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Association between organ damage and mortality in systemic lupus erythematosus: a systematic review and meta-analysis

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ABSTRACT

Objective At least half of patients with systemic lupus erythematosus (SLE) develop organ damage as a consequence of autoimmune disease or long-term therapeutic steroid use. This study synthesised evidence on the association between organ damage and mortality in patients with SLE.

Design Systematic review and meta-analysis.

Methods Electronic searches were performed in PubMed, Embase, Cochrane Library and Latin American and Caribbean Health Sciences Literature for observational (cohort, case-control and cross-sectional) studies published between January 2000 and February 2017. Included studies reported HRs or ORs on the association between organ damage (measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score) and mortality. Study quality was assessed using the modified Newcastle-Ottawa assessment. Pooled HRs were obtained using the DerSimonian and Laird random-effects model. Heterogeneity was assessed using the Cochrane Q (Q) and I^2 statistics.

Results The search yielded 10 420 articles, from which 21 longitudinal studies were selected. Most studies (85%) were of high quality. For 10 studies evaluating organ damage (SDI) as a continuous variable and reporting HR as a measure of association, a 1-unit increase in SDI was associated with increased mortality; pooled HR was 1.34 (95% CI: 1.24 to 1.44, p<0.001; Q p=0.027, I^2=52.1%). Exclusion of one potential outlying study reduced heterogeneity with minimal impact on pooled HR (1.33 (95% CI: 1.25 to 1.42), p<0.001, Q p=0.087, I^2=42.0%). The 11 remaining studies, although they could not be aggregated because of their varying patient populations and analyses, consistently demonstrated that greater SDI was associated with increased mortality.

Conclusions Organ damage in SLE is consistently associated with increased mortality across studies from various countries. Modifying the disease course with effective therapies and steroid-sparing regimens may reduce organ damage, improve outcomes and decrease mortality for patients with SLE.

Strengths and limitations of this study

- We report a systematic review with meta-analysis of high-quality studies across four continents that demonstrates a consistent association between systemic lupus erythematosus (SLE)-related organ damage and increased mortality.
- To our knowledge, this is the first meta-analysis informed by a systematic literature review investigating the association between organ damage, assessed by SDI (Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index), and mortality in patients with SLE.
- A meta-analysis was performed on 10 of 21 identified studies because of variations in methods used across studies; however, we observed consistency in the association between organ damage and mortality across multiple study design types with varying analytical methods.
- Although our search strategy was limited to studies published between 2000 and 2017, it is unlikely that inclusion of studies published after 2017 would change the observed result significantly, because of the consistency of the association between organ damage and mortality informed by the long patient follow-up periods of the studies analysed.
- Statistical evidence of study heterogeneity was identified, potentially attributable to the few studies included in the meta-analysis; however, exclusion of a potential outlying study reduced between-study heterogeneity to moderate, with minimal impact on the pooled association between organ damage and mortality.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease with a reported prevalence of 20 to 150 cases per 100 000 persons.[1] SLE is a chronic and debilitating disease characterised by flares, progressive end organ damage[2] and increased mortality.[3] SLE affects multiple organ systems,[1] including the kidneys, the skin, and

the cardiovascular, musculoskeletal and central nervous systems.[4] Approximately half of all patients with SLE will have some form of organ damage within 10 years of their diagnosis.[5] Furthermore, patients with SLE experience a higher rate of mortality and earlier mortality than the general population.[6]

SLE mortality is an important outcome to patients and providers and may be affected by accumulation of SLE-related organ damage. Organ damage potentially occurs through several different mechanisms. Hyperactive B cells are known to increase the formation and deposition of autoantibodies and immune complexes, which induce inflammatory tissue damage in the microvasculature.[1] In addition, long-term corticosteroid use is associated with an increased risk for the accumulation of organ damage, such as osteoporosis and cardiovascular disease.[7 8] Despite well-recognised adverse effects, corticosteroids are still widely used, in part because there is no optimal treatment for SLE.

Published literature suggests that the extent of accumulated organ damage in patients with SLE is associated with poorer health outcomes, including decreased physical functioning, reduced health-related quality of life and increased mortality.[3 9] Although there have been studies that report mortality in patients with SLE and organ damage, the extent to which organ damage is associated with increased mortality is unknown. We sought to aggregate available evidence on the association between organ damage, as measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), a validated instrument designed to measure irreversible damage in 12 different organ systems in patients with SLE, and risk of mortality through systematic review and meta-analysis.

METHODS AND ANALYSIS

This systematic literature review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[10] Methods of the inclusion criteria and analysis were specified in advance and documented in a study protocol, which underwent internal organisational review and approval prior to study initiation.

Literature search and screen

A systematic literature search of PubMed, Embase, Cochrane Library and Latin American and Caribbean Health Sciences Literature was performed to identify studies published between January 2000 and February 2017 that evaluated the association between organ damage (measured by SDI) and mortality, and the association between organ damage and health-related quality of life, in adults with SLE. This report presents findings on the association between organ damage and mortality. Results regarding the association between organ damage and health-related quality of life have been presented separately.[11] Search terms were chosen based on relevant free text keywords and Medical Subject Headings or Emtree-controlled vocabulary related to SLE and mortality. Details of the search terms for each database are provided in online supplementary appendix 1. Handsearching and citation review of relevant studies were conducted but did not identify additional studies that were not captured by the electronic database search.

Inclusion criteria included observational and case-control studies, cross-sectional studies and systematic reviews. Exclusion criteria included the following: non-English language articles, study designs that did not report original, population-level measures of association and studies of patients <18 years of age. Case series, case reports and studies with limited populations that are not generalisable were also excluded. Full inclusion/exclusion criteria are provided in online supplementary appendix 2. Clarivate Analytics EndNote X7 was used to organise the study titles and abstracts downloaded from the databases. One reviewer screened article titles and abstracts for selection according to inclusion and exclusion criteria. After article selection was complete, a panel of three investigators, working independently, re-examined 20% of the included articles to validate the quality of the initial selection process. Once validated, a full-text screening was conducted by two reviewers working independently to obtain the final set of articles.

Data extraction

Data extraction was performed by two independent reviewers, and discordances were adjudicated by a third independent reviewer. Data extraction forms were created for capturing study characteristics and outcomes reported in the identified studies, including characteristics such as the study country, organ damage, baseline SDI scores and duration of follow-up, which would inform interpretation of the associations of interest. Study quality was assessed using the modified Newcastle-Ottawa quality assessment scale.[12]

Data synthesis and meta-analysis

The primary quantitative analyses focussed on longitudinal cohort studies that assessed the risk of mortality per unit change in SDI. Pooled HRs were obtained using the DerSimonian and Laird random-effects model. A narrative evidence synthesis approach was used for studies that evaluated organ damage as binary based on varying SDI cut-points (SDI=0 vs >0; SDI<2 vs ≥2; SDI<3 vs ≥3 or SDI<5 vs ≥5) and that also reported varying measures of association, ORs and HRs.[5 13–32] Heterogeneity was assessed across studies using the Cochrane Q and I^2 statistics, with consideration given to clinical judgement. Cochrane Q tests with P values <0.10 suggest statistically significant heterogeneity, whereas cut-offs of 25%, 50% and 75% on the I^2 statistic are routinely used to demarcate low, medium and high levels of heterogeneity, respectively.[33–35] Sensitivity

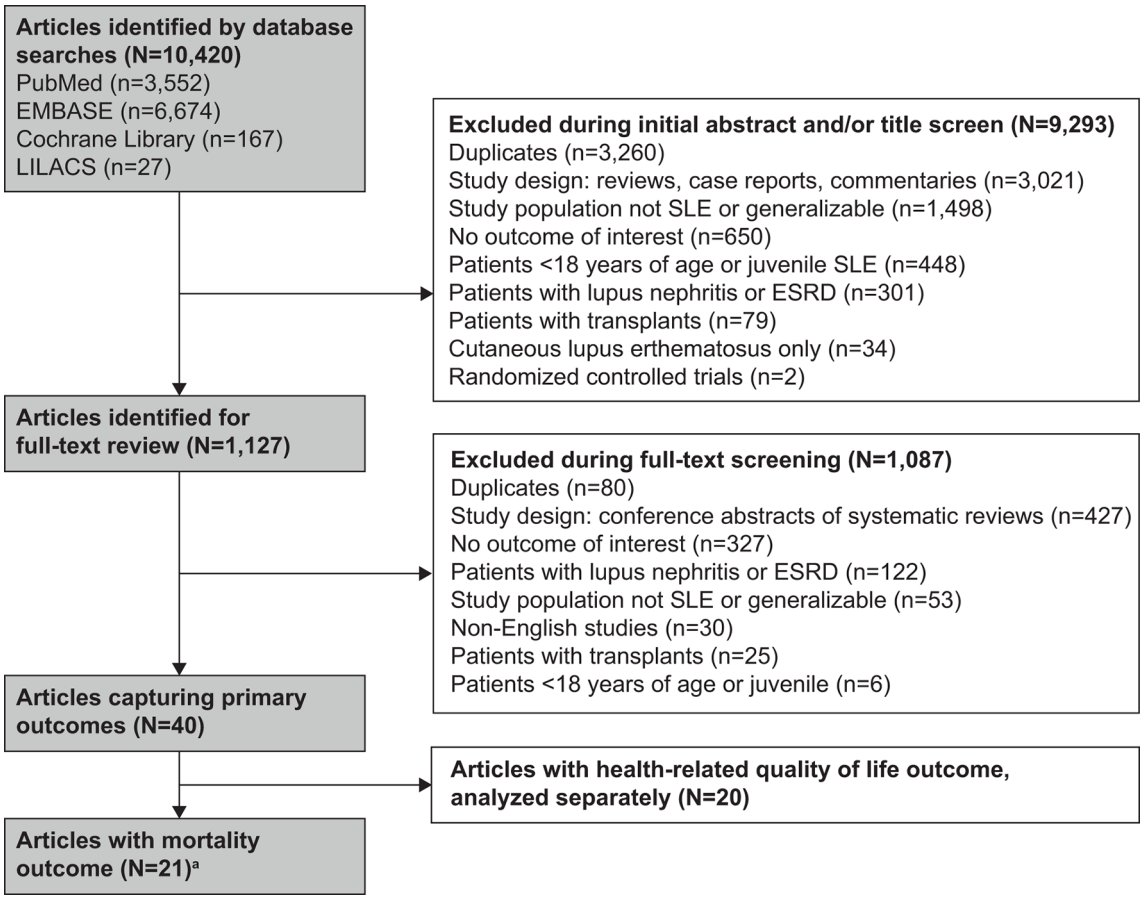

Figure 1 Flowchart of screening process. [a]One study included both health-related quality of life and mortality outcomes. Quality of life will be reported separately. ESRD, end-stage renal disease; LILACS, Latin American and Caribbean Health Sciences Literature; SLE, systemic lupus erythematosus.

analyses were performed to assess the effect of studies with outlying effect estimates. A funnel plot of included studies that reported HRs was visually inspected and Egger's test was used to quantify publication bias, where $p<0.05$ was considered statistically significant.

Patient and public involvement

Neither patients nor the public were involved in the design and conduct of the study. Dissemination of our findings, however, targets a wide audience including patients and members of the public and those who read peer-reviewed publications.

RESULTS

Characteristics of included studies

The combined literature search for mortality and health-related quality of life outcomes yielded 10 420 articles. We identified 1127 articles for full-text review. A total of 21 longitudinal cohort studies were selected that evaluated the association between organ damage and mortality in patients with SLE (figure 1).[5 13–32] Table 1 summarises key characteristics of these 21 identified studies (more detailed study characteristics are provided in online supplementary appendix 3). A total of 20 studies were identified that examine the association between organ damage and quality of life; these findings will be published separately.

The selected studies varied by sample size (ranging from 105 to 1241 patients), geographical location, duration of follow-up and methods by which the association between organ damage measured by SDI and mortality was evaluated.[5 13–32] Five studies reported on populations from North America;[16 28 29 31 32] the remaining 16 reported on populations from Asia,[15 20 21 26] Europe[5 17–19 25 27 30] or South America[14 23 24] or on populations across continents.[13 22] In 11 of the 21 studies, the mean or median reported age of participants (at either study enrolment, SLE onset or SLE diagnosis) was between 30 and 40 years;[5 14 16–19 22 27 29 30 32] six studies contained study groups (eg, patients with late-onset SLE) with a mean or median age >40 years,[13 21 24–26 32] and four contained study groups with mean age <30 years.[15 20 23 31] The populations studied were predominantly female (78% to 97%). The follow-up periods varied across studies—the shortest mean and median follow-up periods were 1.7 years[23] and 3.3 years,[14] respectively. The longest mean and median follow-up periods were 36 years[16] and 26 years,[13] respectively.

Table 1 Longitudinal studies examining the association between organ damage (measured by SDI) and mortality in patients with SLE, shown by use of SDI as continuous variable or binary category (n=21 studies)

Author (year)	Last year of data collection	Sample size	Follow-up duration (years), mean (median) [SD or range]	Baseline SDI, mean (median) [SD or range]	Associations between organ damage (SDI) and mortality		
					Estimator (95% CI)*	Reference group	Covariates†
SDI analysed as a continuous variable							
Mok *et al*[26]	2003	aSLE: 213 LSLE: 22 All: 285	Max 13	Year 1 aSLE: 0.4 [0.7] LSLE: 1.0 [1.1]	aSLE HR 3.65 (1.52 to 8.76) LSLE HR 2.46 (1.86 to 3.25)‡‡	1-point SDI increase in Year 1	Age, antibody, major organ disease, med dose, med use, sex, SLEDAI
Fernández *et al*‡[32]	2006	AA: 221 C: 176 H-PR: 103 H-T: 117	Max 12	Baseline, by race AA: 1.0 [1.4] C: 0.7 [1.1] H-PR: 0.3 [0.6] H-T: 0.6 [1.0]	OR 1.19 (1.02 to 1.39)	1-point SDI increase	Age, poverty, race, sex, SLAMR
Fernández *et al*‡[28]	NS	552	NS	F: 1.7 (1) M: 2.0 (1)	F HR 1.20 (1.00 to 1.44) M HR 1.48 (1.28 to 1.72)‡‡	1-point SDI increase	Age, poverty, race, sex, SF-6D, SLE activity
Hitchon, Peschken[31]	2001	C: 240 AO: 22 FN: 68 All: 330	NS	At diagnosis C: 0.03 [0.12] AO: 0.06 [0.24] FN: 0.09 [0.47]	RR 1.7 (0.8 to 3.7)§	1-point SDI increase	Antibody, education, race, renal damage, sex, SLE duration
Urowitz *et al*[16]	2005	All: 1241 I: 228 II: 364 III: 260 IV: 389	[9–36] I: 36 II: 27 III: 18 IV: 9	I: 0.4 [0.9] II: 0.3 [0.8] III: 0.3 [0.9] IV: 0.2 [0.8]	HR 1.24 (1.14 to 1.35)	1-point SDI increase	Age, AMS, entry cohort, race, sex, calendar period
Cardoso *et al*¶[24]	2007	Alive: 86 Died: 19 All: 105	(6.3) [0.3–7.0]	SDI=0: 18%	Baseline HR 1.34 (1.14 to 1.58) Study end HR 1.35 (1.16 to 1.57)	1-point SDI increase	Age, sex, SLE duration
Chambers *et al***[5]	2004	232	[10–25]	90% SDI=0 0.1 [NS] Year 1	HR 1.40 (1.14 to 1.72) HR 1.32 (1.09 to 1.60)‡‡	1-point SDI increase	Age
Jönsen *et al*[13]	2007	MLC: 499 LLC: 170 All: 669	MLC: (13) [1–50] LLC: Max 26	MLC: 2.5 [0–15]§ LLC: 2.0 [0–13]§	MLC HR 1.20 (0.97 to 1.48)§ LLC HR 1.40 (1.19 to 1.64)§ All HR 1.48 (1.37 to 1.60)§‡‡	1-point SDI increase	Age, APS, CCI, race, sex, SLEDAI
Kang *et al*[15]	2007	1010	Max 11	0.5 [1.0]	OR 19.7 (5.3 to 72.5)	1-point SDI increase	Age, med dose, med use
Lopez *et al***[27]	NS	350	(9)	SDI<3: 97% SDI=0: 73% SDI=1: 18% SDI≥2: 9%	HR 1.70 (p=0.001)	1-point SDI increase	Age, BILAG, ethnicity, med use, race, sex, SLE duration
Gafter-Gvili *et al*[21]	2010	143	9.4 (9.0) [3.3, 1–19]	0.9 [0–1.1]	HR 1.28 (1.08 to 1.50)	1-point SDI increase	Age, biomarker, sex
Telles *et al*[14]	2009	179	(3.3) [3.1–3.5]	SDI≥3: 26%	HR 1.40 (1.08 to 1.82)	1-point SDI increase	APS, med use
Bruce *et al*[22]	NS	671	NS	SDI=0: 81%	HR 1.46 (1.18 to 1.81)	1-point SDI increase	NS
Joo *et al*[20]	2012	979	7.2 [4.3, 0–15]	0.9 [1.5, 0–9]	HR 1.2 (1.0 to 1.4)	1-point SDI increase	Age, AMS, antibody, cSLE, sex, SLE duration
SDI analysed as a binary category							
Manger *et al*[19]	1999	338	(5.4)	Year 1 (2)	RR 7.7 (3.3 to 18.6)	ΔSDI<2, Year 1–3	Age, antibody comorbidities, sex

Continued

Table 1 Continued

Author (year)	Last year of data collection	Sample size	Follow-up duration (years), mean (median) [SD or range]	Baseline SDI, mean (median) [SD or range]	Associations between organ damage (SDI) and mortality		
					Estimator (95% CI)*	Reference group	Covariates†
Pons-Estel *et al*[23]	2000	1214	(1.7) [0–13.5]	0.6 [1.1]§ SDI=0: 66%§	OR 2.8 (1.2 to 6.4)§	SDI=0	Age, country, coverage, diagnosis delay, education, ever hospitalised, marital status, SES, sex
Becker-Merok *et al*[18]	NS	158	11.9 (10.2)	(1.26) [0–8]§ SDI=0: 97%	HR 1.44 (0.67 to 3.09)§	SDI<3	Age, sex, SLEDAI, SLEDAI weighted average
Cardoso *et al*¶[24]	2007	Alive: 86 Died: 19 All: 105	(6.3) [0.3–7.0]	SDI=0: 18%	Baseline HR 3.05 (1.13 to 8.23) Study end HR 4.74 (1.55 to 14.51) All HR 5.10 (1.99 to 13.03)	SDI<3 ΔSDI=0	Age, sex, SLE duration
Danila *et al*‡[29]	NS	635	NS	Renal SDI>0: 20% CV SDI>0: 9%	Renal SDI HR 1.65 (1.03 to 2.66) CV SDI HR 1.55 (0.94 to 2.56)	Renal SDI=0 CV SDI=0	Age, poverty, race, sex, SLAMR
Gustafsson *et al*[30]	2010	208	12.3	SDI≤1: 41%	HR 3.8 (1.3 to 16.4)	SDI<2	Age, arterial disease, biomarker
Martínez-Barrio *et al*[25]	2012	aSLE: 276 LSLE: 77	26	Mean [SD]/ SDI=0 aSLE: 1.7 [2.0]/36% LSLE: 2.5 [2.5]/21%	aSLE OR 12 (1.6 to 92)§ LSLE OR 19.4 (2.6 to 143.1)§‡‡	SDI=0	Age, musculoskeletal manifestations
Tarr *et al*[17]	NS	357	19.1 [9.2, 1–44]††	SDI=0: 22%§ SDI=1: 29%§ SDI=2: 17%§ SDI=3: 16%§ SDI=4: 7%§ SDI=5: 4%§ SDI=6–8: 5%§	HR 55.12 (19.15 to 158.63)	SDI<5	Med dose, sex

*Values are adjusted, unless otherwise noted.
†A few articles were unclear regarding all covariates; we have included only the covariates explicitly stated by the authors.
‡Publications with this footnote indicate different analyses based on data from the same cohort of patients, though specific patients included across studies likely differed. Two cohorts included in our review have multiple publications listed in this table.
§Values are SDI scores at end of follow-up or reported estimates based on SDI values at end of follow-up.
¶Cardoso *et al* (2008) did multiple analyses that are included in both continuous and binary sections of the table.
**Publications with this footnote indicate different analyses based on data from the same cohorts of patients, though specific patients included across studies likely differed. Two cohorts included in our review have multiple publications listed in this table.
††Tarr *et al* (2017) label these values as describing the follow-up duration in their manuscript text but use these same values (to two decimal places, not shown here) to describe their cohort's disease duration.
‡‡Unadjusted estimate.
AA, African-American; AMS, adjusted mean SLEDAI; AO, Asian-Oriental; APS, antiphospholipid syndrome; aSLE, adult-onset SLE; BILAG, British Isles Lupus Assessment Group; C, Caucasian; CCI, Charlson comorbidity index; cSLE, childhood-onset SLE; CV, cardiovascular; F, female; FN, First Nation, the predominant aboriginal peoples of Canada; H-PR, Hispanic (Puerto Rico); H-T, Hispanic (Texan); LLC, Lund Lupus Cohort; LSLE, late-onset SLE; M, male; med, medication; MLC, Montreal Lupus Cohort; NS, not stated; RR, relative risk; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SES, socioeconomic status; SF-6D, short-form six-dimension health survey; SLAMR, Systemic Lupus Activity Measure-Revised; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity.

Assessment of study quality

Most studies (85%) analysed were of high quality as measured using the Newcastle-Ottawa Scale (online supplementary appendix 4).[13–21 23–30 32] All 21 studies scored high regarding selection of patients who were representative of the population of adults with SLE in each country. All studies relied on secure clinical records to determine SLE diagnoses and extent of organ damage. Study quality differed with regard to analysis and follow-up cohort retention. Analyses were rated as adequate in 15 studies that adjusted for age and at least one other factor related to mortality;[13 15 16 18–21 23 24 26–30 32] the remaining studies either were not age adjusted (three studies),[14 17 31] were only adjusted for age (two studies)[5 25] or had no description of adjustment (one study).[22] In eight studies, less than 20% of the cohort was lost to follow-up;[14 17 19 20 24–26 30] four studies lost more than 20% to follow-up,[5 13 15 32] and nine studies did not report losses to follow-up.[16 18 21–23 27–29 31]

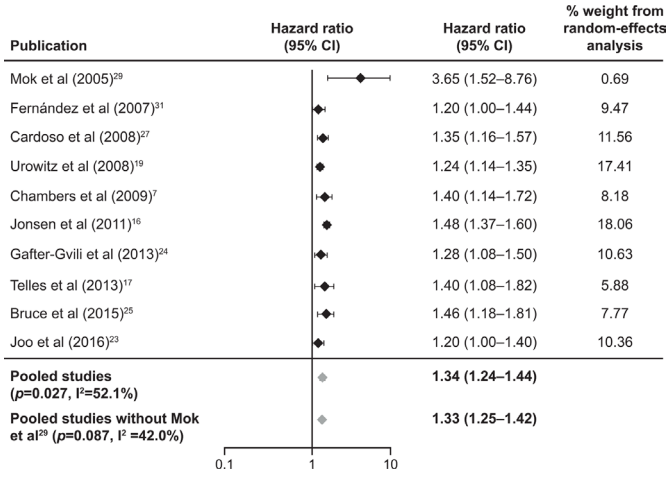

Figure 2 Forest plot of HRs for the association between organ damage (1-point increase in SDI) and mortality for studies included in the meta-analysis (n=10 studies). SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Mortality in patients with SLE

In all of the studies reviewed, standardised mortality ratios (SMRs) or survival rates were reported for patients with SLE. Four studies reported SMRs for patients with SLE relative to the general population within a specific country (online supplementary appendix 5).[16 19 20 30] The SMRs reported ranged from 2.4 over a 12-year period in a Swedish cohort,[30] 2.9 in a Korean cohort[20] over a 5-year period and 2.4 and 2.7 over 5-year and 10-year periods, respectively, in a German cohort.[19] Urowitz *et al*[16] reported on a cohort of Canadian patients with SLE and estimated a 36-year overall SMR of 4.5 in patients with SLE compared with the general population. When this study population was stratified into cohorts based on time of study entry, the reported SMRs varied widely: the 1970 to 1979 and 1996 to 2005 entry cohorts had 10-year SMRs of 12.6 and 3.5, respectively.[16]

Eight studies reported survival rates; six studies reported 5-year survival rates (range: 87% to 99%, in populations/subpopulations from Germany, China, the USA, South Korea and Hungary),[15 17 19 20 26 32] and two studies reported 4-year and 12-year survival rates of 95%[23] (Latin America) and 80%[30] (Sweden), respectively.

Organ damage and mortality

Table 1 summarises the key findings of the 21 included studies regarding organ damage and mortality (full data shown in online supplementary appendix 5). Baseline mean SDI scores ranged from 0.1 to 1.0 (SD range: 0.6 to 1.5). Across studies, SDI was evaluated as a continuous variable or binary category to assess the association between organ damage and mortality; SDI was evaluated as a continuous variable in 14 studies and as a binary category (comparing risk of mortality at various SDI score cut-offs) in eight studies. One study evaluated SDI both as a continuous variable and a binary category (table 1).[24]

Meta-analysis of organ damage and mortality

SDI evaluated as a continuous variable

Fourteen studies evaluated SDI as a continuous predictor of mortality.[5 13–16 20–22 24 26–28 31 32] Of these, 10 performed time-to-event analyses and reported the risk of death per 1-unit increase in SDI. These represent the group of studies that were pooled for meta-analysis. Figure 2 is a forest plot of HRs across the 10 studies included in the meta-analysis. Findings from meta-analysis suggest a 34% increased risk of death for each 1-point increase in SDI score (pooled HR 1.34, 95% CI: 1.24 to 1.44, p<0.001; Cochrane Q p=0.027, I^2=52.1%).

To account for study heterogeneity, the data were analysed excluding Mok *et al*,[26] which evaluated 213 Chinese patients over the course of 13 years and reported a notably greater risk of mortality per 1-unit SDI increase than other studies (HR 3.65, 95% CI: 1.52 to 8.76, p=0.004). The exclusion of the Mok *et al*[26] study reduced heterogeneity to moderate (Cochrane Q p=0.087, I^2=42.0%) but had minimal impact on pooled HR (pooled HR of mortality for a 1-unit increase in SDI=1.33 (95% CI: 1.25 to 1.42, p<0.001), figure 2).

A funnel plot representing HR of organ damage and mortality in patients with SLE was used to evaluate population bias (online supplementary appendix 6). Visual inspection of the funnel plot (excluding Mok *et al*[26]) identified marginal asymmetry, suggesting publication bias, whereas an Egger's test did not suggest publication bias (p>0.05). These findings should be interpreted with consideration given the few studies included in the meta-analysis.[36]

In addition to the studies summarised above in the meta-analysis, three studies that evaluated SDI as a continuous variable reported ORs for a 1-point increase in SDI; these ORs were 1.19 (95% CI: 1.02 to 1.39, p=0.031),[32] 1.70 (95% CI: 0.80 to 3.70, p>0.05)[31] and 19.70 (95% CI: 5.30 to 72.50, p<0.001)[15] (figure 3). The largest likelihood of mortality observed suggests approximately 20-fold increased odds of mortality for a 1-point increase in organ damage, among 1010 patients evaluated in South Korea.[15]

SDI evaluated as binary categories

Of eight analyses that evaluated SDI as binary categories, two assessed the odds of death associated with any organ damage compared with no organ damage (SDI=0 vs SDI>0),[23 25] and four studies,[17 18 24 30] compared the risk of mortality by various SDI categories (SDI<2 vs SDI≥2; SDI<3 vs SDI≥3 or SDI<5 vs SDI≥5) (figure 3). Pons-Estel *et al*[23] studied 1214 patients from Latin America (including 537 mestizo, 507 white and 152 African-Latin American patients) who had been diagnosed with SLE within the previous 2 years. Over a median follow-up period of 20 months, Pons-Estel *et al* reported increased odds of death associated with any organ damage, SDI≥1 vs SDI=0, in patients with SLE (OR 2.8, 95% CI: 1.2 to 6.4). In Spain, Martínez-Barrio *et al*[25] studied 276 patients with adult-onset SLE and 77 patients with late-onset

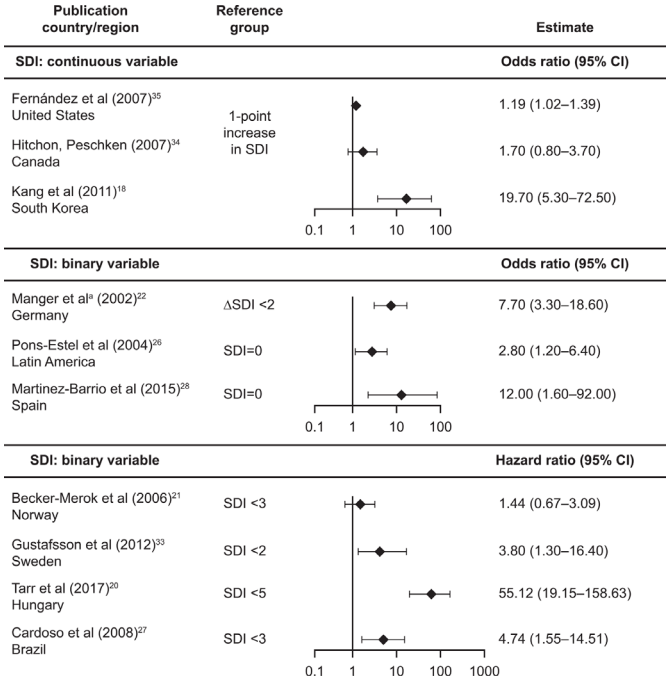

Figure 3 Forest plot of association between organ damage and mortality in remaining studies with SDI as a continuous or binary variable. [a]Reports the relative risk. SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

SLE over a mean 26-year follow-up period and reported significantly increased odds of death associated with any organ damage, SDI=0 vs SDI>0 (OR 12, 95% CI: 1.6 to 92, p=0.01). Other studies reported the odds of death associated with having an SDI≥2 vs SDI<2 (208 patients from Sweden; HR 3.80, 95% CI: 1.30 to 16.40, p=0.01),[30] SDI≥3 vs SDI<3 (105 patients from Brazil; HR 4.74, 95% CI: 1.55 to 14.51, p=0.006)[24] or SDI≥5 vs SDI<5 (357 patients from Hungary; HR 55.12, 95% CI: 19.15 to 158.63, p<0.001).[17] In the study by Becker-Merok and Nossent[18] from Norway (n=158), the authors reported a positive association between greater organ damage and increased mortality risk (SDI≥3 vs SDI<3, HR 1.44, 95% CI: 0.67 to 3.09, p=0.42), although this was not statistically significant.

Two studies identified that additional organ damage accrued during study follow-up was significantly associated with increased risk of mortality.[21 24] In the study by Cardoso *et al*[24] including 105 patients from Brazil, any increase in SDI during follow-up was associated with a significant increase in risk of mortality compared with no change in SDI (HR 5.1, 95% CI: 1.99 to 13.03, p=0.001).[24] Similarly, in 338 patients in Germany, Manger *et al*[19] found nearly eightfold increase in mortality with organ damage accrual (ΔSDI≥2 vs ΔSDI<2 from the first to the third year of follow-up; relative risk 7.7, 95% CI: 3.3 to 18.6, p<0.0001).

Danila *et al*[29] evaluated the association between specific organ damage and mortality in a multi-ethnic cohort of 635 patients from the USA. This analysis identified significantly greater risk of earlier death for patients with SLE who had renal damage compared with those without renal damage (HR 1.65, 95% CI: 1.03 to 2.66, p≤0.05). There was, however, no significant association between cardiovascular damage and earlier death (HR 1.55, 95% CI: 0.94 to 2.56, p>0.05).[29]

DISCUSSION

In this meta-analysis of 10 studies from four continents that evaluated the risk of death among individuals with SLE who had organ damage, we identified that each 1-unit increase in SDI was associated with a 34% increased risk of death. We also identified an increased risk and consistent association between increasing organ damage and greater mortality in all 21 articles that were retained for this systematic review. The increased risk of death associated with organ damage was present across studies from various countries and different patient populations, as well as across studies that used varying epidemiological and statistical methods. It is notable that the association between incremental organ damage and mortality was largely consistent, despite the differences in healthcare delivery systems and life expectancy across countries. The magnitude of the estimated associations between organ damage and mortality varied and may be attributable to differences in how SDI was modelled (eg, as a continuous variable or binary category), the thresholds of SDI used for analysis, and the choice of covariates accounted for when multivariable analyses were performed.

From 1950 to 2000, the 10-year survival rate in patients with SLE has improved from 63% to 91%,[37] and it is postulated that improvements in patient management are responsible for these gains in survival. Despite such positive achievements, it is clear that further gains are needed. Optimising treatment to obtain good control of SLE disease is important for reducing organ damage and mortality risk. For treatment of patients with SLE, the Treat to Target (T2T)/SLE international task force has outlined several overarching principles, including optimising disease control, minimising comorbidities, reducing drug toxicities to enable long-term survival, preventing organ damage and enhancing health-related quality of life.[38]

The T2T task force highlighted the importance of minimising glucocorticoid dosages and eliminating them entirely, if possible. As with other rheumatological diseases, studies of patients with SLE have shown that greater systemic steroid dosage is associated with increasing damage to multiple body systems.[8] New treatments for SLE that would allow steroid sparing would be clinically important for reducing organ damage and improving outcomes for patients.

To our knowledge, this is the first meta-analysis informed by a systematic literature review to quantitatively synthesise published literature on SLE-related organ damage measured by SDI and its association with mortality. We observed some heterogeneity in the studies included in these meta-analyses. However, sensitivity analyses demonstrated that exclusion of one study,[26]

which reported a notably greater HR than other studies, reduced heterogeneity with minimal impact on pooled HR. The search criteria excluded studies published in languages other than English, which may represent a bias in reporting; however, there is limited evidence to suggest language bias with this approach. Morrison *et al*[39] conducted a comprehensive literature review and found no evidence of systematic bias from the use of language restrictions in systematic review-based meta-analyses. Because our search strategy was restricted to the inclusion of publications identified between 2000 and 2017, if there are relevant studies published after 2017, they are not included in this analysis. This is a limitation of our work; however, because of the consistency of our findings across a large number of studies and geographical regions, and long patient follow-up periods for included studies ranging from a few years to 50 years, it is unlikely that studies published after 2017, or in languages other than English, would significantly affect the observed association between organ damage and mortality. An update on the available evidence in the next few years would allow an expanded assessment of the effect of newer treatments on organ damage and how this may be associated with mortality in patients with SLE. In the current study, we were unable to summarise across all identified studies using meta-analytic methods because of variations in methods used across studies. Ten of 21 studies were combined in meta-analysis and the remaining 11 studies were summarised qualitatively. The consistency of the results across multiple study design types and varying methods of analyses corroborates our overall conclusions.

A previous qualitative review, based on studies prior to 2012, supports our findings. A systematic review by Sutton *et al*[40] included five studies examining the association between organ damage and risk of death in patients with SLE. All five studies confirmed a positive association between higher SDI scores and mortality.[40] For example, one study included in the Sutton meta-analysis found a significantly higher 10-year mortality rate (25%) in patients with early damage (SDI≥1 at enrolment) than in patients with no early damage (7.3%, p<0.001).[40]

Biological therapy has recently become available for the treatment of SLE.[41] However, none of the studies we evaluated examined how specific drugs may mediate the association between organ damage and mortality, perhaps because of the relatively short period since biologics were introduced for SLE. Thus, future studies assessing the impact of various SLE therapies, including steroids and biologic treatment, on organ damage and consequent mortality will be needed.

CONCLUSIONS

Organ damage in patients with SLE is consistently associated with increased mortality across studies from around the world that evaluated different patient populations using various study methods. Novel therapies that are potentially disease modifying and steroid sparing could reduce organ damage, improve overall outcomes and decrease mortality for patients with SLE.

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REFERENCES

1 Maidhof W, Hilas O. Lupus: an overview of the disease and management options. *P T* 2012;37:240–9.
2 Taraborelli M, Cavazzana I, Martinazzi N, *et al*. Organ damage accrual and distribution in systemic lupus erythematosus patients followed-up for more than 10 years. *Lupus* 2017;26:1197–204.
3 Mak A, Cheung MW-L, Chiew HJ, *et al*. Global trend of survival and damage of systemic lupus erythematosus: meta-analysis and meta-regression of observational studies from the 1950s to 2000s. *Semin Arthritis Rheum* 2012;41:830–9.

4 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.
5 Chambers SA, Allen E, Rahman A, *et al*. Damage and mortality in a group of British patients with systemic lupus erythematosus followed up for over 10 years. *Rheumatology* 2009;48:673–5.
6 Carter EE, Barr SG, Clarke AE. The global burden of SLE: prevalence, health disparities and socioeconomic impact. *Nat Rev Rheumatol* 2016;12:605–20.
7 Al Sawah S, Zhang X, Zhu B, *et al*. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins lupus cohort. *Lupus Sci Med* 2015;2:e000066.
8 Thamer M, Hernán MA, Zhang Y, *et al*. Prednisone, lupus activity, and permanent organ damage. *J Rheumatol* 2009;36:560–4.
9 McElhone K, Abbott J, Teh LS. A review of health related quality of life in systemic lupus erythematosus. *Lupus* 2006;15:633–43.
10 Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
11 Hammond ER MI, Lin DH, *et al*. SAT0428 association between organ damage and health-related quality of life in systemic lupus erythematosus (SLE): a systematic review. *Ann Rheum Dis* 2018;77:1073–4.
12 Wells GA, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2011. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
13 Jönsen A, Clarke AE, Joseph L, *et al*. Association of the Charlson comorbidity index with mortality in systemic lupus erythematosus. *Arthritis Care Res* 2011;63:1233–7.
14 Telles RW, Lanna CCD, Souza FL, *et al*. Causes and predictors of death in Brazilian lupus patients. *Rheumatol Int* 2013;33:467–73.
15 Kang KY, Kwok S-K, Ju JH, *et al*. The causes of death in Korean patients with systemic lupus erythematosus over 11 years. *Lupus* 2011;20:989–97.
16 Urowitz MB, Gladman DD, Tom BDM, *et al*. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. *J Rheumatol* 2008;35:2152–8.
17 Tarr T, Papp G, Nagy N, *et al*. Chronic high-dose glucocorticoid therapy triggers the development of chronic organ damage and worsens disease outcome in systemic lupus erythematosus. *Clin Rheumatol* 2017;36:327–33.
18 Becker-Merok A, Nossent HC. Damage accumulation in systemic lupus erythematosus and its relation to disease activity and mortality. *J Rheumatol* 2006;33:1570–7.
19 Manger K, Manger B, Repp R, *et al*. Definition of risk factors for death, end stage renal disease, and thromboembolic events in a monocentric cohort of 338 patients with systemic lupus erythematosus. *Ann Rheum Dis* 2002;61:1065–70.
20 Joo YB, Park S-Y, Won S, *et al*. Differences in clinical features and mortality between childhood-onset and adult-onset systemic lupus erythematosus: a prospective single-center study. *J Rheumatol* 2016;43:1490–7.
21 Gafter-Gvili A, Leibovici L, Molad Y. Elevation of inflammatory markers in patients with systemic lupus erythematosus is associated with poorer outcome. *Biomed Pharmacother* 2013;67:48–52.
22 Bruce IN, O'Keeffe AG, Farewell V, *et al*. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the systemic lupus international collaborating clinics (SLICC) inception cohort. *Ann Rheum Dis* 2015;74:1706–13.
23 Pons-Estel BA, Catoggio LJ, Cardiel MH, *et al*. The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". *Medicine* 2004;83:1–17.
24 Cardoso CRL, Signorelli FV, Papi JAS, *et al*. Initial and accrued damage as predictors of mortality in Brazilian patients with systemic lupus erythematosus: a cohort study. *Lupus* 2008;17:1042–8.
25 Martínez-Barrio J, Ovalles-Bonilla JG, López-Longo FJ, *et al*. Juvenile, adult and late-onset systemic lupus erythematosus: a long term follow-up study from a geographic and ethnically homogeneous population. *Clin Exp Rheumatol* 2015;33:788–94.
26 Mok CC, Mak A, Chu WP, *et al*. Long-Term survival of southern Chinese patients with systemic lupus erythematosus: a prospective study of all age-groups. *Medicine* 2005;84:218–24.
27 Lopez R, Davidson JE, Beeby MD, *et al*. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. *Rheumatology* 2012;51:491–8.
28 Fernández M, Alarcón GS, McGwin G, *et al*. Using the short form 6D, as an overall measure of health, to predict damage accrual and mortality in patients with systemic lupus erythematosus: XLVII, results from a multiethnic US cohort. *Arthritis Rheum* 2007;57:986–92.
29 Danila MI, Pons-Estel GJ, Zhang J, *et al*. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. *Rheumatology* 2009;48:542–5.
30 Gustafsson JT, Simard JF, Gunnarsson I, *et al*. Risk factors for cardiovascular mortality in patients with systemic lupus erythematosus, a prospective cohort study. *Arthritis Res Ther* 2012;14:R46.
31 Hitchon CA, Peschken CA. Sm antibodies increase risk of death in systemic lupus erythematosus. *Lupus* 2007;16:186–94.
32 Fernández M, Alarcón GS, Calvo-Alén J, *et al*. A multiethnic, multicenter cohort of patients with systemic lupus erythematosus (SLE) as a model for the study of ethnic disparities in SLE. *Arthritis Rheum* 2007;57:576–84.
33 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
34 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
35 Bowden J, Tierney JF, Copas AJ, *et al*. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RCTs using standard and generalised Q statistics. *BMC Med Res Methodol* 2011;11:41.
36 Lau J, Ioannidis JPA, Terrin N, *et al*. The case of the misleading funnel plot. *BMJ* 2006;333:597–600.
37 Kaul A, Gordon C, Crow MK, *et al*. Systemic lupus erythematosus. *Nat Rev Dis Primers* 2016;2:16039.
38 van Vollenhoven RF, Mosca M, Bertsias G, *et al*. Treat-to-target in systemic lupus erythematosus: recommendations from an international Task force. *Ann Rheum Dis* 2014;73:958–67.
39 Morrison A, Polisena J, Husereau D, *et al*. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care* 2012;28:138–44.
40 Sutton EJ, Davidson JE, Bruce IN. The systemic lupus international collaborating clinics (SLICC) damage index: a systematic literature review. *Semin Arthritis Rheum* 2013;43:352–61.
41 Touma Z, Gladman DD. Current and future therapies for SLE: obstacles and recommendations for the development of novel treatments. *Lupus Sci Med* 2017;4:e000239.