Original article

Large-scale mortality gap between SLE and control population is associated with increased infection-related mortality in lupus

Melinda Kedves [1], Fruzsina Kósa[2], Péter Kunovszki[2], Péter Takács[2],
Melinda Zsuzsanna Szabó[3], Chetan Karyekar[4], Jennifer H. Lofland[4] and
György Nagy[5,6,7]

Abstract

Objective. The aim of the present study was to analyse the incidence, prevalence, mortality and cause of death data of adult SLE patients and matched controls in a full-populational, nationwide, retrospective study.

Methods. This non-interventional study was based on database research of the National Health Insurance Fund of Hungary. A total of 7888 patients were included in the analyses, within which two subgroups of incident patients were created: the 'All incident SLE patients' group consisted of all incident SLE patients (4503 patients), while the 'Treated SLE patients' group contained those who received relevant therapy in the first 6 months after diagnosis (2582 patients).

Results. The median age of the SLE population was found to be 46.5 years (women 85%). The incidence rate was 4.86 and 2.78 per 100 000 inhabitants in the 'All incident SLE patients' and 'Treated SLE patients' groups, respectively. The standardized mortality ratio was 1.63 and 2.09 in the 'All incident SLE patients' and 'Treated SLE patients' groups, respectively. Overall survival was significantly lower ($P < 0.001$) in both groups than in the general population, with hazard ratio = 2.17 in the 'All incident SLE patients' group and hazard ratio = 2.75 in the 'Treated SLE patients' group. There was no significant difference between SLE and control deaths regarding cerebrovascular conditions as the cause of death. Generally, cancer-related deaths were less common, while haematological cancer and infection-related deaths were more common in SLE patients.

Conclusion. Infections, especially sepsis, had the largest positive effect on top of the extra mortality of SLE. This highlights that SLE patients are at increased risk of infection-related death.

Key words: epidemiology, systemic lupus erythematosus, health policies, statistics, outcome measures

CLINICAL SCIENCE

> **Rheumatology key messages**
> - The standardized mortality ratio was significantly higher in SLE than that of the non-SLE individuals.
> - The cause of death distribution was different for SLE patients and controls.
> - Our present data clearly indicate the need for optimal infection management in SLE.

Introduction

SLE is a chronic autoimmune disorder characterized by a widespread spectrum of clinical manifestations of different organs [1–4]. Present mostly in women of childbearing age [5], SLE can affect almost any organ, with renal and neuropsychiatric involvement being the most critical manifestations [6].

Clear geographical and ethnic characteristics have been noticed in the incidence, prevalence, clinical course and outcome of the disease. Worldwide incidence rates range between 0.3 and 23.3/100 000, and

[1]Department of Rheumatology, Hospital of Bács-Kiskun County, Kecskemét, [2]Janssen Global Commercial Strategy Organization, Budapest, [3]New Saint John Hospital and Outpatient Clinic, Budapest, Hungary, [4]Janssen R&D Services, Janssen Global Commercial Organization, Horsham, PA, USA, [5]Department of Rheumatology, 3rd Department of Internal Medicine, Semmelweis University, Budapest, [6]Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest and [7]Department of Rheumatology, Buda Hospital of the Hospitaller Order of Saint John of God, Budapest, Hungary

Correspondence to: Melinda Kedves, Balaton utca 17, Kecskemét, Hungary. E-mail: kedvesmelinda@yahoo.com

prevalence rates between 70 and 241/100 000 [4–11]. The incidence rate among African Caribbean, African American and Hispanic populations is almost three times higher than in the Caucasian population [11–17].

Differences between countries and regions might be due to several factors, including differences between diagnosis rates, access to healthcare services and accessibility of healthcare data for research. Compared with the general population, the risk of mortality was found to be two to five times higher in lupus patients [18, 19]. Higher mortality rates were associated with male sex, black race and renal manifestation. The leading causes of death are cardiovascular disease, infection, tumour and active SLE. Frequencies depend on the population [7, 20]. Although earlier diagnosis, use of immunosuppressive drugs and treatment of comorbidities led to a decrease in mortality over the recent decades [21] and there are signs that the structure of morbidity causes has changed [22], the mortality rate stayed considerably higher among patients with SLE than that in non-SLE persons.

Our study shows the results of a full-populational analysis, comparing SLE and matched non-SLE population from the same database.

The aim of the present study was to analyse the incidence, prevalence, mortality and cause of death data of adult SLE patients and matched controls on a full populational, nationwide, retrospective study.

Methods

Data source

This was an observational, retrospective database analysis of the Hungarian National Health Insurance Fund Administration (NHIF) database.

The nationwide database of NHIF is a longitudinal database that contains detailed healthcare service claims data from the whole population of Hungary, ∼10 million inhabitants. Healthcare events recorded in the NHIF database are linked to individual patients by a social security number that is possessed by all legal residents. Beyond ordinary claims databases, it contains patient-level demographic data of every resident in the country (date of birth, geographical region, gender, date of death) and data of all reimbursed healthcare services in inpatient and outpatient settings and drug dispensation. Medication prescriptions include a diagnosis also. Although, due to privacy, ethnicity is not captured in any database in Hungary, the population of the country is almost entirely (est. >99%) of Caucasian origin.

NHIF has a legal right to handle patients' data (Act No. 80/1997 on mandatory health insurance) and to share it on a claims basis (based on Act 63/2012 on the re-use of public data). Only NHIF had direct access to patient-level data; the research group had access to those data indirectly, through NHIF, according to internal data privacy regulations of NHIF and Regulation (EU) 2016/679 General Data Protection Regulation. Due to

this, and to the retrospective nature of the study, there was no need for patient-level consent to the analysis.

Study design

Inclusion criteria: all adult (age ≥18 years) patients diagnosed with SLE were captured in the database based on the 10th revision of the International Statistical Classification of Diseases (ICD-10) code M32*. Data of 9.5 years were available for detailed analysis from 1 January 2008 to 30 June 2017. Patients who had at least two diagnoses recorded in the in- or outpatient care, or pharmacy drug reimbursement databases, with at least one of them from either inpatient or outpatient care included. Those patients were considered new (incident) who had no diagnoses of SLE before 2008. Data from the period between 1 January 2006 and 31 December 2007 were used to identify patients diagnosed in this retrospective period. The index date for all patients was defined as the date of the first SLE diagnosis observable in the database; thereafter all patients had at least a 2-year retrospective wash-out period.

Two groups were formed to define the incidence of SLE based on two different definitions. The total incident population (patients who had at least a 2-year retrospective diagnosis-free period before index date) was denoted as 'All incident SLE patients', and a narrower subgroup called 'Treated SLE patients' was formed from patients who also had any kind of SLE-related relevant pharmaceutical treatments (supplementary Table S1, available at *Rheumatology* online) in the first 6 months after their index date. In general, the subgroup 'Treated SLE patients' represents a more severe patient population.

To assess the mortality gap between SLE and non-SLE population two parallel approaches were applied.

In the first approach patients who were prevalent at pre-defined time points were followed up within a fixed time window and the number of deaths of patients was compared with the number of deaths in the full population of Hungary within the same period. The latter data are publicly available from the Hungarian Central Statistical Office.

The second approach assessed the survival. Patients were followed from the time of diagnosis and the overall survival was compared with that of a matched non-SLE population. In this case both populations were selected from NHIF database and the normal population was matched on age, gender and permanent residency (county) at a 1:5 ratio.

Although the direct cause of death is reported, we used a complex approach of analysing healthcare events of patients closely prior to and at the time of their deaths. For the small portion of patients who went through autopsy, the first choice of data source was the result of autopsy, a diagnosis code recorded as 'cause of death based on the result of the autopsy' was used. Patients who died while being treated in hospital were studied and all diagnosis codes recorded during their last inpatient stay—including the autopsy result—were

assessed to identify the relevant diagnoses. Furthermore, all deceased patients were evaluated using their pre-death healthcare events and relevant diagnoses within 6 months prior to the date of death and all diagnosis codes related to both in- and outpatient visits were assessed. The list of ICD codes for relevant diagnoses are listed in supplementary Tables S2.1.a–S2.4.b, available at *Rheumatology* online.

The diagnoses were compiled into four categories—cardiovascular, neoplasms, cerebrovascular and infections—which were further subdivided into subgroups. Patients were assigned to a category or subgroup if they had at least one record of any of the diagnosis codes corresponding to the category or subgroup. Some patients could not be classified, in cases where they had no diagnoses that appear on the list of ICD codes that were searched for.

This analysis was repeated in the matched control (non-SLE) group as well and the frequencies were compared. This study has been approved by Medical Research Council – Research and Ethics Committee (TUKEB), Hungary (Appr. no.: 53229-2-2018/EKU).

Statistical analysis

The epidemiology of SLE in Hungary was described using crude rates of prevalence and incidence. Standardized mortality ratio (SMR) with indirect standardization was used to compare the death rates in the patient and the full population. The age and gender distribution were obtained for patients prevalent on the first day of the year in each year between 2010 and 2016. Furthermore, the number of deaths within the given year out of these patients was also collected.

The age and gender distribution of the total population of Hungary on the first days of each year between 2010 and 2016 and the number of deaths in the given years using the same stratification was available from Hungarian Central Statistical Office. Based on these, the age- and gender-specific death rates for each of the studied years could be obtained for the general population of Hungary. Using these death rates, the expected number of deaths within the patient population was calculated for every year in the study. Using the crude death counts from the patient population as the observed number of deaths and the estimated values, an estimated SMR was calculated for every year. Assuming that the SMR is constant within this time period, by averaging these estimates an overall estimate for the SMR was obtained.

Overall survival of patients from the time of diagnosis date (defined as their index date) was estimated using a Kaplan–Meier estimation. Overall survival for controls was also estimated and the patients and controls were compared using a Cox proportional hazards model.

Instead of using SMRs to compare the proportion of patients dying due to a certain cause of death within the total patient population (dead and living included), an alternative method was applied. In this method only the deceased patients were considered and the proportion belonging to the previously defined categories were calculated. This way the cause of death pattern differences between SLE patients and the general population could be observed as an interaction effect on top of the excess mortality of the SLE group. These effects were expressed as odds ratios, SLE *vs* control group.

The probabilities of patients and controls dying due to a certain cause of death was compared using χ^2 tests of equal probabilities.

Statistical analysis was performed using R 3.5.1. software [R Development Core Team (2018) R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria; URL https://www.R-project.org/].

Results

Prevalence and incidence of SLE

A total of 7888 patients with at least two diagnoses of SLE were identified in the database between 1 January 2008 and 30 June 2017, having a minimum of one visit in inpatient or outpatient care. Some 4503 patients made up the 'All incident SLE patients' group with the first date of SLE care—the index date—identified between 1 January 2008 and 30 June 2017. The 'Treated SLE patients' group consisted of 2582 patients who started relevant SLE treatment within 6 months after index date (Fig. 1).

The annual prevalence increased during the examined period (36.1–70.5 per 100 000 persons) (Fig. 2). Detailed information about the age- and gender-specific prevalence can be found in the supplementary Table S3, available at *Rheumatology* online.

In the group 'All incident SLE patients' the yearly incidence per 100 000 inhabitants decreased from 6.21 patients in 2008 to 3.79 patients in 2016, whereas the incidence in the group 'Treated SLE patients' was more stable, varying between 2.27 and 3.37 patients per 100 000 inhabitants during the same period (Fig. 3).

Women had a majority in both groups (85%). Men had a uniformly low incidence with regards to age. Women, on the other hand, had a distinct peak incidence between 30 and 49 years of age with 9–13 patients in the group 'All incident SLE patients' and 5–7 patients in the group 'Treated SLE patients' per 100 000 inhabitants. Median age of patients at the time of diagnosis was 46 and 47 years in the two groups, respectively (Fig. 3). Detailed information about the age- and gender-specific incidence can be found in the supplementary Tables S4.1 and S4.2, available at *Rheumatology* online.

Mortality, SMR

Calculation of the age- and gender-specific death rates and estimated number of deaths for all years and both incident patient groups can be found in the supplementary Tables S5–S9, available at *Rheumatology* online.
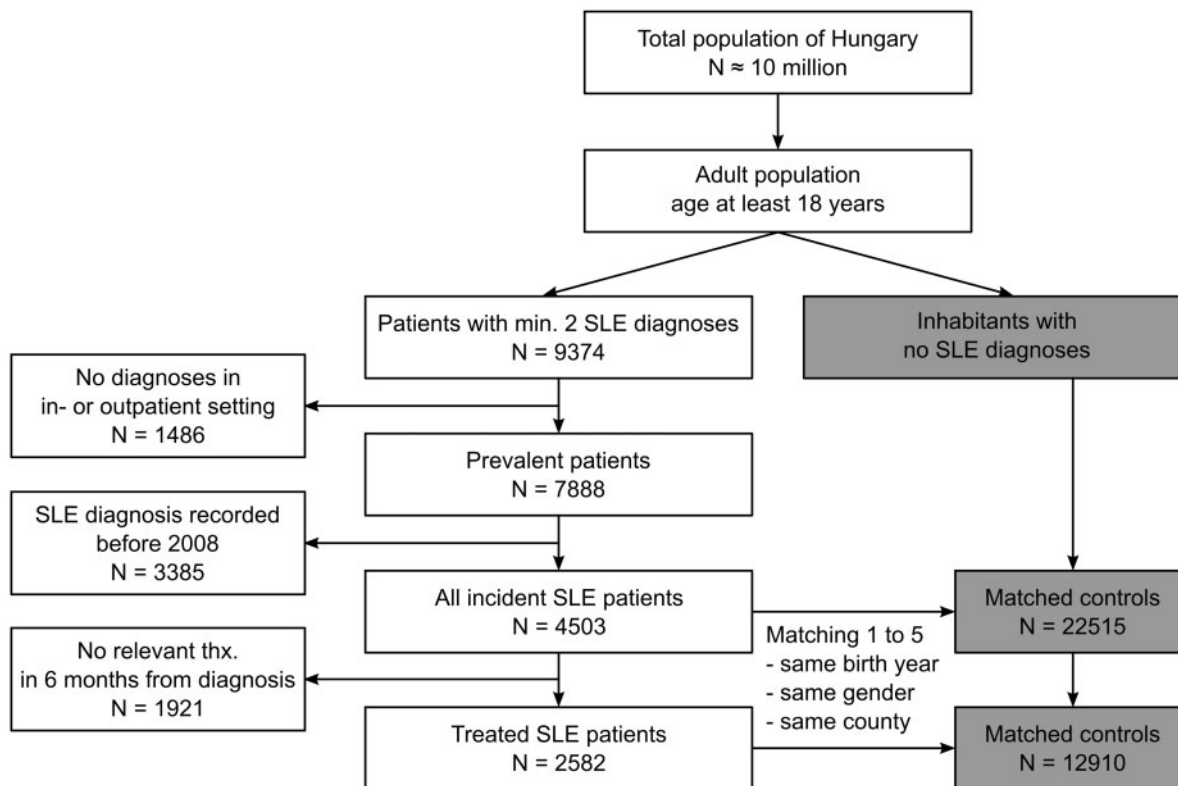
All dark rectangles denote people with no SLE diagnosis. Matching between SLE patients and controls was performed on a person to person basis. Matched individuals have the same birth year, the same gender and live in the same county.

Fɪɢ. 2 Description of the prevalent population
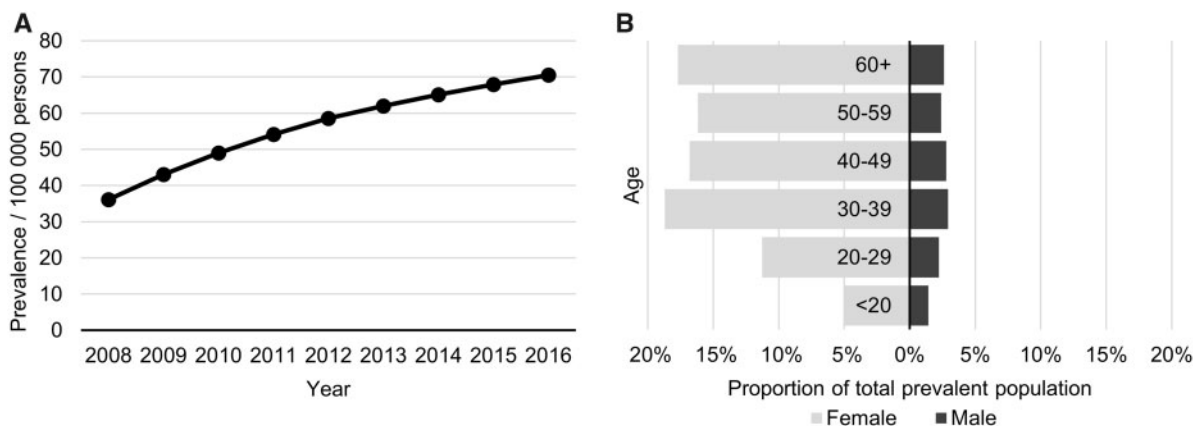
(**A**) Annual prevalence of SLE in Hungary. (**B**) Demographic distribution of the total prevalent population.

Table 1 shows the observed number of deaths, the expected number of deaths and the estimated SMR for each year in the two incident patient groups.

Overall SMR was 1.63 (95% CI 1.43, 1.83) in the 'All incident SLE patients' group and 2.09 (95% CI 1.80, 2.39) in the 'Treated SLE patients' group.

Survival

Estimated survival probability at year 1 from diagnosis was 98.0% in both incident patient groups. It was reduced to 95.0 and 94.0% at 3 years and to 91.8 and 89.6% at 5 years in the groups 'All incident SLE patients' and 'Treated SLE patients', respectively. These

FIG. 3 Description of the incident population
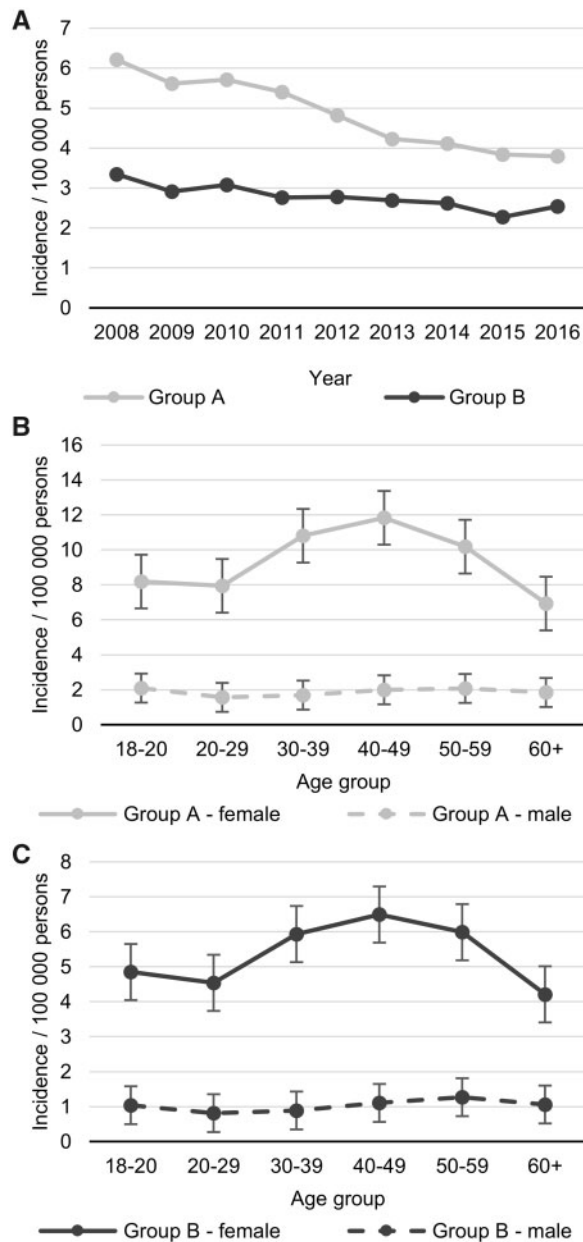
(A) Annual incidence in the groups 'All incident SLE patients' and 'Treated SLE patients'. (B) Age- and gender-stratified incidence in the group 'All incident SLE patients'. (C) Age- and gender-stratified incidence in the group 'Treated SLE patients'. Error bars denote within-year standard deviations. Group A: 'All incident SLE patients'; Group B: 'Treated SLE patients'.

survival probabilities were significantly worse than those of the matched reference populations ($P < 0.001$).

Hazard ratios (HRs) for all-cause mortality vs the matched non-SLE population obtained from the Cox proportional hazards regression were HR = 2.17 (95% CI 1.94, 2.44) in the 'All incident SLE patients' group and

HR = 2.75 (95% CI 2.38, 3.17) in the 'Treated SLE patients' group (Fig. 4).

Cause of death

Differences between the cause of death distribution could be observed between SLE and non-SLE populations. While the relative frequency of cardio- and cerebrovascular events as the cause of death were not different, that of neoplasms was significantly lower, while the relative frequency of infections was found to be significantly higher in the SLE group compared with non-SLE patients (Fig. 5A and C). Results in the 'Treated SLE patients' group vs non-SLE population were: all cardiovascular causes 46 vs 45% with an odds ratio (OR) = 1.03 ($P = 0.91$); and all cerebrovascular causes 6 vs 10% with an OR = 0.57 ($P = 0.10$). Interestingly, neoplasms were significantly less common, 14 vs 33%, OR = 0.35 ($P < 0.001$). On the other hand, infections had a highly significant positive effect (47 vs 31%, OR = 2.01, $P < 0.001$). Based on the subgroup analysis this increase is attributable to the increase of the frequency of sepsis, 35 vs 11%, OR = 4.46 ($P < 0.001$). With the methodology used, the cause of death could not be identified for 14 and 15% of patients in the SLE and the control groups respectively. Cause of death based on autopsy report also showed the increased frequency of sepsis (supplementary Table S10, available at Rheumatology online).

Widening the analysis to all deceased patients, most effects remained similar (Fig. 5B and D). Cardiovascular conditions were significantly more frequent in SLE cases (45 vs 38%, OR = 1.33, $P = 0.04$), attributable to the heart failure cause of death also becoming significant with a positive effect (41 vs 33%, OR = 1.46, $P = 0.008$). In case of neoplasms, they were still less frequent in SLE patients (21 vs 37%, OR = 0.47, $P < 0.001$); however, haematological cancers were found to be more frequent (5 vs 2%, OR = 2.14, $P = 0.04$). In this analysis the percentage of patients for whom no potential cause of death could be identified was 17% for SLE patients and 24% for controls.

Discussion

While patient registries are essential in characterizing the wide range of conditions, these databases lack the whole populational features of diseases. On the other hand, full-populational databases, especially with appropriate controls, are available only in a few countries. According to our best knowledge, this is the first full-populational epidemiology and mortality database study in Hungary, which includes data for the incidence, prevalence, mortality as well as cause of death of SLE. Our analyses confirmed and extended previous observations regarding the prevalence and mortality of SLE, shed light on the large-scale gap between the mortality of SLE and the control population, and showed the

TABLE 1 Observed and expected number of deaths and estimated SMR in patient groups

Year	All incident SLE patients			Treated SLE patients		
	Deaths obs.	Deaths exp.	Est. SMR	Deaths obs.	Deaths exp.	Est. SMR
2010	17	12.3	1.38	14	6.9	2.04
2011	41	19.0	2.16	27	10.4	2.59
2012	35	23.8	1.47	26	13.2	1.97
2013	42	28.0	1.50	30	15.6	1.92
2014	48	31.4	1.53	32	17.7	1.81
2015	56	35.8	1.56	48	20.6	2.33
2016	67	36.8	1.82	42	21.1	1.99

'All incident SLE patients' and 'Treated SLE patients'. The overall (average) SMR is 1.63 (95% CI 1.43, 1.83) in the group 'All incident SLE patients' and 2.09 (95% CI 1.80, 2.39) in the group 'Treated SLE patients'. SMR: standardized mortality ratio; obs.: observed; exp.: expected, est.: estimated.

FIG. 4 OS from the time of diagnosis compared with the OS of matched controls
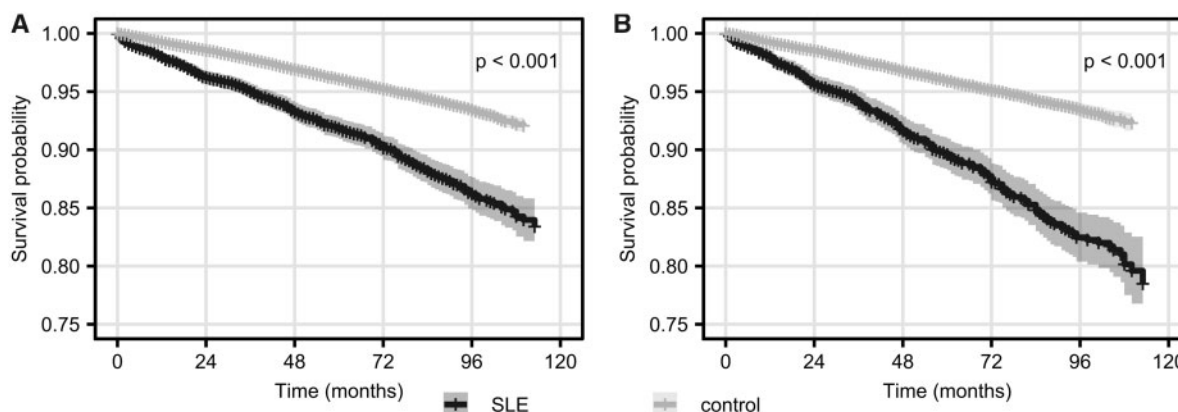
HR = 1 is tested using a z-test. (**A**) OS in the group 'All incident SLE patients', HR = 2.17 (95% CI 1.94, 2.44), $P < 0.001$. (B) OS in the group 'Treated SLE patients', HR = 2.75 (95% CI 2.38, 3.17), $P < 0.001$. OS: overall survival; HR: hazard ratio.

different distribution of causes of death in lupus compared with controls.

According to our data, the female predominance, incidence (4.86/100 000 persons in the 'All incident SLE patients' group and 2.78/100 000 persons in the 'Treated SLE patients' group) and the trend for increasing prevalence with time (from 36.1 to 70.5/100 000 persons) of SLE in Hungarian population is similar to earlier reports of Caucasian ethnic groups [4, 12, 23]. Interestingly, the annual incidence shows a descending trend in the 'All incident SLE patients' group, but not in the 'Treated SLE patients' group where adequate treatment after diagnosis was part of the definition. The reason for these trends is explained by our methodology. A patient might not visit healthcare services for an extended period, possibly due to remission/low disease activity and/or non-compliance. Patients who were identified as incident in 2008 only have a 2-year period without diagnoses, while this period was longer for patients identified as incident later. With longer times, the probability of catching non-incident cases decreases considerably.

In line with other observations, the overall SMR was found to be 1.63 ('All incident SLE patients') and 2.09 ('Treated SLE patients') in our study. While a recent study investigating a longer time period demonstrated a significant reduction of all-cause and cause-specific SMR compared with the general population from 13.5 to 2.2 [24] and early survival among SLE patients has improved substantially, epidemiological studies still show an increased mortality rate in SLE compared with the general population [25–27]. A wide range of recent studies report values of SMR for the adult SLE population between 2.4 and 3.5 in Europe and North America [18, 20], and up to 2.58–5.25 in Asian countries [18, 19, 28].

The survival of SLE patients has improved significantly over the past 65 years. An earlier US study [29] reported a survival rate of <50% at 5 years. Later studies conducted in the European region and in the US presented that >93% of patients with SLE survive for 5 years from

FIG. 5 Frequency of potential causes of death within the deceased population, compared with controls
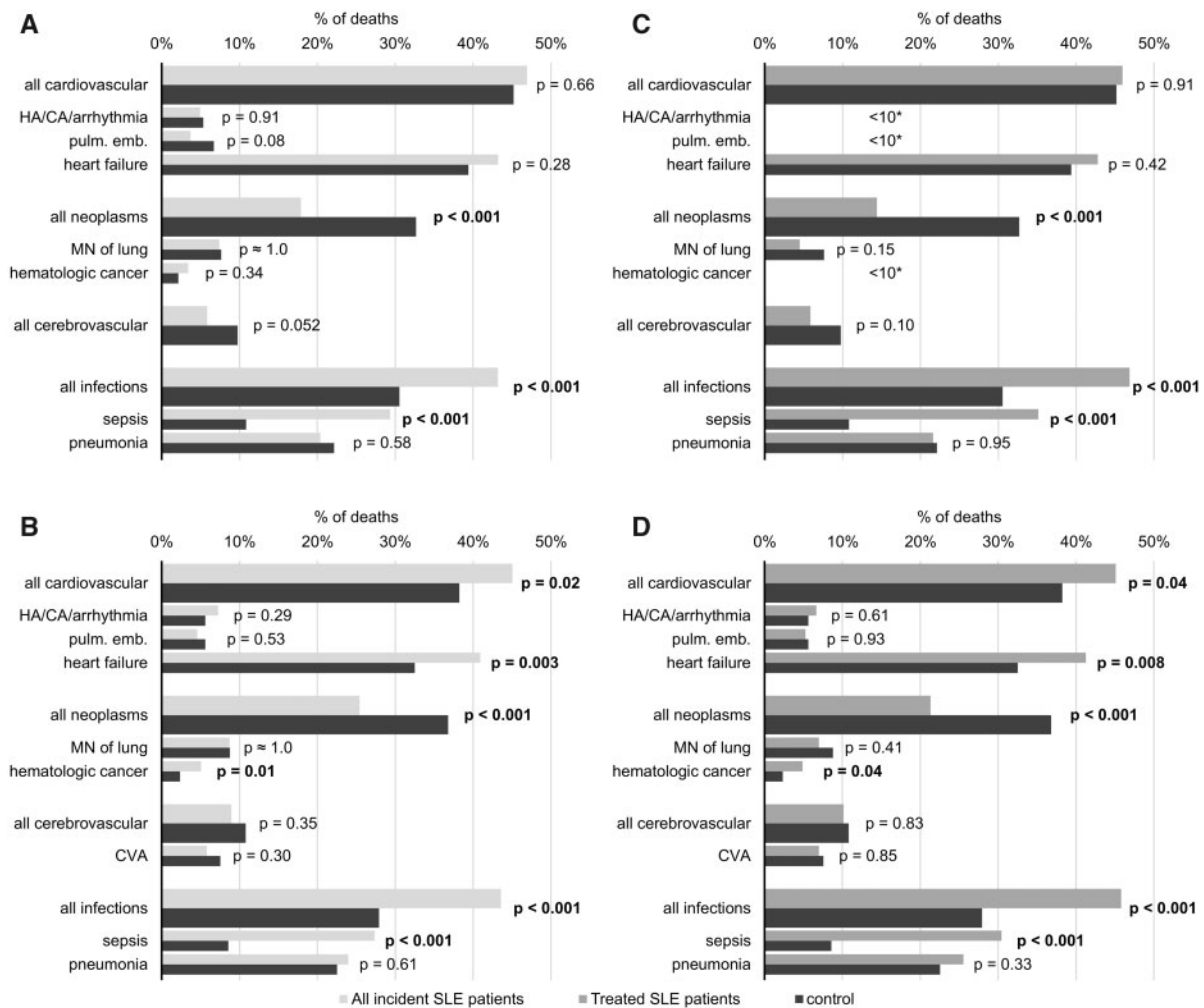
The probabilities are compared using a χ^2 test of equal probabilities, $P < 0.05$ values are highlighted in bold. (**A**) 'All incident SLE patients', deaths reported during the last hospital stay. (**B**) 'All incident SLE patients', diagnoses reported within 6 months prior to death. (**C**) 'Treated SLE patients', deaths reported during the last hospital stay. (**D**) 'Treated SLE patients', diagnoses reported within 6 months prior to death. HA: heart attack; CA: cardiac arrest; pulm. emb.: pulmonary embolism; MN of lung: malignant neoplasm of lung; CVA: cerebrovascular accident. <10*: frequencies are not reportable where the number of persons is <10.

diagnosis [30, 31]. In the Asia-Pacific region a 5-year survival of 83% was reported [28]. By contrast we found 91.8 and 89.6% survival rates at 5 years in the group 'All incident SLE patients' and 'Treated SLE patients', respectively.

While the causes of deaths of SLE patients are well reported and known, the way they are reported varies considerably. Patients may die while in hospital with a well-documented history of their last weeks/months and an autopsy result afterwards, while others may die in their homes without a clear final diagnosis of the cause of death. This may be affected not only by different access to healthcare, to active hospital or palliative care systems, but also by different regulations in different countries for necessity of autopsy, documentation of

cause of death and other factors. Another reason for uncertainty can be the lack of a clear and objective cause of death due to the complexity and interdependency of the condition: a patient may suffer from a terminal malignant disease while the direct cause of death may be sepsis, or a patient with chronic renal failure may have a cardiovascular event as well.

The availability of the exact date of death and all healthcare-related events in the pre-death period allowed us to use various approaches. It is noteworthy that patients may suffer from more than one condition that may lead to death; therefore, our approach was to collect and analyse all data regarding the most common causes of death (cardio- and cerebrovascular disease, infection and malignant diseases).

In addition to the actual causes of death, we aimed to determine the effect of the major potentially life-threatening conditions (e.g. cardiovascular disease, severe infection or cancer) on the life expectancy. To this aim, the most frequent, potentially lethal conditions were selected and studied prior to death in order to characterize the distribution of potential causes of death in both the SLE and control groups. Critical analysis of these data may provide important information regarding the actual risk factors of death.

We assessed cerebrovascular and cardiovascular diseases separately in our study. No significant difference was found between SLE patients and controls regarding cerebrovascular conditions as a potential cause of death. Frequency of cardiovascular conditions as a potential cause of death was not found to be different for patients who died in hospital, but the difference was significant in the wider patient population when the full pre-death 6-month period was analysed. Björnådal *et al.* found that cardiovascular mortality remained high, especially in younger population between 1964 and 1995 [32]. Tselios *et al.* [24] used ICD-10 codes that cover the atherosclerotic diseases (both cardiac or cerebrovascular) and found that the cause-specific SMR decreased from 8.3 in the 1980s to 3.2 in the most recent years (2010–13), with an average of 4.7. An SMR of 2.97 for coronary heart disease and stroke was reported in Sweden for the period of 1964–95 [32]. In two meta-analyses, the SMR for cardiovascular causes of death was 2.25 [19] and 2.72 [18], while Bernatsky *et al.* reported an SMR of 1.7 that remained unaltered from 1970 to 2001 [20].

Regarding the infection-related mortality, our results show a significant positive interaction for infection-related mortality in SLE. Tselios *et al.* reported an SMR of 4.4 [24], likewise, two meta-analyses reported an SMR of 4.98 [18, 19]. Bernatsky *et al.* reported an infection-related SMR of 5.0 [20]. These are all in line with our results.

Although a highly significant negative effect of malignancies was found in our study as a potential cause of death, considering the increased overall mortality of SLE patients compared with controls, altogether our present results show similar effects to the previous studies. Importantly, we observed an increased risk of death due haematological malignancies when studying all patients in the 6-month period prior to death. Previously presented studies and meta-analyses reported a not significantly increased risk of malignancy-related death (SMRs of 1.19, 1.16, 0.8 and 1.4) [18–20, 24].

Infections, specifically sepsis, had the largest positive effect on top of the extra mortality of SLE. This highlights that SLE patients are at increased risk of infection-related death, further supporting the importance of optimal prevention and management of infections.

The robustness and the major benefit of our study come from two factors: (i) we used a nationwide database that captures the entirety of a population of a country of 10 million; and (ii) we used a 1:5 matched (age, gender and geographical localization) control of the non-SLE population from the same database, thus bias resulting from matching different databases could be avoided.

The care of SLE patients in Hungary is addressed by different levels of health care, such as general practitioners, dermatologists, nephrologists, internists, county hospitals and rheumatology/immunology centres. One of the limitations of our study is that the data were collected for claims purposes and not for research. Another limitation of our study is that individual patient data and data of <10 patients were not available, due to data protection regulations. Consequently, the detailed stratification of causes of death by age and sex is not feasible. In addition, the detailed analysis of the relevant medications, stratified by specific cause of death, are not available in our database. Another limitation was that ICD codes were not available at the 3-digit level; thus, subtypes of SLE could not be distinguished.

Although a wide range of therapeutic options have become available for SLE in the past decades, the mortality and survival compared with the general population is still significantly worse for these patients, predominantly due to the excess infection-related death, clearly showing an unmet need in the management of SLE.

Disclosure statement: F.K., P.K., P.T., C.K. and J.H.L. are employees of Janssen. The other authors have declared no conflicts of interest.

References

1 Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. J Clin Pathol 2003;56:481–90.

2 Cooper GS, Dooley MA, Treadwell EL *et al*. Hormonal, environmental, and infectious risk factors for developing systemic lupus erythematosus [review]. Arthritis Rheum 1998;41:1714–24.

3 Karlson EW, Watts J, Signorovitch J *et al*. Effect of glutathione S-transferase polymorphisms and proximity to hazardous waste sites on time to systemic lupus erythematosus diagnosis: results from the Roxbury Lupus Project. Arthritis Rheum 2007;56:244–54.

4 Siegel M, Lee SL. The epidemiology of systemic lupus erythematosus. Semin Arthritis Rheum 1973;3:1–54.

5 Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. Lupus 2006;15:308–18.

6 Gladman DD, Urowitz MB, Rahman P *et al*. Accrual of organ damage over time in patients with systemic lupus erythematosus. J Rheumatol 2003;30:1955–9.

7 Borchers AT, Naguwa SM, Shoenfeld Y *et al*. The geoepidemiology of systemic lupus erythematosus. Autoimmun Rev 2010;9:A277–87.

8 Somers EC, Marder W, Cagnoli P *et al*. Population-based incidence and prevalence of systemic lupus erythematosus. Arthritis Rheum 2014;66:369–78.

9   Dall'Era M, Cisternas MG, Snipes K *et al*. The incidence and prevalence of systemic lupus erythematosus in San Francisco County, California. Arthritis Rheum 2017;69: 1996–2005.

10 Elfving P, Puolakka K, Kautiainen H *et al*. Incidence of systemic lupus erythematosus in Finland, 2000–2007, a nationwide study. Clin Expl Rheumatol 2014;32:953–5.

11 Rees F, Doherty M, Grainge MJ *et al*. The worldwide incidence and prevalence of systemic lupus erythematosus: a systemic review of epidemiological studies. Rheumatology (Oxford) 2017;56:1945–61.

12 González LA, Toloza SM, Alarcón GS. Impact of race and ethnicity in the course and outcome of systemic lupus erythematosus. Rheum Dis Clin North Am 2014;40: 433–54.

13 Ferucci ED, Johnston JM, Gaddy JR *et al*. Prevalence and incidence of systemic lupus erythematosus in a population-based registry of American Indian and Alaska Native People, 2007–2009. Arthritis Rheumatol 2014;66: 2494–502.

14 Gómez-Puerta JA, Barbhaiya M, Guan H *et al*. Racial/ethnic variation in all-cause mortality among U.S. Medicaid recipients with systemic lupus erythematosus: an Hispanic and Asian paradox. Arthritis Rheumatol 2015;67:752–60.

15 Molina MJ, Mayor AM, Franco AE *et al*. Prevalence of systemic lupus erythematosus and associated comorbidities in Puerto Rico. J Clin Rheumatol 2007;13: 202–4.

16 Flower C, Hennis AJ, Hambleton IR, Nicholson GD, Liang MH; Barbados National Lupus Registry Group. Systemic lupus erythematosus in an African Caribbean Population: incidence, clinical manifestations, and survival in the Barbados National Lupus Registry. Arthritis Care Res (Hoboken) 2012;64: 1158.

17 Barnabe C, Joseph L, Belisle P *et al*. Prevalence of systemic lupus erythematosus and systemic sclerosis in the First Nations Population of Alberta, Canada. Arthritis Care Res (Hoboken) 2012;64:138–43.

18 Yurkovich M, Vostretsova K, Chen W *et al*. Overall and cause-specific mortality in patients with systemic lupus erythematosus: meta-analysis of observational studies. Arthritis Care Res (Hoboken) 2014;66:608–16.

19 Lee YH, Choi SJ, Ji JD *et al*. Overall and cause-specific mortality in systemic lupus erythematosus: an updated meta-analysis. Lupus 2016;25:727–34.

20 Bernatsky S, Boivin JF, Joseph L *et al*. Mortality in systemic lupus erythematosus. Arthritis Rheum 2006;54: 2550–7.

21 Fors Nieves CE, Izmirly PM. Mortality in systemic lupus erythematosus: an update review. Curr Rheumatol Rep 2016;18:21.

22 Anver H, Dubey S, Fox J. Changing trends in mortality in systemic lupus erythematosus? An analysis of inpatient mortality at University Hospital Coventry and Warwickshire NHS Trust from 2007 to 2016. Rheumatol Int 2019;39:2069–75.

23 McCarty DJ, Manzi S, Medsger TA Jr *et al*. Incidence of systemic lupus erythematosus: race and gender differences. Arthritis Rheum 1995;38:1260–70.

24 Tselios K, Gladman DD, Sheane BJ *et al*. All-cause, cause-specific and age-specific standardised mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971-2013). Ann Rheum Dis 2019;78:802–6.

25 Feldman CH, Hiraki LT, Liu J *et al*. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum 2013;65:753–63.

26 Bartels CM, Buhr KA, Goldberg JW *et al*. Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. J Rheumatol 2014;41: 680–7.

27 Jorge AM, Lu N, Zhang Y *et al*. Unchanging premature mortality trends in systemic lupus erythematosus: a general population-based study (1999–2014). Rheumatology (Oxford) 2018;57:337–44.

28 Jakes RW, Bae SC, Louthrenoo W *et al*. Systemic review of the epidemiology of systemic lupus erythematosus in the Asia-Pacific region: prevalence, incidence, clinical features, and mortality. Arthritis Care Res (Hoboken) 2012;64:159–68.

29 Merrel M, Shulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. J Chron Dis 1955;1:12–32.

30 Swaak AJG, van den Brink HG, Smeenk RJT *et al*. Systemic lupus erythematosus. Disease outcome in patients with a disease duration of at least 10 years: second evaluation. Lupus 2001;10:51–8.

31 Cervera R, Khamashta MA, Font J *et al*. Morbidity and mortality in systemic lupus erythematosus during a 10-year period. A comparison of early and late manifestations in a cohort of 1000 patients. Medicine 2003;82:299–308.

32 Björnådal I, Yin L, Granath F *et al*. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population-based study 1964-1995. J Rheumatol 2004;31:713–9.