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Temporal-spatial analysis of mortality from Lupus in Brazil, between 2011 and 2021

Análise têmporo-espacial da mortalidade por Lupus Eritematoso Sistêmico no Brasil, entre 2011 e 2021

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ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) has a global epidemiology marked by variations in prevalence that can be attributed to genetic, environmental, and socioeconomic factors. It predominantly affects women of childbearing age. Studies have shown that its prevalence is higher in Black and Asian populations, while white populations have lower rates.

Objective: To analyze mortality from in Brazil between 2011 and 2021, taking into account its temporal-spatial distribution.

Method: It was developed under the descriptive epidemiological scope and based on data extracted from the Mortality Information System (SIM/DATASUS). Variables such as sex, age group, ethnicity, marital status, education, place of death, and residence were analyzed. The temporal trend was assessed by joinpoint regression, and the spatial distribution was assessed by Global and local Moran indices.

Result: Between 2011 and 2021, 11,195 deaths from SLE were recorded, representing an average mortality rate of 0.49/100,000 inhabitants, with a predominance of women (89%) and a higher incidence in individuals aged 40-49 years (19.46%). The highest rates were in the South, Southeast, and Central-West regions. The analysis demonstrated positive autocorrelation and significant clusters in the aforementioned regions.

Conclusion: Regional disparities exist, and specific strategies to expand access to early diagnosis and appropriate treatment are needed, especially in vulnerable regions.

KEYWORDS: Systemic lupus erythematosus. Mortality. Epidemiology. Spatial distribution. Brazil.

RESUMO

Introdução: LES apresenta epidemiologia global marcada por variações na prevalência que podem ser atribuídas a fatores genéticos, ambientais e socioeconômicos. Afeta predominantemente mulheres em idade fértil. Estudos demonstraram que a prevalência dele é maior em populações negras e asiáticas, enquanto populações de etnia branca apresentam taxas menores.

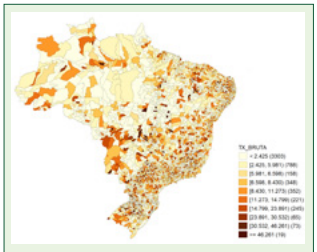
Objetivo: Analisar a mortalidade por Lúpus Eritematoso Sistêmico (LES) no Brasil entre 2011 e 2021, levando em consideração sua distribuição têmporo-espacial.

Método: Desenvolveu-se sob o escopo epidemiológico descritivo e baseado em dados extraídos do Sistema de Informação sobre Mortalidade (SIM/DATASUS). Foram analisadas variáveis como sexo, faixa etária, etnia, estado civil, escolaridade, local do óbito e residência. A tendência temporal foi avaliada por regressão joinpoint, e a distribuição espacial, por índices de Moran Global e local.

Resultados: Entre 2011 e 2021, foram registrados 11.195 óbitos por LES, dado este que representa taxa de mortalidade média de 0,49/100 mil habitantes, com a predominância de mulheres (89%) e maior incidência em indivíduos de 40-49 anos de idade (19,46%). As maiores taxas foram nas regiões Sul, Sudeste e Centro-Oeste. A análise demonstrou autocorrelação positiva e aglomerados significativos nas regiões mencionadas.

Conclusão: Existem disparidades regionais e estratégias específicas para ampliar o acesso ao diagnóstico precoce e tratamento adequado são necessárias, especialmente nas regiões vulneráveis.

PALAVRAS-CHAVE: Lúpus eritematoso sistêmico. Mortalidade. Epidemiologia. Distribuição espacial. Brasil.



Crude mortality rate from lupus in Brazil (2011-2021)

Central Message

SLE has a global epidemiology marked by variations in prevalence that can be attributed to genetic, environmental, and socioeconomic factors. It presents with a wide range of signs and symptoms. Clinically, patients may experience dermatologic manifestations such as rashes and photosensitivity, as well as arthritis or arthralgia. Systemic symptoms include fatigue, fever, and weight loss. It is a complex disease that presents diagnostic challenges due to its wide range of clinical manifestations and overlaps with other conditions.

Perspective

SLE predominantly affects women of childbearing age, with a ratio of approximately 9:1 to men. Studies have shown that its prevalence is higher in black and Asian populations, while white populations have lower rates. Differences in prevalence also reflect the influence of environmental factors and access to medical care, impacting the diagnosis and management of the disease.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a complex autoimmune disease affecting multiple body systems, characterized by clinical heterogeneity and significant potential morbidity and mortality. Recent advances include new classification criteria from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), as well as new biomarkers and definitions of remission and low disease activity. The International Classification of Diseases (ICD) for SLE is M32 (disseminated lupus erythematosus) and L93 (lupus erythematosus). These developments are guiding new therapeutic strategies and disease management.[1]

It presents a global epidemiology marked by variations in prevalence that can be attributed to genetic, environmental, and socioeconomic factors. SLE predominantly affects women of childbearing age, with a ratio of approximately 9:1 to men.[2] Studies have shown that its prevalence is higher in black and Asian populations, while white populations have lower rates. Differences in prevalence also reflect the influence of environmental factors and access to medical care, impacting the diagnosis and management of the disease.[3]

SLE is of multifactorial origin, whose etiology involves a complex combination of genetic, environmental, and hormonal factors. Genetic predisposition is evidenced by a higher incidence in individuals with a family history. Environmental factors such as exposure to ultraviolet light also play a significant role in development. In addition, because it predominantly affects women, SLE suggests a hormonal component, with estrogens potentially modulating the immune response and contributing to increased risk in women of reproductive age.[4]

It presents with a wide range of signs and symptoms. Clinically, patients may experience dermatologic manifestations such as rashes and photosensitivity, as well as arthritis or arthralgia. Systemic symptoms include fatigue, fever, and weight loss. In more severe cases, there may be renal involvement (lupus nephritis), neurological manifestations (such as seizures and psychosis), and hematological complications, such as anemia. The clinical presentation is highly variable and may overlap with other conditions, complicating the diagnosis.[5]

In addition, it is a complex disease that presents diagnostic challenges due to its wide range of clinical manifestations and overlaps with other conditions. Its classification follows the 2019 ACR/EULAR criteria that consider a combination of clinical and laboratory findings, such as skin rashes, arthritis, kidney dysfunction, the presence of specific autoantibodies, among others, to which different weights are assigned. It is necessary to present at least 10 points for classification as SLE.[1]

Treatment aims to achieve disease remission or a state of low activity, improving quality of life. Recent advances include the use of new biological therapies, such as belimumab and anifrolumab, monoclonal antibodies that have shown efficacy in clinical trials, mainly by generating a decrease in corticosteroid consumption. The management of SLE also involves the use of traditional immunomodulatory agents, such as hydroxychloroquine, which has a favorable safety profile and can reduce the risk of thrombosis and reduce disease outbreaks, and corticosteroids, which have a very rapid effect on reducing disease activity, but generate significant side effects with prolonged use, to control inflammation and prevent organ damage.[6] The new therapeutic options are expanding the personalized treatment strategies for him.[7]

Lupus nephritis is one of the most serious and common manifestations; cardiovascular manifestations, such as pericarditis, myocarditis, and increased risk of atherosclerosis, which can result in myocardial infarction or stroke; pulmonary events, involving pleuritis, lupus pneumonitis, and pulmonary hypertension; oral problems; risks during pregnancy, and neurological and psychiatric impacts, including depression, anxiety, seizures, psychosis, Peripheral neuropathy and other neurological disorders are manifestations that affect the quality of life and survival of these patients.[8]

The objective of this study was to analyze SLE mortality in Brazil between 2011 and 2021 taking into account its temporospatial distribution.

METHOD

The data used to compose the survey are available on the internet for free consultation. Thus, there is no possibility of causing physical or moral damage from the perspective of the individual and the collectivity. Therefore, the present study did not need to be approved by an ethics committee.

This is an epidemiological study of secondary data analysis in health with a focus on temporospatial analysis. Data on cases of death were obtained from the Mortality Information System (SIM) of the Department of Informatics of the Unified Health System (DATASUS) of the Ministry of Health (MS), via Tabnet, through the place of death and place of occurrence. The population data used as denominator for the purpose of calculating mortality rates come from DATASUS.

Statistical analysis

For the analysis of the SLE mortality trend in Brazil, the period from 2011 to 2021 was selected, in order to better understand the outcome in this historical series. For the population, individuals were selected according to the data available in DATASUS for adults who were registered with deaths from lupus. The following variables were considered for the analysis: sex, age group, color/race, marital status, education, deaths by residence, year of death, place of death, and place of occurrence.

For the underlying cause of these deaths, ICD

L93 AND M32 of chapter IX of the International Classification of Diseases (ICD-10) was adopted. Information on the epidemiological profile and frequency of deaths were tabulated using the Microsoft Excel for Microsoft 365 MSO software. Thus, the nominal variables were analyzed by means of the absolute frequency and percentage of occurrence in the study population. Annual mortality was calculated using the total number of deaths in the state as the numerator and the population of the state in that year as the denominator, taking 100 thousand inhabitants as a reference for this coefficient. The mortality of each municipality was calculated based on standardization by the indirect method, using the average number of cases in the period, divided by the average population between 2001 and 2021, multiplied by 100 thousand inhabitants.

Initially, the temporal trend of SLE mortality was analyzed (Figure 1). Thus, the Annual Percent Change (APC) of the studied trend was evaluated, with a 95% confidence interval (95%CI) and statistical significance $p < 0.05$. The temporal pattern analysis was performed using the Joinpoint Regression Program 5.0.2 2023 software. Next, the spatial distribution of mortality in Brazil was analyzed. Initially, the mean mortality of SLE in the municipalities of Brazil was created (Figure 1). As there is a probability of identifying a heterogeneous pattern between municipalities, the municipal values were smoothed by the local empirical Bayesian method. This method weights the value of the municipal tax in relation to the municipalities that border it by means of a spatial proximity matrix. The spatial analyses were carried out in the GeoDa 1.22.0.4 2023 program, as well as the creation of the thematic maps.

For the identification of spatial clusters, the Global Moran and Local Index was used, which measures the correlation between first-order neighbors and was used to test the hypothesis of spatial dependence. The method identifies spatial autocorrelation and can vary between -1 and +1, in which values close to zero indicate the absence of spatial dependence, considering a significant $p < 0.05$. If the hypothesis of dependence is accepted, the Local Index of Spatial Association (LISA) is used to observe the presence of spatial aggregates, given $p < 0.05$. The results of the analyses described above were demonstrated by Moran Map and LISA Map (Figures 4 and 5). The Moran Map graphically demonstrates the degree of similarity between neighbors, being represented by 4 quadrants: 1) high-high (upper right quadrant): corresponds to municipalities that have high mortality rates and are close to municipalities that also have high mortality rates; 2) low-low (lower left quadrant): corresponds to municipalities that have low mortality rates and are close to others that also have low mortality rates; 3) high-low (lower right quadrant): correspond to municipalities that have high mortality rates and are close to municipalities that have low mortality rates; 4) low-high (upper left quadrant): corresponds to municipalities that have low mortality rates and are close to municipalities that have high mortality rates.

RESULT

As shown in Table, the analysis of the profile of SLE victims in the period from 2011 to 2021 revealed a higher incidence among individuals aged between 40-49 years, representing 19.46% of all cases. This percentage is close to that observed in the 20-29 age group, which concentrated 17.74% of the cases. In addition, a significant predominance of females was found, which corresponded to 89%. Regarding the ethnic distribution, most of the affected individuals belonged to the white ethnicity, representing 43.43% of the total. Regarding marital status, 45.06% were single, indicating a relevant prevalence within this specific group.

Regarding educational level, it was observed that most deaths occurred among individuals with 8-11 years of complete schooling, corresponding to 32.21% of the cases. Secondarily, in 21.13%, the educational level was 4-7 years. It is also noteworthy that most deaths due to SLE occurred in a hospital environment, representing 87.23% of the cases.

From 2011 to 2021, 11195 deaths from SLE were recorded in Brazil. The average mortality in this period was (0.49/100 thousand inhabitants), with the lowest mortality recorded in 2013 (0.46/100 thousand inhabitants) and the highest in 2019 (0.53/100 thousand inhabitants). The analysis of the temporal pattern of mortality in the period from 2011 to 2021 showed a significant average increase of 0.74% per year in the mortality rate per 100 thousand inhabitants ($p < 0.05$, Figure 1). Pearson›s correlation coefficient was 0.7955125531 with $p =/< 0.05$, indicating that there is a significant linear correlation and, directly proportional over the years, there was a significant increase in the mortality rate.

Through the spatial analysis, which can be seen in Figure 2, there is dispersion of mortality, with a focus of incidence in the South, Southeast and Midwest regions. Jacutinga (83/100 thousand inhabitants), Herdeiras (66.2/100 thousand inhabitants), Tupanci do Sul (65.9/100 thousand inhabitants) and Coqueiro Baixo (65.7/100 thousand inhabitants) were the 4 municipalities that had the highest number of SLE mortality in Brazil between 2011 and 2021, all of these municipalities located in Rio Grande do Sul.

With the smoothing of the crude rates by the local empirical Bayesian method (Figure 3), it is possible to observe a more apparent spatial pattern, with aggregation of municipalities with higher mortality rates in the South, Southeast and Midwest regions. Spatial autocorrelation was identified using the Global Moran›s Index ($I = 0.482$; $p = 0.01$), demonstrating evidence of positive autocorrelation.

The application of the local Moran›s Index allowed the identification of spatial clusters with both high and low values (Figure 4). The pattern of high values (high-high) was predominant in the north, central-west, and

south, as well as small clusters in the southeast and northeast. The low-low pattern was identified in the north, northeast, and south regions. Figure 4 illustrates the degree of statistical significance of the clusters, as indicated by the LISA Map.

TABLE — Epidemiological profile of individuals who died from SLE in Brazil between 2011-2021

Education (years)	n	%
No	431	3.85%
1 to 3	1594	14.24%
4 to 7	2365	21.13%
8 to 11	3606	32.21%
12 or more	1233	11.01%
Silenced	1996	17.56%
Marital status	**n**	**%**
Single	5044	45.06
Married	3386	30.25
Widowed	731	6.53
Separate	733	6.55
Other	502	4.48
Silenced	799	7.14
Place of occurrence	**n**	**%**
Hospital	9.765	87.23
Other		
Health center	489	4.37%
Domicile	832	7.43%
Public road	24	0.21%
Other	79	0.71%
Ignored	6	0.05%
Age group (years)	**n**	**%**
(-) 1	4	0.04%
1 to 4	11	0.10%
5 to 9	44	0.39%
10 to 14	268	2.39%
15 to 19	698	6.23%
20 to 29	1986	17.74%
30 to 39	224	2.00%
40 to 49	2179	19.46%
50 to 59	1709	15.27%
60 to 69	1197	10.69%
70 to 79	588	5.25%
(+) 80	271	2.42%
Sex	n	%
Male	1265	11%
Female	9930	89%
Color/Race	**n**	**%**
White	4862	43.43%
Black	1142	10.20%
Yellow	56	0.50%
Brown	4657	41.60%
indigenous	39	0.35%
Silenced	439	3.92%

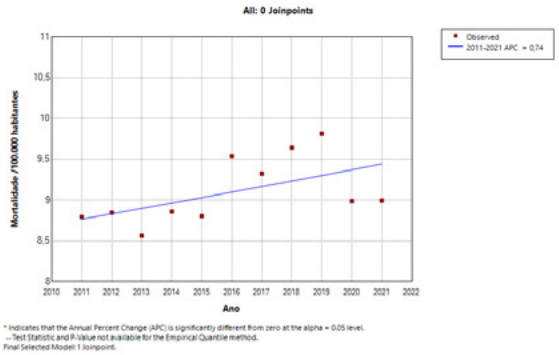

FIGURE 1 — Time pattern of SLE mortality in Brazil between 2011 and 2021.

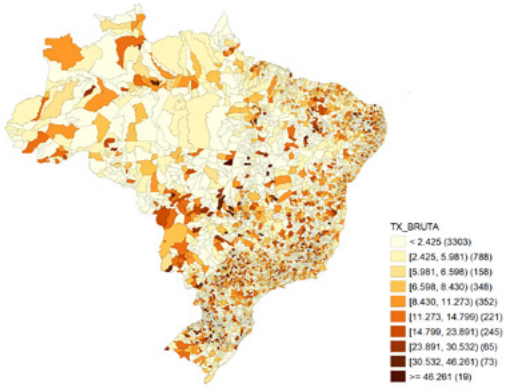

FIGURE 2 — Crude mortality rate from lupus in Brazil (2011-2021)

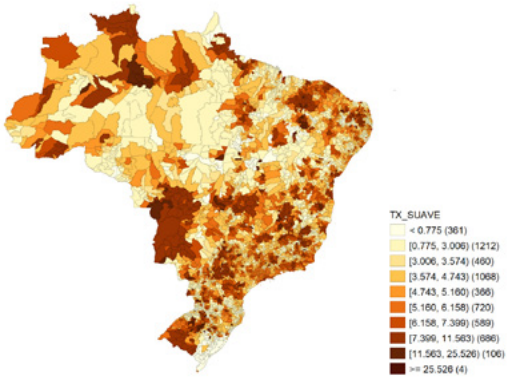

FIGURE 3 — Mortality rate smoothed by the local empirical Bayesian method for lupus in Brazil (2011-2021).

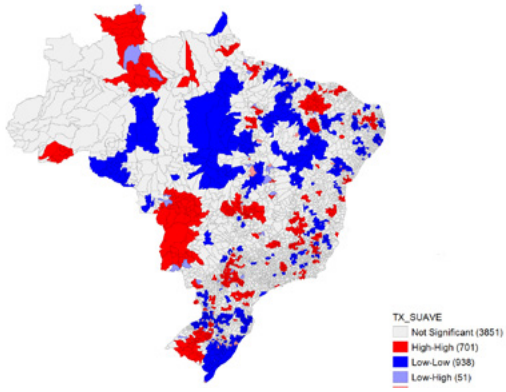

FIGURE 4 — Spatial clusters of lupus mortality in Brazil (2011 to 2021)

DISCUSSION

The temporal and spatial analysis of SLE mortality in Brazil between 2011 and 2021 reveals a complex mosaic of determinants and public health challenges. Its incidence reflects a higher prevalence in the South, Southeast, and Midwest regions of the country, where cities such as Jacutinga, Herdeiras, Tupanci do Sul, and Coqueiro Baixo are the most affected by mortality. Such a spatial pattern is indicative of variations in living conditions, health habits, and access to medical services. Regional studies in Brazil have already shown how health disparities can be rooted in socioeconomic differences, shaping the risk of autoimmune diseases and the responsiveness of the health system. The Southeast region, on the other hand, stands out as the most affected by the disease due to greater access to health and because of its higher population density, which is reflected in a higher prevalence of diagnoses.[9] In other regions such as the South and Midwest there are no conclusive studies on why they have the highest mortality.

Total mortality from SLE requires careful analysis, given the relevance of autoimmune diseases in Brazil. Comparing SLE mortality rates with other diseases is critical to prioritizing health interventions and policies. SLE often presents with serious complications such as lupus nephritis, thromboembolic events, cardiovascular involvement, and infective endocarditis, reflecting the significant impact of autoimmune diseases as a growing public health challenge.[10]

This reality does not occur in a vacuum, but rather in a context where social and economic factors play crucial roles. Autoimmune diseases, such as SLE, are often associated with inequalities in access to early diagnosis and appropriate management. The interaction between genetic, environmental, and social factors can influence both the manifestation and progression of these conditions. Individuals in situations of socioeconomic vulnerability are more likely to have delays in diagnosis and greater exposure to triggering factors, such as infections and chronic stress, aggravating clinical outcomes and disease burden. Regarding access to health services, there is a greater concentration of resources and better results in the diagnosis and management of SLE in the more developed regions of the country. This fact raises questions about equity in access to specialized care and high-complexity treatments throughout Brazil, especially in less financially favored regions.[11]

The demographic characteristics of those affected by SLE point to a predominance of women (89%) aged between 40 and 49 years (19.46%); this is due to hormonal issues, which are much more present in women, thus favoring the emergence of autoimmune disease.[12] In contrast to what was stated by Luquetti et al.[3] regarding the prevalent ethnicity in the cases (blacks and Asians), the analysis of the DATASUS platform revealed a higher prevalence in the white population (43.43%). However, Brazil is a country characterized by a high rate of racial miscegenation, in which the phenotype does not always correspond to the genetic load, justifying the need for local studies that reflect this Brazilian peculiarity.

The mortality and morbidity associated with SLE in Brazil are of concern. The lack of specialized centers, late diagnosis, and difficulty in managing the complications of the disease may be contributing to these statistics. This reinforces the need to strengthen local health systems, ensuring access to rheumatologists and specialized treatments for the population.[13] The management of SLE, which ranges from immunomodulatory and immunosuppressive therapies in general to specific treatment of certain forms of manifestation, such as lupus nephritis or cardiovascular complications, can be a costly and complex process. Education about the disease and its treatment are essential to control its progression and avoid serious complications. However, adherence to treatment can be hampered by factors such as the high cost of medications, lack of access to diagnostic tests, and difficulty in finding specialists.[14]

Finally, the intersection between these factors demonstrates the intricate network of influences that shapes the clinical outcomes of SLE in Brazil. The unequal distribution of morbidity and mortality associated with it in the country reflects the disparity in the distribution of health resources and variations in demographic and genetic profiles. Intervention programs should therefore be multifaceted, ranging from training professionals for early diagnosis to expanding access to specialized treatments and raising awareness of the disease among the population. The central question is not limited to understanding the causes of the high burden of SLE, but also how to intervene. The creation of more robust health care systems, education campaigns aimed at early recognition of symptoms and healthy lifestyles, and policies that reduce economic barriers to treatment may be the key to improving the quality of life and clinical outcomes of patients with SLE in Brazil.[15]

The secondary data used in this research are a limiting factor, which can generate biases, such as underreporting, lack of information, and inconsistencies in filling in the causes of death. The results found for the general population may not be reflected at the individual level, due to the effects of data aggregation, characteristic of the ecological fallacy. It is noteworthy that the mortality analysis was based only on the underlying cause of death and not on multiple causes. Thus, there may be an underestimation of deaths from SLE.

CONCLUSION

The temporospatial analysis allowed the identification of the municipalities in the state with high mortality from SLE. In this way, the need for strategies that are in line with the reality and particularities of these places is exposed. This research serves as a scientific subsidy for the organization and planning

of actions aimed at improving health care in the most vulnerable places, especially Primary Health Care (PHC), aiming to ensure access and care for this population and consequently promote health and prevent SLE diseases.

Authors' contributions

Thelma Larocca Skare – Conceptualization, writing, project management
Vitor Hugo Mariano - Formal analysis, methodology
Davi Canteri Mendelski – Software
Fernanda Ritt de Souza – Validation, conceptualization
Isadora Candotti Sperotto – Validation, methodology
Leonardo Moreira Dias – Research, validation
Pedro Canteri Mendelski – Methodology
Tailla Cristina de Oliveira – Research, writing

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