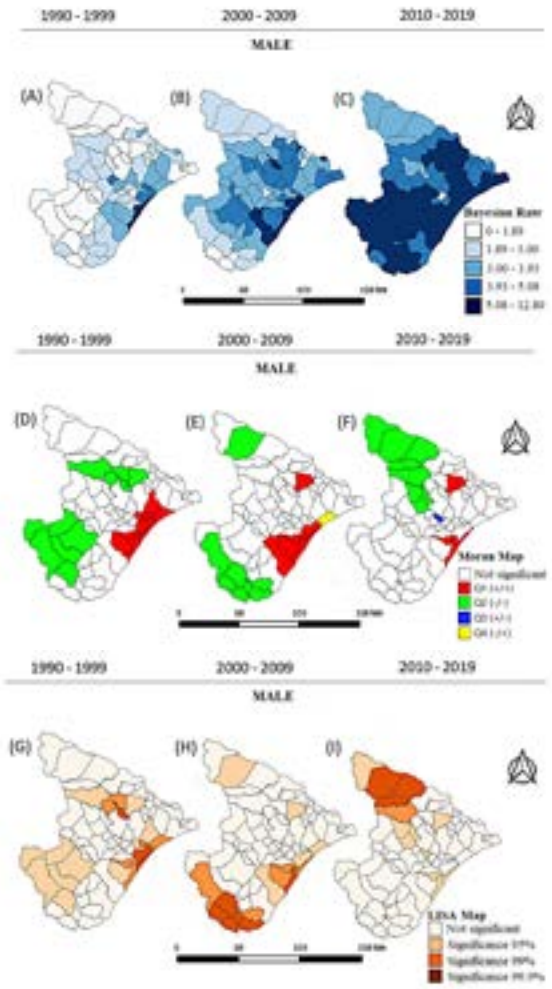

Figure 2. Bayesian rates of spatial distribution of HM for males between 1990 and 2019

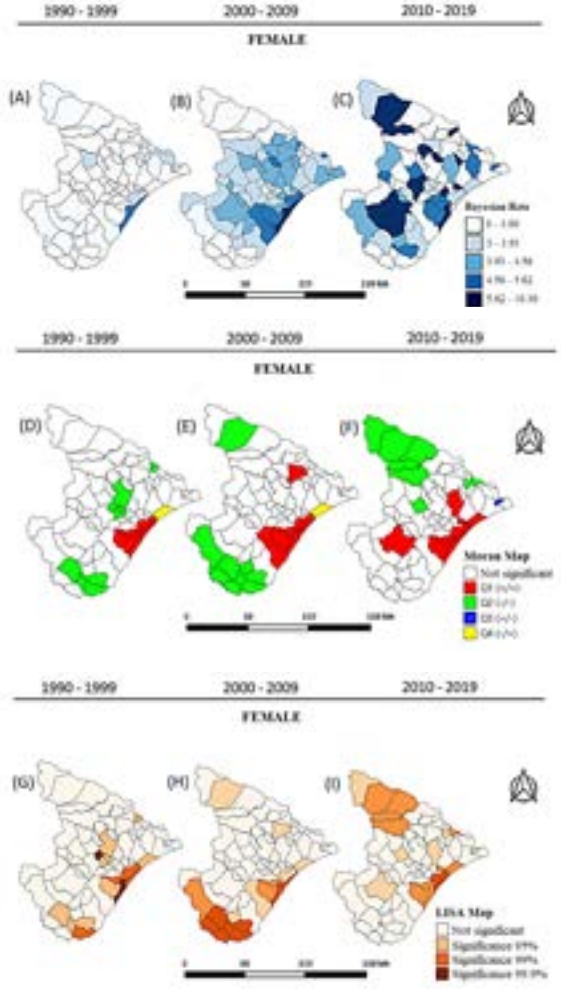

Figure 3. HM spatial distribution of Bayesian rates for females in Sergipe between 1990 and 2019

Mortality by HM was higher in men, with increase without inflection points of the standardized mortality ratio of the period for all ages. The predominance of males mortality ratio is seen for other cancer topographies in the State, in other Brazilian regions and according to studies in USA and Europe[18-24]. This can be associated with more exposure to risk factors as tobacco, infections, occupational and environmental factors[25-27].

Mortality by HM has also increased for women from 1992 to 2019, standing out the 65+ group from 1980 to 2019. The last years of the series even for this age range did not present significant changes of mortality during the COVID-19 pandemic and for men, in despite of changes in health access and positive relation among the disease and HM that, together, contribute for poor prognosis[28-30].

Non-Hodgkin lymphoma was the neoplasm with higher disparity of mortality ratio between the sexes, possibly due to hormone and environmental factors which require more studies[18,30,31].

Multiple myeloma was the neoplasm most associated with advanced age, the age-range with higher mortality was 65+, consistent with studies that indicate as one of the main risk factors for the appearance of hematological neoplasms[32-36].

Spatial distribution of HM showed concentration of deaths in *Grande Aracaju, Leste* and *Agreste* regions, matching the areas with high populational density, suggesting relation with carcinogenic lifestyle, impacting the incidence of these cancers and consequently, the mortality[37,38].

Aracaju and *Barra dos Coqueiros*, the highest Gini index of the State, are highly poverty affected areas in great social disparity regions, high incidence of poverty and urban habits, possibly related to little effective public policies for prevention, early diagnosis and treatment of these cancers[19,39,40].

The State lacks professional training and elucidation about risk factors or damage reduction policies for these

neoplasms in case of workers exposed to pesticides, carcinogenic chemicals or ionizing radiation[2,4,22,26,28].

Early diagnosis requires access to health services, which, quite often have obstacles as distance from oncological treatment centers, socioeconomic difficulties for the majority of the population and poor elucidation of the diagnosis to the patient and family. Bone marrow transplantation is the treatment of choice for some HM, for example, all acute leukemias and in cases of low therapeutic fragility, for multiple myeloma; in addition, other chemotherapeutic drugs are not available for most of the patients due to financial difficulties to purchase them[5].

The drop of mortality rates by HM in Brazil can occur late due to structural failures of the health system as difficulty of access to timely adequate therapies. This is particularly relevant in low-or-middle HDI countries where inequalities to access health services are more pronounced[11,41-45].

The regions of *Grande Aracaju* and the municipalities of *Aquidabã, Lagarto* and *Capela* have great risk of mortality by HM according to the Bayesian rates distribution maps. These risk areas can be related to agricultural practices, sedentarism and poor local feeding habits that can increase the incidence and mortality by these causes. The Brazilian Association of Collective Health (Abrasco) states that Brazil is the greatest user of pesticides in the world and the regions with the biggest agricultural production as *Leste Sergipano*, *Centro-Sul* and *South*, can have significant impact on the mortality by HM[38,46,47] due to the use of these products.

The strong point of the study is the presentation of a scenario of mortality by hematologic cancers in Sergipe in a long time series based on formal data of quality and representative of the population[48]. However, some patients may have informed wrong addresses or have moved to cities closer to health services before death which can lead to sub-notification of mortality by HM in the rural area[49].

CONCLUSION

Rising trend of mortality by HM was found in Sergipe, standing out death by leukemias. The decreasing order of mortality was leukemias, non-Hodgkin lymphoma, multiple myeloma and other HM.

Increasing trend for men did not show inflection points for the whole period investigated; for women, increasing trend presented annual percent changes for total neoplasms. Higher mortality rates were found for 65+ individuals and men for all neoplasms analyzed.

Mortality spatial distribution occurred on the Mesoregions *Leste* and *Agreste*, standing out *Grande Aracaju* and municipalities with high HDI, populational density, Gini index and significant agricultural production for all neoplasms investigated.

Due to Sergipe rising mortality rates by these diseases, plotting risk areas is relevant for mortality control, requiring strategies as the Oncologic Attention National Policy (PNAO), ensuring better access to health services for these patients. Concomitantly, public health investments in diagnostic methods and therapeutic strategies and timely screening programs are necessary to detect these cancers.

CONTRIBUTIONS

Ríllary de Oliveira Silva Ferreira, Alex Rodrigues Moura, Carlos Anselmo Lima and Angela Maria da Silva contributed to the study design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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