European Journal of Internal Medicine 112 (2023) 45–51

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Mortality and causes of death in systemic lupus erythematosus over the last decade: Data from a large population-based study

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ARTICLE INFO

Keywords:
Systemic lupus erythematosus
Mortality
Survival
Standardized mortality ratio, Causes of death
Cardiovascular diseases, Infections
Cancer

ABSTRACT

Objective: To assess mortality rates (MRs), standardized mortality ratios, and causes of death in systemic lupus erythematosus (SLE) in a population-based study.
Methods: We analyzed linked administrative health databases of the Veneto Region (Italy, 4,900,000 residents). SLE was defined by any hospital diagnosis or healthcare copayment exemption for SLE. We analyzed mortality from January 1st, 2012, until December 31st, 2021. MRs per 1000 were stratified by year, sex, and age group. Standardized mortality ratios were derived by comparing MRs of the general regional population. Causes of death were coded using the ICD-10 coding system and they were grouped in: SLE, infectious diseases, cardiovascular diseases (CVD), cancer, or others.
Results: Among 4283 SLE prevalent cases, 603 deaths occurred, corresponding to an average annual standardized MR of 18.6 per 1000 person/year (95% CI 17.0-20.2). Out of 1092 incident SLE patients, 90 died with a peak in the first year after diagnosis (MR 26.5 per 10,000 person/month). Standardized mortality ratio was 2.65 (95% CI 2.13-3.26) overall, and highest among younger patients (<45 years: 5.59, 95% CI 2.05-12.4). Five- and 8-year survival were 91% and 89%, respectively. About half of the deaths had CVD or cancer as underlying cause, whereas infections were less frequently reported.
Conclusions: Although the medium-term survival since diagnosis is good, SLE mortality is still higher than that of the general population, especially in youngest patients. Nowadays, CVD seems to be the major cause of deaths in SLE, whereas infections account for a low proportion of deaths, at least in Western countries.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex, severe autoimmune disease which can potentially lead to life-threatening manifestations and therapy-associated complications. Common causes of death in SLE patients include severe refractory manifestations, infections, cardiovascular diseases (CVD), and malignancies [1]. A meta-analysis of studies published between 1950 and 2016 on SLE mortality worldwide showed an increasing survival in both high-income and low-/-middle-income countries until the mid-1990s, which was followed by a stable plateau [2]. In this meta-analysis, infections were the first cause of death in both high-income (15.1%) and low-/middle-income countries (37.5%), and the 10-year survival estimates in adult SLE patients were 89% and 85% in high- and low-/middle income countries, respectively [2]. More recently, CVD has been reported as the most common cause of death among SLE patients in Western countries, accounting for 27–52% of deaths [3–8], whereas infections were responsible for 15–43% [3–6] and malignancies for 13–33% of fatalities [3–6,9].

Ethnicity, socioeconomic and educational factors, barriers in the access to healthcare with delayed diagnosis, are all risk factors affecting mortality and disease outcomes in SLE patients [4,10].

Updated information on SLE mortality across Europe are scanty, with five studies from the UK [5–7,11,12], two from northern Europe [8,13], two from central Europe [14,15], and no studies from southern Europe. However, mortality rates were consistent among these studies, ranging between 13.8 and 16 deaths per 1000 patient-years [6,11]. Standardized

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https://doi.org/10.1016/j.ejim.2023.02.004
Received 5 January 2023; Received in revised form 2 February 2023; Accepted 4 February 2023
Available online 9 February 2023

mortality ratios (SMR) were also similar in these cohorts, ranging from 1.7 to 3.1 [3,7,8,11–14], thus showing an excess in mortality among SLE patients compared to the general population. In extra-European countries, similar SMRs were reported in the US and Canada [9,16,17], whereas studies from Asia reported higher SMRs, ranging from 2.1 to 11.1 [18–22], likely due to the higher prevalence and severity of lupus nephritis in Asian SLE patients. No updated information regarding SLE mortality from South America, Australasia, and Africa are available according to a recent systematic review [23].

Our aim was to assess mortality according to age and sex, and causes of death in SLE between 2012 and 2020 in the Veneto Region, northeastern Italy. Interestingly, the approval of belimumab for the treatment of SLE in Italy dates back to 2013, thus our survival analyses cover the period corresponding to the first 8 years of availability of this biological drug.

2. Patients and methods

2.1. Study design and data sources

This is a retrospective population-based study carried out in Veneto Region, located in northeastern Italy. The Veneto population counts about 4.9 million residents, includes 8% of the entire Italian population, and is composed by Caucasians (95%), Africans (2.1%), Asians (2%), and other minorities (<1%) [data derived by the Veneto population registry, 2020].

The population registry of all residents in the region from January 2012 has been linked with the database of healthcare copayments exemptions, hospital discharge records, and the regional mortality register, as previously described [24]. The population registry contains socio-demographic data on all residents in the region, as well as the date of death for those who died, regardless of where the death occurred. Co-payment exemptions are assigned after a specialist diagnosis. Hospital discharge records contain data on each single inpatient episode, comprising clinical and hospital information (hospitalization ward, admission and discharge date, primary and secondary diagnoses). Diagnoses and procedures are currently coded according to the International Classification of Diseases Ninth Revision, Clinical Modification (ICD-9-CM). The regional mortality record includes data on all deaths of the residents in the region, regardless of the place of death. Causes of death are coded using the ICD-10 coding system and are available up to December 31st, 2020.

Sex of participants was defined based on biographical data as assigned at birth. The study was conducted on previously anonymized records routinely collected during delivery of healthcare services, without any possibility of retrieving the identity of patients. All data in the Local Health Authority registries are recorded with the patient's consent and can be used as aggregate data for scientific studies without further authorization (Garante per la protezione dei dati personali, Resolution n.85 of 1 March 2012). This study complies with the Declaration of Helsinki and the Italian Decree n.196/2003 on personal data protection.

2.2. SLE prevalent cohort

As previously described in detail [24], all residents in the region with a healthcare copayment exemption for SLE (code 028) or a hospitalization with a primary or secondary diagnosis of SLE (ICD-9-CM 710.0) were defined as affected with SLE. Only residents in the Veneto Region between January 1st, 2012, and December 31st, 2020 were included in the cohort. This time interval was chosen based on the availability of data required for SLE case identification in the regional population registry [23].

2.3. SLE incident cohort

The cohort of SLE incident cases was composed of all cases with disease onset between January 1st, 2013, and December 31st, 2020, defined as the first date between hospitalization or the date in which the healthcare copayment exemption was activated. Since the healthcare copayment exemption database was established in 2012, SLE cases identified within the first study year (2012) were excluded to minimize the risk of prevalent cases being identified as incident cases.

2.4. Mortality analysis

Vital status was available up to December 31st, 2021, while cause of death was available up to December 31st, 2020. From the mortality register, all diseases mentioned in the death certificate (multiple causes of death) as well as the underlying cause of death (the single cause analyzed in standard mortality statistics, selected from all conditions reported in the certificate according to rules set by the WHO) were analyzed. Causes of death (both the underlying and multiple cause of death) were grouped in: SLE (ICD-10 codes: M32.0-M32.9, M35.9), kidney diseases (ICD-10 codes: N00-N06, N17-N19), infectious diseases (ICD-10 codes: A00-B99, G00.0-G00.9, J10-J22, J44.0, J69.0, J85-J86, N10-N12, N13.6, N15.0-N15.9, N39.0, R57.2, R65.1, U07.1, U07.2), cardiovascular diseases (ICD-10 code I00-I99), cancer (ICD-10 codes: C00.0-D48.9), or other conditions.

Between 2012 and 2020 (the years in which the prevalent SLE cohort was defined), mortality rates by sex, age group, and overall were estimated as the number of deaths that occurred during the year among prevalent SLE cases on January 1st of that year. Both the underlying and multiple causes of death were reported for these deaths (available only up to December 31st, 2020).

Among the incident SLE cohort, yearly mortality rates were estimated for the first 5 years since diagnosis. Survival analysis by sex and age group for incident cases was extended up to 8 years since diagnosis. The underlying cause of death was reported separately for those who died in the first year since SLE diagnosis and for those who died later on during follow-up (available only up to December 31st, 2020).

3. Statistical analysis

Univariate and bivariate analyses were performed to summarize data according to the patient demographic characteristics. Continuous variables were reported with descriptive statistics (mean, standard deviation, median and interquartile range). For categorical variables, frequencies and percentages were calculated. The difference between groups were examined by Student's t-test or Mann–Whitney test, Pearson's Chi-square or Fisher's exact test, as appropriate. A p value <0.05 was considered statistically significant.

Mortality rates were stratified by year, sex and age group. Direct standardization by age and sex was performed using the SLE cohort in 2017, as reference.

Kaplan-Meier survival analyses were restricted to incident cases that were followed up to 8 years. Follow-up started at the date of diagnosis until death, migration or end of follow-up (December 31st, 2021), whichever came first. Comparison of survival between males and females and among different age groups was performed through the log-rank test.

Standardized Mortality Ratios (SMR) were computed as the ratio between deaths observed in the incident SLE cohort and those expected based on sex and age-specific mortality rates registered in the general Veneto population during the study period.

All analyses were conducted using Statistical Analysis Software (SAS) software version 9.4 (SAS Institute Inc., Cary, NC, USA).

4. Results

During the study period, we identified 4283 prevalent SLE cases of which 3636 were females (85%). Of these, 1092 were incident cases, with a median age at diagnosis of 45 years (IQR: 34-59), and a median follow-up of 5 years (IQR: 3-7). The process for the selection of the cohort is reported in Supplementary Fig. 1.

4.1. Mortality - prevalent SLE cases

Among prevalent cases, we observed 603 deaths between January 1st, 2012 and December 31st, 2021. Causes of death were available only for 544 deaths (90.2%) that occurred before December 31st, 2020. Mortality rates and distribution of age at death are reported in Table 1 and Supplementary Fig. 2.

Mean age at death was 74.2 years (SD: ±13.2) without significant differences between males and females.

Mortality rates were significantly higher among patients aged 60 and over, while they were much lower below 30 years, as reported in Fig. 1. Above 30 years, mortality rates among males were slightly higher than those observed in female counterpart, as reported in Fig. 1 and Supplementary Table 1.

The most frequent underlying causes of death were CVD (148 deaths, 27.6%) and neoplasms (131 deaths, 24.4%) (Table 2).

SLE was the underlying cause of death in 10.8% of death certificates (58 cases) but was mentioned in 27.1% of certificates (145 cases). Infectious diseases and kidney diseases were reported in one out three and one out five deaths, respectively, although these conditions were more rarely selected as the underlying cause of death. During 2020, 6 deaths related to COVID-19 were recorded. Causes of death reported as "other conditions" not related to SLE are detailed in Supplementary Table 2.

4.2. Mortality - incident SLE cases

Between 2013 and 2020, 1092 incident cases of SLE were recorded. Among these patients, we observed 90 deaths: 64 (71.1%) were females, mean age at death was 72.2 years (SD ±13.4) and mean follow-up since diagnosis was 1.83 years (SD ±2). Mortality rates peaked in the first year after the diagnosis and were stable through the subsequent follow-up (Fig. 2).

Among the 90 incident SLE cases who died, the cause of death was missing in 13 cases (related to deaths that occurred after December 31st, 2020). The distribution of the main causes of death was overall similar to that observed among prevalent cases, except for a higher proportion of SLE as the underlying cause, which accounted for 18.2% of all deaths among incident cases. Notably, SLE was recognized as the underlying cause of death in 21.7% of deaths that occurred within the first year after diagnosis (Table 3).

Unfortunately, SLE manifestations responsible for death in these cases were not available. The causes of death referred to as "Other conditions" are detailed in Supplementary Table 3.

Survival at 1 year since diagnosis was 96%, it decreased to 91% at 5 years, and was 89% at 8 years. Survival by sex and age classes are reported in Fig. 3. Notably, survival was higher in females compared to males throughout the entire follow-up. The majority of deaths were observed in patients older than 75 years, while few occurred in patients aged 59 years or less.

4.3. SLE standardized mortality ratio (SMR)

Compared to age- and sex-matched reference subjects, SLE incident cases had a significantly increased mortality (Fig. 4). Overall SMR was 2.65 (95% CI 2.13, 3.26), and was inversely associated with age, with the highest SMR of 5.59 (95% CI 2.05, 12.38) in the youngest age group (0–44 years), that decreased progressively up to 2.14 (95% CI 1.59, 2.83) in the oldest age group (≥75 years).

Excess mortality compared to the regional population was slightly larger in male patients aged 45–59 years (SMR 5.32, 95% CI 1.95, 11.80) than in female patients in the same age group (SMR 3.18, 95% CI 1.27, 6.54), whereas SMRs were similar between sexes in older patients (Fig. 4 and Supplementary Table 4).

5. Discussion

In this study we evaluated SLE mortality and causes of death in a large population of SLE patients, and we found that overall mortality during the period 2012–2020 was 18.6 (95% CI 17.0, 20.2) events per 1000 person-years, with an overall standardized mortality ratio of 2.65. Our results are consistent with data from other European countries, reporting mortality rates ranging between 13.8 and 16.0 deaths per 1000 person-years[6–9,11] and overall SMRs between 1.7 and 3.1 [8, 11–14]. Thus, we confirmed that SLE patients had an increased mortality compared to the general population. One study showed that SLE reduces life expectancy among females and males by an average of 22 and 12 years, respectively, compared to the general population [4]. Notably, in our study SMR was particularly high in young patients, i.e. in those aged 44 or less, who had a 5.59 fold higher risk of death compared to that of matched counterparts, although the number of events was relatively low. This means that the gap in lupus mortality compared to the general population is wider in younger people.

Studies from around the world reported a considerable variability in mortality ratios, ranging from 2 to 5 compared to the general population [3,7–9,11,13–22,25–27]. Differences in terms of mortality rates and causes of death in different cohorts might be related to population characteristics, including ethnicity, prevalence of renal involvement and comorbidities, but also to socioeconomic factors, including the type of healthcare service, the access to care and drug availability [28–32].

Mortality rates remained unchanged during the study period. In this

Table 1
Yearly standardized mortality rates, overall and by sex among 4283 prevalent SLE cases (Veneto Region, 2012–2020).

Year	Prevalent SLE cases on January 1st			Deaths between January 1st and December 31st			Standardized mortality rates (95% CI) per 1000 SLE patients**		
	Overall	Males	Females	Overall	Males	Females	Overall	Males	Females
2012	3034	448	2586	59	13	46	21.2 (15.8; 26.6)	32.5 (14.8; 50.1)	19.3 (13.7; 24.8)
2013	3092	453	2639	52	12	40	18.0 (13.1; 22.9)	28.7 (12.4; 44.9)	16.1 (11.1; 21.1)
2014	3182	468	2714	48	11	37	15.9 (11.4; 20.4)	25.3 (10.3; 40.2)	14.3 (9.7; 18.9)
2015	3259	480	2779	74	14	60	23.5 (18.1; 28.8)	30.8 (14.7; 47.0)	22.2 (16.6; 27.8)
2016	3321	491	2830	47	6	41	14.6 (10.4; 18.8)	12.5 (2.5; 22.6)	15.0 (10.4; 19.5)
2017	3394	504	2890	77	14	63	22.7 (17.6; 27.8)	27.8 (13.2; 42.3)	21.8 (16.4; 27.2)
2018	3427	507	2920	61	14	47	17.7 (13.3; 22.1)	27.6 (13.1; 42.1)	16.0 (11.4; 20.5)
2019	3448	509	2939	64	11	53	17.9 (13.5; 22.3)	20.7 (8.5; 32.9)	17.4 (12.7; 22.1)
2020	3472	501	2971	62	17	45	16.7 (12.6; 20.9)	30.7 (16.1; 45.3)	14.3 (10.1; 18.5)
Total*	**29,629**	**4361**	**25,268**	**544**	**112**	**432**	**18.6 (17.0; 20.2)**	**26.1 (21.3; 31.0)**	**17.3 (15.7; 18.9)**

* Total person-years, total deaths, average annual mortality rate.
** Direct standardization using the SLE cohort of 2017 as a reference.

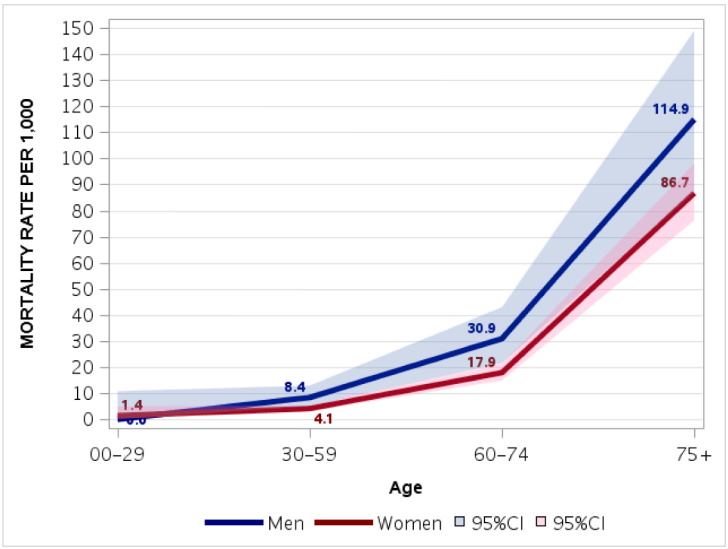

Fig. 1. Sex- and age-specific mortality rates (per 1000 person-years) among the 4283 SLE prevalent cases (N. of deaths=544) (Veneto Region, 2012–2020).

Table 2
Causes of death of the decedents among the 4283 SLE prevalent cases (Veneto Region, 2012–2020).

Cause of death	Underlying cause		Multiple causes[b]	
	N	%	N	%
Cardiovascular disease[a]	148	27.6	326	60.8
Neoplasm	131	24.4	154	28.7
Infectious disease	59[c]	11.0	175	32.6
SLE	58	10.8	145	27.1
Kidney disease	15	2.8	103	19.2
Other conditions	125	23.3	–	–
Total	536[d]	100	n.a	n.a

[a] for multiple causes, cardiac arrest was excluded (I46.9).
[b] Since for each decedent, more concomitant causes of deaths may be reported, the total number is higher than the total number of deaths.
[c] 6/59 deaths due to infections were related to COVID-19 during 2020.
[d] the cause of death was missing for 8 cases.
n.a., not applicable.

regard, a longer follow-up is needed to understand whether the introduction of new biological therapies has exerted any beneficial impact on SLE mortality.

One-year survival since SLE diagnosis was 96%, 5-year survival 91%, and 8-year survival 89%. Similar results were depicted in a study by Ingvarsson et al. [13], who found a 91% survival after 5 years, and 85% after 10 years since SLE diagnosis. A recent paper which examined mortality trends over the past 40 years in a US population reported a survival of 93% at 5-years, 83% at 10 years, and 69% at 20 years after diagnosis [17]. Interestingly, this study did not observe any decrease in mortality rates over the four decades [17].

We observed a higher mortality rate in males compared to female patients, both among prevalent and incident cases, confirming a worse prognosis in males as reported in some [1,3,11], but not all studies [7,9,13].

In the prevalent SLE cohort, cardiovascular diseases were the most common cause of death, followed by cancer. Other studies recently

Table 3
Causes of death among decedents in the cohort of 1092 incident SLE cases.

Underlying cause of death	Within the first year [a]		Overall [b]	
	N	%	N	%
Neoplasm	12	26.1	21	27.3
Cardiovascular disease	10	21.7	17	22.1
SLE	10	21.7	14	18.2
Infectious disease	6	13.0	11	14.3
Kidney disease	1	2.2	2	2.6
Other conditions	7	15.2	12	15.5
Total	**46**	**100**	**77**	**100**

[a] Cause of death was missing in 3 cases.
[b] Cause of death was missing in 13 cases.

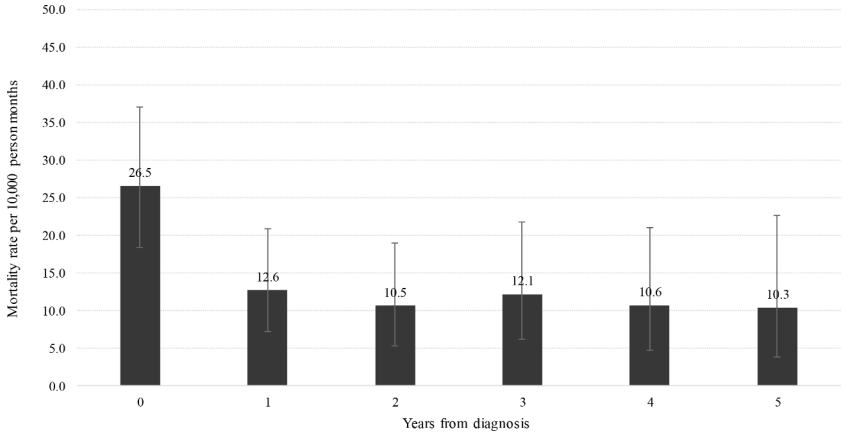

Fig. 2. Mortality rates among SLE incident cases and 95% CI per 10,000 person-months by year from diagnosis.

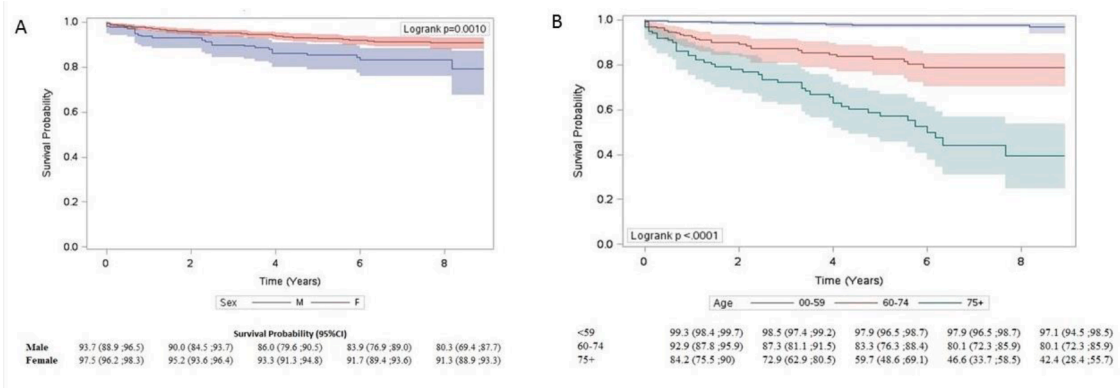

Fig. 3. Kaplan–Meier survival estimates by sex (A) and age at diagnosis (B), among 1092 SLE incident cases, Veneto Region, 2013–2021.

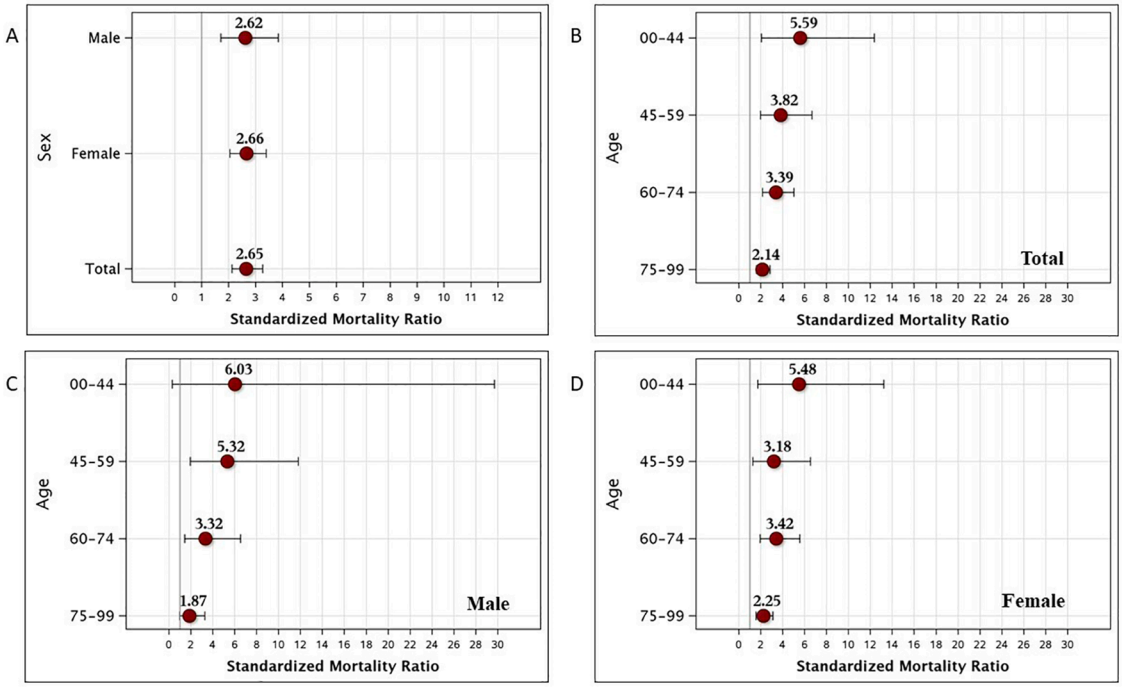

Fig. 4. Standardized mortality ratio among 1092 SLE incident cases, overall and stratified by sex (A), age group (B) and both (C, D).

carried out in Europe also found that cardiovascular diseases is the leading cause of death in SLE [13–16]. On the other hand, infections still remain the first cause of death in Asia and in South America [23]. In our population, infections were rarely selected as the underlying cause of death (11% of cases). This percentage of deaths attributable to infectious diseases, lower than that previously reported in Italy [1], has various potential explanations: advances in antimicrobial therapy, with the availability of new drugs; a reduction in the use of cyclophosphamide in favor of mycophenolate; a better and more conscious use of glucocorticoids, with lower cumulative doses; the availability of belimumab, which contributed in decreasing disease activity and steroid intake, thus dampening two major risk factors for infections. It has to be mentioned that during the year 2020 deaths due to COVID-19 were 6 among the prevalent cases and 3 among the incident cases.

Not surprisingly, cardiovascular diseases were the most frequent cause of death in our prevalent cohort: atherosclerosis occurs early and is accelerated in SLE, and patients with SLE have a higher number of traditional cardiovascular risk factors, which add to other disease-related cardiovascular risk factors, such as antiphospholipid antibodies, disease activity, in addition to the side-effects of prolonged glucocorticoid treatment [33].

Interestingly, SLE was recognized as the underlying cause of death in 10.8% of prevalent SLE decedents (although it was mentioned in 27.1% of deaths), whereas it accounted for 18.2% of deaths among incident cases, a proportion that increased up to 21.7%, when considering patients deceased within the first year after the diagnosis. This finding suggests that SLE-related mortality is especially high in the earlier stages of the disease, whereas mortality during the disease course is more likely to be associated with SLE comorbidities, including those consequent to the damage attributable to poorly controlled disease activity and side effects of therapies [34,35], suggesting a possible bimodal pattern in mortality as described by Urowitz et al. in 1976 [36].

Altogether, our findings entail several clinical implications: first, they should encourage the use of highly effective therapies early in the disease course, in order to avoid premature damage accrual, and deaths; second, they enforce the need for early, appropriate evaluation of risk factors for comorbidities in SLE, and sex- and age-specific cancer screening in SLE patients; third, they highlight the importance of reducing risk factors for infections, such as poor control of disease activity and misuse of glucocorticoids, as well as promoting high

vaccination coverage among SLE patients and their close contacts, including COVID-19 vaccines [37–39].

Additionally, it has to be mentioned that kidney disease was reported in one out of five deaths in our study, but it was very rarely identified as the underlying cause of death. Considering that up to half of patients with SLE can experience nephritis during the disease course, the relatively small contribution of acute or chronic kidney disease to mortality might be partially explained by the generally good prognosis of kidney involvement in Caucasian SLE patients, but also by the large availability of new therapies (including on- and off-label drugs) [40]. In addition, improvement in the classification of SLE patients, and earlier diagnosis of lupus nephritis (LN) with the recognition (and treatment) of milder cases may have contributed to improve the outcome of patients with renal involvement [41].

In addition, at least for incident cases, the low kidney-related mortality can be due to the relatively short follow-up of our study, since deaths due to renal disease usually occur later in the disease course. Different scenarios have been depicted in cohorts of patients with different ethnicities, including studies in the UK, the US, and Asia [3,8,9,21,22].

Our study has some limitations: no temporal trend in mortality could be calculated due to the relatively short follow-up; thus, we were not able to assess whether mortality has decreased in the last decade compared to the previous one. Furthermore, most of the population in the Veneto Region is composed by Caucasians and the possibility of generalizing our results to other populations is limited. Also, no data were available on the type of SLE therapy adopted, not allowing us to perform prognostic comparisons in relation to different therapeutic regimens. The SLE clinical manifestations accounting for SLE-related mortality were also not available in our registries. The automatic extraction of SLE cases from the electronic registry prevented the feasibility of verifying the accuracy of the diagnosis, although for this type of source, it is quite elevated and the addition of chart review over automatic data extraction from registries using specific codes alone has not proved superiority [42]. Furthermore, mortality rates in the cohort of prevalent SLE patients might be slightly underestimated compared to life-long studies of incident cohorts due to survival bias.

Our study has also some relevant strengths: we used the Veneto population registry, which includes all residents in the region and linked records with the database of healthcare copayment exemptions, and with hospital discharge records to increase the sensitivity of the algorithm. By examining data on SLE mortality over the last decade, our results are indicative of the current survival of patients affected with this disease.

6. Conclusions

The results of this study have shown a 2.6-fold increase in all-cause mortality rate among patients with SLE compared to the general population; the risk for all-cause mortality was especially high among younger patients, with a 5.5 fold increased risk of death among patients aged 44 years or less. Cardiovascular diseases and cancer were the most frequent causes of death in this cohort, whereas infectious diseases accounted for a proportion of deaths lower than that previously reported.

Our results highlight the importance of early diagnosis and treatment of SLE, and the urgency of implementing preventive strategies such as screening for specific comorbidities and vaccination to ensure prompt diagnosis and treatment of cardiovascular diseases, cancer, and infections, in order to reduce mortality.

Funding information

There are no funders to report for this manuscript.

Ethical approval information

All analyses were carried out on routinely collected anonymized records; all data in the Local Health Authority registries are recorded with the patient's consent and can be used as aggregated data for scientific studies without further authorization (Garante per la protezione dei dati personali, Resolution n.85 of 1 March 2012).

Data sharing

Additional data from this study can be shared upon reasonable request.

CRediT authorship contribution statement

Margherita Zen: Conceptualization, Writing – original draft, Methodology, Resources, Writing – review & editing, Visualization. **Laura Salmaso:** Data curation, Formal analysis, Visualization, Methodology, Writing – review & editing. **Claudio Barbiellini Amidei:** Data curation, Formal analysis, Visualization, Writing – review & editing. **Ugo Fedeli:** Data curation, Formal analysis, Visualization, Writing – review & editing. **Stefania Bellio:** Validation, Writing – review & editing, Visualization. **Luca Iaccarino:** Validation, Writing – review & editing. **Andrea Doria:** Conceptualization, Resources, Validation, Writing – review & editing, Visualization. **Mario Saia:** Conceptualization, Resources, Validation, Writing – review & editing, Visualization.

Declaration of Competing Interest

All Authors declare they have no competing interests to report.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2023.02.004.

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