RHEUMATOLOGY

Original article

Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus *vs* matched controls

Irene E. M. Bultink [1], Frank de Vries[2,3], Ronald F. van Vollenhoven[1] and Arief Lalmohamed[2,4]

Abstract

Objectives. We wanted to estimate the magnitude of the risk from all-cause, cause-specific and sex-specific mortality in patients with SLE and relative risks compared with matched controls and to evaluate the influence of exposure to medication on risk of mortality in SLE.

Methods. We conducted a population-based cohort study using the Clinical Practice Research Datalink, Hospital Episode Statistics and national death certificates (from 1987 to 2012). Each SLE patient ($n = 4343$) was matched with up to six controls ($n = 21\,780$) by age and sex. Cox proportional hazards models were used to estimate overall and cause-specific mortality rate ratios.

Results. Patients with SLE had a 1.8-fold increased mortality rate for all-cause mortality compared with age- and sex-matched subjects [adjusted hazard ratio (HR) = 1.80, 95% CI: 1.57, 2.08]. The HR was highest in patients aged 18–39 years (adjusted HR = 4.87, 95% CI: 1.93, 12.3). Mortality rates were not significantly different between male and female patients. Cumulative glucocorticoid use raised the mortality rate, whereas the HR was reduced by 45% with cumulative low-dose HCQ use. Patients with SLE had increased cause-specific mortality rates for cardiovascular disease, infections, non-infectious respiratory disease and for death attributable to accidents or suicide, whereas the mortality rate for cancer was reduced in comparison to controls.

Conclusion. British patients with SLE had a 1.8-fold increased mortality rate compared with the general population. Glucocorticoid use and being diagnosed at a younger age were associated with an increased risk of mortality. HCQ use significantly reduced the mortality rate, but this association was found only in the lowest cumulative dosage exposure group.

Key words: cause of death, glucocorticosteroids, hydroxychloroquine, mortality, systemic lupus erythematosus, treatment

Rheumatology key messages

- SLE patients have a 1.8-fold increased mortality rate for all-cause mortality.
- Cumulative glucocorticoid exposure is associated with an increased mortality rate in SLE patients.
- HCQ exposure is associated with a 45% reduced mortality in the lowest cumulative dosage group.

[1]Department of Rheumatology, Amsterdam Rheumatology and immunology Center, VU University Medical Center, Amsterdam, [2]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, [3]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht and [4]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

Correspondence to: Irene E. M. Bultink, Department of Rheumatology, Amsterdam Rheumatology and immunology Center, Amsterdam UMC, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
E-mail: iem.bultink@amsterdamumc.nl

Introduction

SLE is a chronic systemic autoimmune disease that is associated with considerable morbidity and mortality. Recent studies have reported that the 5-year survival of patients with SLE has improved over the last decades from 50% in the 1950s [1] to >90% since the 1990s [2–4]. The improved prognosis of SLE might be attributed to a number of factors, including earlier diagnosis and treatment, more judicious use of glucocorticoids (GCs) and immunosuppressive drugs and better management of disease complications.

However, despite the improved survival, mortality rates have been reported to be 1.4–5 times increased in SLE patients in comparison to the general population [4–11]. Improving knowledge regarding the factors that contribute to the increased risk of mortality in patients with SLE is of major importance to develop strategies to improve survival.

Observational studies have suggested several determinants associated with an increased mortality risk in patients with SLE, including a younger age [5–11], disease activity [2, 12–14], organ damage [12, 15–17], co-morbidity [16, 18], high-dose GC treatment [2] and use of CYC [19]. In addition, the mortality risk in SLE is influenced by ethnicity [20] and socioeconomic status [12], and geographical variations have been reported [8].

Although results vary among studies, particularly high mortality rates have been reported for patients with nephritis [3, 5, 7, 18, 21], neuropsychiatric complications [3, 21–23], cardiovascular disease [5, 7, 21, 24], respiratory failure [18], thrombocytopenia [2, 18] and infections [5, 7, 18]. The risk of death attributable to malignancies in patients with SLE is still under debate. Recent studies have reported no increase in the overall risk of mortality owing to malignancy in SLE [5, 7, 10], but a significant increase in the risk of death attributable to specific malignancies, particularly non-Hodgkin lymphoma [25–27] and lung cancer [5, 28].

Studies on the influence of sex on mortality risk in SLE show conflicting results [4, 5, 9, 10, 21, 29, 30], and a meta-analysis of observational studies demonstrated similar mortality risk between sexes [7].

Despite the number of studies conducted on causes of death, few data are available on the influence of medication use on mortality risk in SLE. A strong association has been demonstrated between GC use and accrual of organ damage [31, 32], whereas HCQ use has been associated with reduced accrual of damage [32] and with an increased survival in three smaller studies [33–35]. In line with these findings, we hypothesize that GC use might be associated with an increased risk of mortality and HCQ use with a reduced risk of mortality in SLE.

Methods

Study design and source population

Information for this retrospective cohort study was obtained from the Clinical Practice Research Datalink (CPRD, data from January 1987 to March 2012), linked to national death certificate data, as collected by the Office of National Statistics (ONS) for England (from January 1998 to March 2012). The CPRD contains computerized medical records of 10 million patients (in 625 primary care practices) in the UK, representing 8% of the British population. The database provides demographic information, prescription details, clinical events, specialist referrals and hospital admissions. The accuracy and completeness of these data have been well documented and validated [36, 37].

In the UK, death certificates are filled in upon death of a patient by a registered medical practitioner who has attended the patient during the last period of his or her life. Death certificates consist of two parts, containing the original underlying cause of death (part I) and diseases that might have contributed significantly to death (part II).

Selection of SLE patients and control subjects

Two separate cohorts were created for the present study (Supplementary Fig. S1, available at *Rheumatology* online). For both cohorts, adult SLE patients were identified using CPRD READ codes for SLE at any time during the period of valid CPRD data collection (i.e. from January 1987 to March 2012; Supplementary Material, available at *Rheumatology* online). For the full CPRD cohort, the index date was defined as the date of first SLE record, and patients were followed up from this date. For the CPRD-ONS cohort, the follow-up time for death was restricted to the period of valid ONS data linkage only (i.e. from January 1998 to March 2012); hence, if the first SLE record was before the period of ONS data overlap, follow-up started at the first day of valid ONS linked data and was set as the index date. Patients without valid ONS linked data were excluded from this CPRD-ONS cohort. The full CPRD cohort was used for the main analyses. For analyses concerning the underlying cause of death, we used the restricted CPRD-ONS cohort.

Each SLE patient was matched by year of birth (in increments of 1 year, to a maximum of 5 years), sex and practice to up to six control patients (without a history of SLE, including non-specific codes for SLE, cutaneous lupus erythematosus and antiphospholipid syndrome). Referent subjects were assigned the same index date as their matched patients with SLE.

The study complies with the Declaration of Helsinki. The study was approved by the Multicentre Research Ethics Committee (MREC) and by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency database research (ISAC protocol number 14_116R). The CPRD Group has obtained ethical approval by the MREC for all purely observational research using anonymised CPRD data, i.e. studies which do not include patient involvement.

Outcomes

Study patients were followed up from the index date to the end of data collection or the date of transfer of the patient out of the practice area (e.g. owing to a move to a primary care practice for which medical records are not included in the CPRD or owing to emigration) or until the occurrence of all-cause mortality, whichever came first. In the full CPRD cohort, all-cause mortality was assessed using CPRD data, whereas ONS death

certificates were used in the restricted CPRD-ONS co-hort. To determine underlying cause(s) of death in the CPRD-ONS cohort, specific causes were divided according to the International Classification of Diseases, Tenth Revision (ICD-10). These included: SLE (ICD-10 category M32); cardiovascular, cerebrovascular and per-ipheral vascular disease (I10–I99); cancer (C00–C97) and the subcategories non-Hodgkin lymphoma (C82–C85), malignant neoplasm of lung (C34) and malignant neo-plasm of breast (C50); infectious diseases (A00–B99); non-infectious respiratory diseases (J30–J99); renal fail-ure (N17–N19); accidents and suicide (V01–Y98) and all other causes (see Supplementary Material, available at *Rheumatology* online for ICD-10 codes). Corresponding ICD9 codes (for ONS data up to 2001) are shown in the Supplementary Material, available at *Rheumatology* online.

Potential confounders

Covariates assessed at baseline included: sex, alcohol use, smoking status and BMI. Based on the nature of the covariate, confounding variables were assessed at baseline or in a time-dependent manner. For the pur-pose of time-dependent assessments, the total period of follow-up was divided into 6-month intervals. For these time-dependent risk factors, the presence of these covariates was assessed by reviewing the computerized medical records for any record of risk factors before the start of an interval. These included: age, disease dur-ation, a history of underlying co-morbidities, such as malignancy (excluding non-melanoma skin cancer), car-diovascular disease (heart failure, ischaemic heart dis-ease, atrial fibrillation/flutter, coronary artery disease or myocardial infarction), cerebrovascular disease/stroke, chronic renal disease (defined as an estimated glomeru-lar filtration rate <60 ml/min/1.73 m^2), meningitis or sep-sis, and recent use (in the past 6 months) of immunosuppressive agents, systemic GCs, HCQ, sta-tins, antihypertensive drugs, thromboprophylaxis, anti-diabetic drugs, antidepressants or antipsychotics. These covariates were handled differently according to whether they were present at baseline and were real-time revers-ible (for example, current medications) or real-time irre-versible (for example, diagnosis of chronic diseases, such as diabetes, where, once diagnosed, the condition will be present for the individual's remaining time in the study). For time-dependent systemic GC and HCQ use (i.e. at least one prescription in the previous 6 months), cumulative amounts of daily defined dosages (DDDs) [38] were calculated (before the start of each period), allowing a maximum non-use gap of 6 months.

SLE disease duration was assessed using all SLE records from the start of CPRD data recording (i.e. January 1987). Hence, the CPRD-ONS cohort included a mix of incident (new) and prevalent SLE patients if there was an SLE record before January 1998.

In a time-dependent manner, SLE patients were strati-fied according to their treatment intensity in the previous 6 months, which was based on the revised BILAG index [39]. This stratification includes the following categories:

- High intensity: daily GC exposure of >20 mg oral pred-nisolone equivalents, which is equal to two DDDs [38], assessed by reviewing the latest prescribed daily dose, or use of immunosuppressive drugs.
- Medium intensity: daily GC exposure of less than two DDDs or use of antimalarials/epileptics/antidepressants in combination with NSAIDs or topical CSs.
- Low intensity: symptomatic treatment only (i.e. use of analgesics/NSAIDs).
- No drug use: none of the aforementioned drugs.

In addition, we stratified the results for risk factors of death included in the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index (SDI) [40]. These risk factors include a his-tory of seizures, cerebrovascular accident, chronic renal disease, osteoporotic fracture, use of blood glucose-low-ering agents (proxy for diabetes mellitus), malignancies and cognitive impairment. Given that cognitive impair-ment is not measured routinely by general practitioners, we used a recording of dementia as a proxy.

Statistical analysis

Mortality rates in patients with SLE were compared with control subjects using Cox proportional hazards models to derive adjusted hazard ratios (HRs; SAS v.9.2, PHREG procedure). Potential confounders were entered into the final model if they independently changed the β coefficient for SLE by $\geq5\%$.

Within SLE patients, we evaluated the influence of im-munosuppressive treatment, systemic GCs and HCQ use on mortality using time-dependent Cox models. For this purpose, current use (i.e. a drug prescription in the 3 months before a 6-month interval) was compared against never use (no prescription ever before), recent use (3–12 months before) or past use (>12 months be-fore). The results were stratified further according to cu-mulative amounts of DDDs, as described in the Potential confounders section.

All analyses concerning all-cause mortality were con-ducted within the full CPRD cohort (main analyses and predictor analyses). For the purpose of assessing disease-specific causes of death, we used the restricted CPRD-ONS cohort.

Results

Characteristics of SLE patients and matched controls

Baseline characteristics are shown in Table 1.

The full CPRD cohort yielded a total of 4356 eligible SLE patients and 21 845 age- and sex-matched controls (see flowchart in Supplementary Fig. S1, available at *Rheumatology* online). The mean follow-up duration was 6.4 years for SLE patients and 6.6 years for matched controls. Owing to matching, the age and sex distribution was similar between the two groups. The SLE patients were more likely

Table 1 Baseline characteristics of SLE patients and age- and sex-matched controls (full CPRD cohort)

Characteristic	SLE patients N = 4356	(%)	Matched controls N = 21 845	(%)
Follow-up, mean (S.D.), years		6.4 (5.1)		6.6 (5.1)
Females	3.878	(89)	19.456	(89)
Age, real-time, mean (S.D.), years		46.7 (16.3)		46.7 (16.3)
BMI, baseline, mean (S.D.), kg/m²				
<20.0	366	(8.4)	1.610	(7.4)
20.0–24.9	1.583	(36.3)	7.427	(34.0)
25.0–29.9	1.139	(26.1)	5.712	(26.1)
≥30.0	830	(19.1)	4.210	(19.3)
Unknown	438	(10.1)	2.886	(13.2)
Smoking status, baseline				
Never	2.355	(54.1)	12.422	(56.9)
Current	1.165	(26.7)	5.294	(24.2)
Ex	714	(16.4)	3.072	(14.1)
Unknown	122	(2.8)	1.057	(4.8)
History of diseases (real-time irreversible)				
Fractures	633	(14.5)	2.973	(13.6)
Heart failure	67	(1.5)	165	(0.8)
Ischaemic heart disease	239	(5.5)	722	(3.3)
Cerebrovascular event	202	(4.6)	344	(1.6)
Dementia	6	(0.1)	72	(0.3)
Seizures	175	(4.0)	451	(2.1)
Chronic renal disease	142	(3.3)	278	(1.3)
Malignancies[a]	225	(5.2)	1.026	(4.7)
Drug use, 6 months before, real-time reversible				
Systemic glucocorticoids	1.004	(23.0)	431	(2.0)
Topical glucocorticoids	747	(17.1)	1.488	(6.8)
Antimalarials	881	(20.2)	35	(0.2)
AZA	255	(5.9)	25	(0.1)
Anticonvulsants	190	(4.4)	373	(1.7)
Antidiabetics	107	(2.5)	559	(2.6)
Antidepressants	802	(18.4)	2.245	(10.3)
Anxiolytics/hypnotics	394	(9.0)	1.125	(5.1)
Bisphosphonates	259	(5.9)	257	(1.2)
Calcium/vitamin D	421	(9.7)	428	(2.0)

[a]Excluding non-melanoma skin cancer. CPRD: Clinical Practice Research Datalink.

than controls to have a history of ischaemic heart disease, cerebrovascular events, seizures and renal disease and were more frequently treated with systemic GCs, antimalarials, AZA, anticonvulsants, antidepressants and anxiolytics. After excluding patients without valid ONS data linkage (i.e. the restricted CPRD-ONS cohort), a total of 2603 SLE patients and 13 050 matched referent subjects remained eligible.

All-cause, age-specific and sex-specific mortality (full CPRD cohort and restricted CPRD-ONS cohort)

Table 2 shows mortality rates in patients with SLE and matched controls, stratified by age and sex.

A total of 442 out of 4356 SLE patients died during the study period. In comparison to age- and sex-matched referent subjects, SLE patients had a significantly increased HR for all-cause mortality (Fig. 1), and the HR remained significantly elevated after adjustment for potential confounders [adjusted (adj) HR = 1.80, 95% CI: 1.57, 2.08; Fig. 2].

We found an effect modification by age, with the highest adjHR of 4.87 (95% CI: 1.93, 12.3) in the youngest age group (18–39 years), decreasing through age groups to 1.07 (95% CI: 0.79, 1.46) in the oldest age group (≥80 years). The risk of mortality was slightly higher in female patients (adjHR = 1.82, 95% CI: 1.56, 2.13) compared with male patients with SLE (adjHR = 1.68, 95% CI: 1.19, 2.39), but this difference was not statistically significant (P = 0.332). Comparison of all-cause mortality rates between the full CPRD cohort and the restricted CPRD-ONS cohort demonstrated comparable hazard ratios: HR = 1.82 (95% CI: 1.57, 2.08) in the CPRD cohort *vs* HR = 1.64 (95% CI: 1.40, 1.93) in the restricted CPRD-ONS cohort.

Cause-specific mortality (CPRD-ONS cohort)

Cause-specific mortality rates in SLE patients and matched controls using the ONS restricted dataset are shown in Table 3.

TABLE 2 Risk of all-cause mortality in SLE patients *vs* matched controls

	Deaths	Age/sex-adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
Full CPRD cohort			
No SLE	1.112	1	1
SLE	442	2.51 (2.23, 2.81)	1.80 (1.57, 2.08)
By age, years			
18–39	24	9.72 (4.98, 19.02)	4.87 (1.93, 12.32)
40–59	112	4.35 (3.37, 5.63)	2.58 (1.83, 3.64)
60–79	224	2.50 (2.13, 2.95)	1.80 (1.48, 2.19)
≥80	82	1.37 (1.06, 1.78)	1.07 (0.79, 1.46)
By sex[b,c]			
Males	81	2.26 (1.73, 2.95)	1.68 (1.19, 2.39)
Females	361	2.57 (2.26, 2.92)	1.82 (1.56, 2.13)
By SLE disease duration, years			
<1	71	3.08 (2.29, 4.14)	2.34 (1.62, 3.39)
1–4.9	179	2.70 (2.24, 3.25)	1.83 (1.45, 2.30)
5.0–9.9	113	2.27 (1.80, 2.86)	1.66 (1.25, 2.21)
≥10	79	2.27 (1.68, 3.07)	2.01 (1.40, 2.88)

Results are stratified by age, sex and SLE disease duration (full CPRD cohort). [a]Adjusted for potential confounders that change the β estimate by ≥5%: a history of seizures, chronic renal disease (estimated glomerular filtration rate <60 ml/min/1.73 m^2) and recent use of CSs, antimalarials or antidiabetics. [b]Not adjusted for sex. [c]Wald-test, males *vs* females: *P* = 0.332. CPRD: Clinical Practice Research Datalink; HR: hazard ratio.

After adjustment for potential confounders (history of seizures, renal disease and recent use of GCs, antimalarials or antidiabetics), mortality rates for cardiovascular disease, infectious disease, non-infectious respiratory disease and for death attributable to accidents or suicide were all significantly increased in SLE patients compared with age- and sex-matched subjects, whereas the mortality rate for cancer was reduced. Additional analyses did not demonstrate a statistical difference in reduced risks for mortality attributable to solid tumours (HR = 0.56, 95% CI: 0.38, 0.80) *vs* haematological malignancies (HR = 0.64, 95% CI: 0.35, 1.17), both compared with age- and sex-matched subjects.

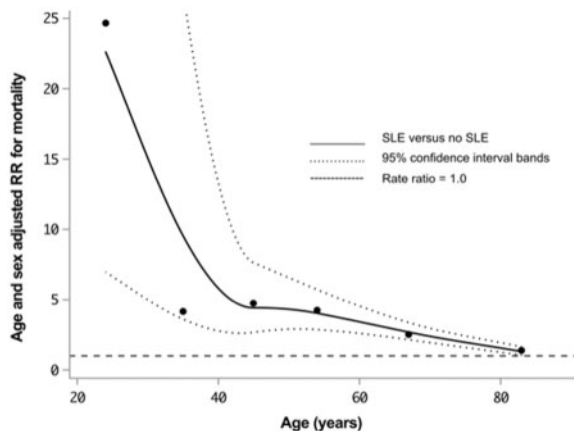### Determinants of all-cause mortality (full CPRD cohort)

Table 4 displays the risk of all-cause mortality within SLE patients, stratified by SLE treatment intensity, cumulative use of GCs or HCQ and the risk factors included in the SDI. Cumulative GC treatment was associated with an increased mortality rate. Cumulative use of HCQ was associated with a reduced mortality risk, but this association was significant only for the subgroup of HCQ users with the lowest cumulative exposure. Within SLE patients, dementia, seizures, renal disease, use of antidiabetics (as a proxy for diabetes mellitus) and a history of malignancy were all associated with an increased risk of mortality.

Discussion

The results of this study demonstrate a 1.8-fold increase in the all-cause mortality rate amongst patients with SLE compared with age- and sex-matched reference subjects. The risk for all-cause mortality was increased further with younger age and with cumulative systemic GC exposure, whereas the HR was decreased by 45% with exposure to cumulative low-dose HCQ. Furthermore, SLE patients had increased relative mortality rates for cardiovascular disease, infections, non-infectious respiratory disease and for death attributable to accidents or suicide. Moreover, the risk of mortality was increased in SLE patients in whom the disease course had been complicated by dementia, seizures, a cerebrovascular event, renal disease, diabetes, or malignancy, whereas the relative risk of mortality attributable to malignancy was reduced compared with matched reference subjects.

The observed overall 1.8-fold increase in mortality rate is in the lower range of findings from other population-based studies [4–6, 8–11] and a meta-analysis of 12 studies [7] reporting 1.4–5.0 times increased mortality rates in SLE patients compared with the general population, which might be explained by several factors. The first factor is the selection of SLE patients in our study from a general practitioners' database, in contrast to other population-based studies, in which patients were recruited from university hospitals providing tertiary care for SLE patients. It might be expected that a general practitioners' database contains

Fig. 1 Spline regression plot of age and RR for mortality in SLE patients *vs* matched controls

Adjusted for age and sex. RR: rate ratio.

Fig. 2 Spline regression plot of age and RR for mortality in SLE patients *vs* matched controls

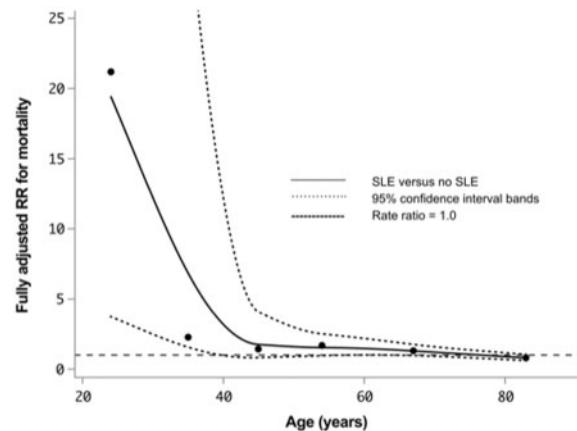Adjusted for confounders as shown in Table 2. RR: rate ratio.

relatively more SLE patients with a mild disease course, which might influence the mortality risk. The second factor is that differences in ethnic background, disease severity and medication use between patient populations might influence mortality risk.

The age-specific mortality risk was highest in the youngest age group, which is in concordance with previous studies reporting young age as a risk factor for mortality in SLE [5, 11].

Our study demonstrates an increased relative risk of mortality in both male and female patients with SLE, but no difference between sexes. This finding is confirmed by the results of a meta-analysis of population-based studies [7].

The association found between cumulative GC exposure and an increased risk of mortality is consistent with the results of two cohort studies. A prospective study in 168 SLE patients from Hong Kong [2] demonstrated high-dose GC treatment (either ≥1 mg/kg/day of oral prednisone or equivalent or pulse methylprednisolone therapy) as a predictor of mortality, independent of the presence or absence of organ damage. A study in 218 Chilean SLE patients showed that high-dose GC treatment of patients with more severe disease was associated with increased mortality [41]. We did not find a dose-dependent effect of GC exposure on mortality risk. This finding might be explained by the method used to assess cumulative GC exposure: in the present study, only oral GCs were taken into account because methylprednisolone pulses administered i.v. are not assessed in CPRD. We cannot exclude the possibility that a dose-dependent effect of exposure to GCs would have been found when oral GCs plus methylprednisolone pulses administered i.v. were taken into account.

HCQ use was associated with a 45% reduction in the mortality rate in SLE patients in the lowest cumulative dosage exposure group compared with non-users. This finding is in line with the results of two prospective

studies in 232 Spanish SLE patients [33] and in 803 SLE patients from Hong Kong [42] and with a case–control study in 608 patients from the LUMINA cohort [34] demonstrating significantly reduced mortality rates in antimalarial users *vs* non-users. In these studies, a conditional logistic regression model (including a propensity score) was used to assess the contribution of HCQ use to survival independent of clinical and socioeconomic–demographic characteristics, because SLE patients treated with antimalarials tend to have milder disease [33–35] and tend to have better socioeconomic status than non-users [34]. In addition, an inception cohort study in 1480 SLE patients from Latin America [35] demonstrated a 38% reduction in the mortality rate in antimalarial users *vs* non-users and suggested a time-dependent effect of antimalarial use on survival. Several mechanisms underlying the positive effects of antimalarials in patients with SLE have been reported. They reduce IFN production [43, 44] and have lipid-lowering effects [45] and favourable effects on glucose metabolism [46]. In addition, antithrombotic effects of antimalarials were demonstrated in animal studies [47] and in patients with SLE [33, 48]. Therefore, antimalarials might positively influence survival in patients with SLE by their anti-inflammatory and antithrombotic effects and their favourable effects on lipid and glucose metabolism, resulting in reduced risk of disease flares [49], less damage accrual [32] and fewer thrombotic [33] and vascular events, which might subsequently improve survival. However, the finding that HCQ use was protective only in the low cumulative dosage exposure group is remarkable and not fully explained. A possible explanation for this finding might be the occurrence of drug toxicity in the higher cumulative dosage exposure groups.

Our findings regarding cause-specific mortality are in accordance with other studies reporting an increased risk of death attributable to cardiovascular disease [5, 7, 21, 24], infections [5, 7, 18] and renal disease [3, 5, 7,

TABLE 3 Risk of mortality in SLE patients *vs* matched controls

	Deaths	Age/sex-adjusted HR (95% CI)	Fully adjusted HR[a] (95% CI)
CPRD-HES/ONS cohort			
No SLE	937	1	1
SLE			
All-cause mortality	335	2.18 (1.91, 2.48)	1.64 (1.40, 1.93)
By underlying cause of death[b]			
SLE			
SLE as any underlying cause	52	–	–
SLE as primary cause	17	–	–
Cardiovascular disease	149	2.49 (2.03, 3.04)	1.75 (1.37, 2.24)
Cancer	88	1.38 (1.08, 1.75)	0.65 (0.47, 0.90)
By type of cancer			
Solid tumours	73	1.32 (1.01, 1.72)	0.56 (0.38, 0.80)
Haematological malignancies	26	1.29 (0.83, 2.01)	0.64 (0.35, 1.17)
Infectious and respiratory disease	144	3.21 (2.60, 3.98)	1.91 (1.46, 2.48)
Non-infectious respiratory disease	60	2.91 (2.10, 4.03)	1.75 (1.16, 2.63)
Accidents and suicide	32	4.31 (2.65, 6.99)	3.17 (1.75, 5.73)
Other	47	2.71 (1.88, 3.89)	2.94 (1.92, 4.52)

Stratified by underlying cause of death (CPRD-ONS cohort). [a]Adjusted for potential confounders that change the β estimate by $\geq$5%: a history of seizures, renal disease and recent use of CSs, antimalarials or antidiabetics. [b]Sum of individual causes exceeds the number of 335 deaths, because multiple causes might have contributed to the same death. CPRD: Clinical Practice Research Datalink; HES: Hospital Episode Statistics; HR: hazard ratio; IR: incidence rate; ONS: Office of National Statistics.

TABLE 4 Determinants of all-cause mortality within SLE patients (full CPRD cohort)

	Deaths	Adjusted HR (95% CI)
SLE patients	442	–
By SLE treatment intensity (reference = no associated drug use)		
Low	78	1.60 (1.15, 2.23)
Medium	196	1.23 (0.83, 1.84)
High	99	1.07 (0.70, 1.65)
By cumulative DDD of systemic glucocorticoid exposure ever before among current users (reference = no current use)		
Any current use	251	2.60 (2.12, 3.20)
1–181	36	3.37 (2.35, 4.81)
182–730	49	2.06 (1.49, 2.85)
>730	166	2.66 (2.11, 3.35)
By cumulative DDD of HCQ exposure ever before among current users (reference = no current use)		
Any current use	111	0.85 (0.68, 1.06)
1–181	12	0.55 (0.31, 0.98)
182–730	40	0.85 (0.61, 1.19)
>730	59	0.95 (0.71, 1.26)
By a history of risk factors included in the SDI (reference = no risk factor)		
Dementia	14	2.99 (1.74, 5.14)
Seizures	37	2.33 (1.66, 3.28)
Cerebrovascular events	73	1.28 (0.99, 1.65)
Chronic renal disease	86	1.40 (1.09, 1.78)
Osteoporotic fracture	110	1.06 (0.85, 1.32)
Use of antidiabetics	45	1.90 (1.39, 2.59)
Malignancy	95	1.90 (1.50, 2.40)

[a]Adjusted for potential confounders that change the β estimate by $\geq$5%: a history of seizures, chronic renal disease (estimated glomerular filtration rate <60 ml/min/1.73 m^2) and recent use of CSs, antimalarials or antidiabetics. CPRD: Clinical Practice Research Datalink; DDD: daily defined dosage; HR: hazard ratio; IR: incidence rate; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

18, 21] in patients with SLE. Respiratory failure was demonstrated to be a predictor of short-term mortality among hospitalized patients with SLE [18].

Malignancy was the cause of death in 26.2% (88/335) of the SLE patients in our study. However, the mortality rate for cancer was reduced in SLE patients compared with reference subjects. This finding is in line with an international multicentre study [5] and two meta-analyses [7, 10] demonstrating no increased overall mortality attributable to malignancy in SLE.

Strengths of this study include the large study population and the linkage of a general practitioners' database, including data on medication exposure, to death certificate registration and the national hospitalization registry. This allowed us to assess relative age-, sex- and cause-specific mortality rates and to investigate associations between medication exposure and mortality.

This study also has limitations. We did not have data on disease activity and organ damage in the SLE patients. Therefore, we were not able to study the association between disease activity and mortality risk and between cumulative organ damage and risk of death. However, we examined the influence of disease severity on the risk of mortality by stratifying SLE patients according to their treatment severity in the previous 6 months, which may be regarded as a surrogate marker of disease severity in SLE. However, this stratification also included systemic GC exposure and antimalarial use and, therefore, it is not possible to differentiate definitively between influences of disease severity and those resulting from medication use. Another limitation is that data on socioeconomic status and ethnicity are available for only a subset of individuals in the CPRD. Limiting the study to these individuals would have led to a much smaller sample size; therefore, it was decided not to adjust for these confounders. Furthermore, we were not able to study the influence of cognitive impairment attributable to causes other than dementia on the risk of mortality within SLE patients, because we did not have data on cognitive impairment in general. In addition, assessment of disease-specific causes of death in SLE patients and matched controls could be performed only using data from the restricted CPRD-ONS cohort and, therefore, we cannot exclude the possibility that the results of these analyses might have been slightly different if they could have been performed using data from the full CPRD cohort. However, the restricted CPRD-ONS cohort still contains data from 2603 SLE patients and 13 050 matched controls and represents data from 60% of the individuals from the full CPRD cohort. Finally, we cannot exclude a possible loss of associations attributable to correction for several potential confounding factors in the fully adjusted analyses.

In summary, British patients with SLE have a 1.8-fold increased mortality rate compared with age- and sex-matched subjects. Young age and cumulative GC exposure further increased mortality, whereas low-dose HCQ use was associated with a 45% reduction in the risk of mortality. SLE patients had increased mortality rates for cardiovascular disease, infections, non-infectious respiratory disease and for death attributable to accidents or suicide, but a reduced risk of death attributable to malignancy compared with referent subjects. Further research is necessary to unravel the mechanisms behind the increased mortality in SLE and to develop interventions to improve survival.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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