Title Page

Title: Clustering of systemic lupus erythematosus mortality in southwestern Spain

Running Head: Clustering of systemic lupus mortality in Spain

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Statements

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ABSTRACT

Objective: To analyse time trends in ~~S~~systemic ~~L~~lupus ~~E~~erythematosus (SLE) mortality and explore possible provincial clustering of SLE mortality in Spain (2001-2020).

Methods: We conducted an ecological study using deaths registered in SLE at the Spanish National Institute of Statistics between 2001 and 2020. Jointpoint regression models have been used to evaluate temporal trends. To analyse the spatial pattern of SLE mortality in men and women in Spain, crude rates, age standardised mortality rates (ASMRs), smooth relative risk (RR), and posterior probabilities (PP) for RR greater than 1 for the period 2001-2020 were calculated. The Global Moran I index was used to assess the existence of global spatial autocorrelation. Local indicators of spatial association (LISA) and Kulldorff's spatial scan statistic were used to identify clusters.

Results: During the 20 years analysed of the study, the SLE average ASMR for the period was 2.7 for women and 0.7 for men, with a sex ratio (female/male) of 3.8. In men, no province showed a RR>1. Conversely, in women, eight provinces showed values of RR> 1 with a PP greater than 0.8 (Seville, Cadiz, Huelva, and Murcia in the south, Barcelona, Zaragoza, Huesca, and Leon in the north). In men, neither of the two methods detected a clustering of provinces. However, in women, both methods identified a cluster of provinces located in the southwest of the country (Huelva, Cádiz, Seville and Malaga) as a cluster with significant excess mortality. In the second cluster (centered on the province of Huelva) obtained with the Kulldorff method, two more provinces were added (Badajoz and Cordoba, also located in the southwest).

Conclusions: We detected a cluster of provinces with an excess risk of female SLE mortality in the southwest of Spain.

KEY WORDS

Systemic lupus erythematosus, autoimmune disease, rheumatic disease, Spain

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that predominantly affects women, presenting diverse range of clinical manifestations and complex pathogenesis that can lead to severe organ damage and eventual death, making it difficult to manage and diagnose[1,2].

A recent study estimated at 400,000 (60,000 men and 340,000 women) new diagnoses worldwide annually, and an overall global incidence of 5.14 per 100,000 cases-years (1.53 in men and 8.82 in women). In terms of prevalence, the estimated affected population was 3.41 million people (43.7 cases per 100,000 people). Of these cases, 3.04 million were estimated in women and 360,000 cases in men[3]. The incidence and prevalence of SLE are increasing, presumably due to an accurate diagnosis and an increased survival since diagnosis[4].

The incidence, prevalence, survival and mortality of SLE has been found to vary not only between countries but also within them[5–7]. Similar disparities were also observed in population groups of the same ethnicity living in different parts of the world, suggesting not only a genetic predisposition, but also the influence of geographical and environmental factors[8]. Despite the heterogeneous nature of SLE, the broad spectrum of presentation, and the severity of disease, these outcomes may be related to differences in ethnicity, economic status, educational level, well-being status, level of social support, geographical location, and treatment adherence[9].

Previous epidemiological studies with standardised methodologies have examined the SLE mortality rates in Spain over large periods of time[10,11]. These studies showed that overall age-standardised mortality rates (ASMRs) due to SLE increased from 1980 to 1999 and remained stable until 2018.

To our knowledge, one study assessed the Spanish mortality at provincial level, but it was only with the 89 deceases registered on 2005[12]. Therefore, in addition to the update on mortality trends data, an analysis of spatial patterns of death in Spain over a large

period is still needed. In this study, we aimed to analyse time trends in SLE mortality and to explore possible provincial clustering of SLE mortality in Spain (2001-2020).

Methods

Data Sources

The deaths of SLE and the populations needed for the analyses were obtained from the Spanish National Institute of Statistics (INE)[13]. All deaths coded as M32 according to the 10th International Classification of Diseases (ICD-10) were analysed.

Statistical analysis

To examine time trends by sex during the period 2001-2020, ASMRs were obtained using the direct method and the European standard population[14]. Reported rates per 100,000 inhabitants were assessed using a joinpoint regression with a maximum of three possible trend changes. For this purpose, a segmented Poisson model was applied using the Joinpoint Regression software[15].

The neighbourhood structure, necessary for our estimates was developed using the "queen criterion", which identifies neighbours by defining them as spatial units that share a common edge or vertex. This analysis and the maps were performed using GeoDa software[16].

We assessed overdispersion with the Chi-square test and Potthoff-Whittinghill test, using the “DCluster” R package. Additionally, to test the global spatial clustering, the Tango's test of global clustering from the “DCluster” was conducted, and the Global Moran’s index from GeoDa software. For the local analysis of possible clusters, we applied Moran's local index (using GeoDa software), so-called local index of spatial autocorrelation (LISA). Provinces were assigned to four classes according to the value of autocorrelation: high-high (provinces with a high rate constrained by other provinces with a high rate), low-low (provinces with a low rate constrained by other provinces with a low rate), low-high (provinces with a low rate constrained by provinces with a high rate), and high-low (the opposite of low-high). The p-value of both tests was calculated using the Monte Carlo permutation test (999 permutations).

To detect spatial clustering with “DCluster”, we used the likelihood ratio test formulated by Kulldorff and Nagarwalla, which performs a circular scanning window[17]. To define the

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window, we used a 15% of the total population. Furthermore, only clusters with P<0.05 were considered.

To explore provincial spatial patterns of SLE mortality in men and women, the standardized mortality ratio (SMR), the smoothed relative risk (RR), and posterior probabilities (PP) of RR greater than 1 were calculated for the period 2001-2020. Mortality and population count in Spain provided the basis for age and sex-specific SLE mortality rates. Indirect standardization was used to adjust these rates to the population structure of each province and an expected count of SLE deaths at the provincial level was calculated. The observed and expected counts for each province were compared by calculating the SMR. Since SMRs are highly variable when analysing causes of death with few cases or areas with small populations, it is necessary to use statistical models that allow risk smoothing by taking into account information from spatial neighbours.

The provincial estimators of the risk (RR) for SLE mortality and the distribution of PP when RR > 1 were calculated using the model of Besag, York & Mollié[18]. This model is based on fitting a spatial Poisson model with observed cases as the dependent variable, log-expected cases as the offset, and two types of random effect terms that take into account the following (I) contiguity (spatial autocorrelation term); and (II) nonspatial heterogeneity. For adjustment purposes, spatial dependence has been assumed, which means that risk estimates in a given province depended on neighbouring provinces. As there are no border areas, the island provinces and the cities of Ceuta and Melilla were omitted. Model fitting and inference were performed using the approximate Bayesian inference technique called INLA (Integrated Nested Laplace Approximation) implemented in free software R through the R package R-INLA[19,20].

We considered the value 0.05, 0.20, 0.80 and 0.95 of PP with RR > 1, as thresholds. When PP was greater than 0.8 a province was at risk. Excess mortality was considered significant when the probability was greater than 0.95. Probabilities between 0.2 and 0.8 show little evidence of a RR greater than 1, so the specific mortality rate for these provinces is similar to the baseline mortality rate. Provinces with values below 0.20 are

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considered low-risk provinces, and those with probabilities below 0.05 are considered provinces with a mortality risk significantly lower than the Spanish national rate.

Results

A total of 1557 deaths were recorded in Spain due to SLE, being 279 males and 1278 females.

Figure 1 shows the temporal patterns of risk and joinpoint analyses of SLE mortality in Spain between 2001-2020 by sex. Both results showed a stable trend over 20 years of the study. Additionally, the jointpoint analysis reported that the pairwise analysis failed to reject parallelism in the trends between men and women (average percentage of change 2001-2020: -0.1% not significant in both sexes). The average ASMR for the period was 2.7 for women and 0.7 for men with a sex ratio (female/male) of 3.8.

Figure 2 shows the age and sex specific rates at the national level that were used to estimate the expected cases at the provincial level. In all age groups, women achieved higher rates than men, and the average sex ratio was 4.8. In both cases, the rates increased as age went by.

Figure 3 shows the Standardised Mortality Ratios (SMRs) by sex in the peninsular provinces of Spain (2001-2020). For men, ratios ranged from 0 (no cases are observed in five provinces) to 2.9 with a mean of 1.1, for women, ranging from 0.5 to 1.9 with a mean of 1.0.

Figure 4 shows the RR and PP of RR>1 for males and females. In men, no province showed a RR>1 with a PP higher than 0.8. In women, 8 provinces showed RR>1 values with a PP >0.8 (Seville, Cadiz, Huelva and Murcia in southern Spain, Barcelona, Zaragoza, Huesca and Leon in the north).

Figure 5 shows the results of the cluster analysis (Local Moran Statistic and Kulldorff method). Both methods provided similar results. Only provincial clusters that were significant (P≤0.05) were presented and ordered according to the Kulldorff statistic, being the highest one the first cluster The spatial units corresponding to the centre of the clusters are shaded in a darker grey than the rest.

For men, both methods did not detect a clustering of provinces. However, in women, both methods identified a cluster of provinces located in the southwest of the country

(Huelva, Cadiz, Seville and Malaga) as a cluster with a significant excess mortality. In the second cluster, focused on the province of Huelva, obtained with the Kulldorff method, two more provinces are added (Badajoz and Córdoba, also located in the southwest).

Discussion

Our results showed that the risk of dying from SLE remains stable during the studied period for both sexes, which is consistent with previous studies in our country[9,10].

Worldwide, the ASMR of SLE increased slightly between 2003 and 2014 (+0.6% per year, $p<0.05$), mainly due to an increase in the ASMR in Asia and Latin America. ASMR decreased significantly in Europe, North America, and Oceania. In 2014, the ASMR of SLE in Europe (1.1 deaths/million) was markedly lower than in Latin America (5.5), North America (2.7), Asia (2.2) and Oceania (1.3)[21]. In contrast to the mentioned countries, the Spanish mortality rates for SLE were slightly lower than the European average of 2014. Furthermore, in Spain the SLE mortality have not decreased despite the improvement in diagnose and therapeutic options. The reasons under this stabilization are unknown and need further study.

In line with previous research, our data revealed a marked difference between men and women[22]. We identified two spatial patterns differentiated by sex. In male, no clusters were detected, while in female a higher risk of SLE mortality was recorded in southwest of the country.

The incidence of SLE increases with decreasing latitude. Possible explanations are genetic variations and the gradient of ultraviolet radiation gradient at different latitudes[23,24]. SLE mortality in the United States "clusters" into geographic areas with significantly high and low rates[9]. Women in the Southwest states faced a more than twofold higher risk of mortality from SLE than women in the Northeast states. The underlying reasons for this difference in mortality by region are believed to be multifactorial, showing that higher mortality is observed in areas of high poverty and / or a higher concentration of Hispanic residents, as well as due to evidence of regional differences in access to and quality of care[25]. Similar data from British Columbia showed that variability in the incidence of lupus nephritis was partly associated with the place of residence of cases[26]. In Greece, a relatively low frequency of SLE has been described in the northwest of the country[27].

In China, an increased risk of SLE has also been detected in the south-west and southern areas. In these populations, a much higher frequency of the DR-specific HLA-DR2 locus has been found than in other Chinese populations[28].

There is evidence of the division of Spain into two very different halves: the provinces from Madrid to the north have low rates of poverty and/or social exclusion - between 1.5 and 13.1 percentage points below the national average and are perfectly compatible with European average rates and those of some of the most advanced European countries. In contrast to the former, those located in the south maintain extraordinarily high rates (between 2.8 and 10.9 percentage points above the national average). Moreover, within each half, a certain increasing gradation can be noted in an east-west direction, with those communities located in the so-called Mediterranean Development Axis registering lower poverty rates than those located further west. Furthermore, this north-south inequality increased markedly during the years of the Spanish economic crisis of the 1980s, and the subsequent macroeconomic recovery was not sufficient to compensate for the increase in poverty rates[29]. Our results are consistent with this pattern of poverty showing a clustering of provinces in southern Spain, suggesting that the observed excess mortality observed may be determined by socioeconomic factors related to geographic location in genetically predisposed individuals. Also relevant is the significant increase in solar irradiation observed toward the south of the Sierra Morena and the Betic System, with the highest peninsular values recorded in the coastal areas of the Gulf of Cadiz, the Guadalquivir valley, and the eastern provinces of Andalusia[30] which coincides with the cluster of provinces with excess mortality.

Ethnic differences are essential in SLE, leading to disparities on incidence and prevalence, and affecting to survival and mortality because of variabilities in disease severity and clinical manifestations. The mentioned differences could be related to genetic factors that regulate the adaptative immune response depending on the ethnicity[31]. A sub-analysis of the RELESSER project showed that SLE in mestizo-Latin American patients living in Spain has clinical differences compared to SLE in the Spanish

Caucasian European population, including greater severity, activity, and mortality, with more severe renal involvement[32]. In Spain, from 1998 to 2011, there was significant immigration of Latin Americans, and many of them settled in the south (in the provinces detected as a cluster of SLE) and the Mediterranean coastal area[33].

In addition, the Romani population (the second most frequent ethnic group in Spain) has differences in the distribution of HLA alleles in relation to the white Caucasian Mediterranean population[34] (the main ethnic group) and in the clinical presentation of SLE (presents onset at earlier ages and higher frequency of thrombosis and ~~A~~antiphospholipid ~~S~~syndrome)[35,36]. Approximately 15% of the Spanish Romani population resides in the four Andalusian provinces that make up the SLE mortality cluster[37].

This study has several limitations to bear in mind. First, the validity of our results depends on the precision of the cause of death reported on death certificates by physicians, which is difficult to determine. The under-reporting of SLE in death certificates has been reported[38–40]. The ecological design of our research has some major limitations that must be considered when interpreting our results. On the one hand, the statistical techniques used allowed us to describe spatial patterns and clusters of SLE mortality, but did not explain the observed differences. As the data are aggregated, the level of exposure to risk factors for a deceased person is unknown. Furthermore, the lack of specific data of where and how long a person lived before dying, make impossible to establish association between excess mortality and environmental, social or individual factors. Thus, associations were not performed to avoid the ecological fallacy[41].

Given these limitations, one of the main strengths of this study is the use of Bayesian spatial models to obtain province-level estimates of SLE mortality over the two decades of our study. By borrowing statistical power across space (neighboring provinces), Bayesian models can produce accurate estimates of rates, even in provinces with sparse populations or small numbers of cases. In addition, Geographic Information Systems tools allow the systematic use of complex statistical processes that integrate spatial and

health data and provide cartographic results that allow a better and faster understanding of inequalities in terms of health indicators, both for specialised professionals and for the population in general. In fact, they are used for descriptive purposes; to generate etiological hypotheses; in public health surveillance to detect areas of higher risk; and as an aid in defining health policy and resource allocation[42]. They are also useful for identifying clusters[12].

Finally, we observed that in men there are no provinces with significant excess risk and none of the methods used detect spatial clustering. However, in women, eight provinces (having excess mortality whose PP is greater than or equal to 0.8) are identified that would require further study to try to identify the determinants of their elevated risk of SLE mortality. Four of these (Seville, Cádiz, Málaga, and Huelva) form part of the cluster identified in southwestern Spain.

One of the major conclusions of our results is the need to achieve sound associations between genetic, environmental and other factors and SLE mortality, so further research is required in this line.

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Figure legends

Figure 1: Temporal pattern of risk analysis and joinpoint. Systemic ~~L~~lupus ~~E~~erythematous mortality in Spain, 2001-2020 by sex.

Figure 2: Age and sex-specific mortality rates per 1000000 inhabitants-year. Systemic ~~L~~lupus ~~E~~erythematous Mortality in Spain, 2001-2020.

Figure 3: Standardised Mortality Ratios (SMR) by sex. Mortality of systemic ~~L~~lupus ~~E~~erythematosus in the Peninsular Provinces of Spain, 2001-2020.

Figure 4: Relative risk (RR) and posterior probability (PP) of RR are higher than 1 in men and women. Mortality of systemic ~~L~~lupus erythematosus in the peninsular provinces of Spain, 2001-2020.

Figure 5: LISA cluster maps and Kulldorff method maps by sex. Mortality of systemic ~~L~~lupus erythematosus in the peninsular provinces of Spain, 2001-2020.