Measuring Disease Activity and Damage with Validated Metrics: A Systematic Review on Mortality and Damage in Systemic Lupus Erythematosus

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ABSTRACT. *Objective.* To identify the effect of disease activity and damage, measured by validated indices, on mortality and damage accrual, in order to inform upcoming Canadian systemic lupus erythematosus (SLE) recommendations.

Methods. Following GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology to fill in evidence-to-decision tables to create recommendations for "minimal investigations needed to monitor SLE patients at baseline and subsequent visits," a systematic literature review was performed. The effect of disease activity and damage, measured by validated metrics, on mortality and damage was systematically reviewed, with metaanalyses performed when available.

Results. A title/abstract screen of 5599 articles identified 816 articles for full paper review, with 102 meeting inclusion criteria and 53 with extractable data. Thirty-three articles describing outcomes related to disease activity and 20 articles related to damage were identified. Mortality was associated with higher SLE Disease Activity Index-2000 scores in 6 studies (HR 1.14, 95% CI 1.06–1.22) and higher Systemic Lupus International Collaborating Clinics/ACR Damage Index scores in 6 studies (HR 1.53, 95% CI 1.28–1.83). Higher SLE Activity Measure scores were associated with increased risk of damage in 3 studies (OR 1.06, 95% CI 1.04–1.08). British Isles Lupus Assessment Group was associated with mortality in 1 study with HR of 1.15.

Conclusion. Active SLE disease and damage are associated with and predict greater mortality and damage. The use of validated disease activity and damage metrics is important in the assessment of disease activity and damage and will inform upcoming Canadian recommendations for the assessment of SLE. (J Rheumatol First Release August 15 2018; doi:10.3899/jrheum.171310)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS   DISEASE ACTIVITY
DISEASE DAMAGE   MORTALITY

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Systemic lupus erythematosus (SLE) is a complex autoimmune disease that includes targeted autoantibody production, resulting in heterogeneous disease phenotypes[1]. Manifestations vary considerably, requiring careful in-depth clinical assessments to clearly define the degree of disease activity. Disease damage is another important domain in the assessment of patients with SLE, driven both by the burden of disease activity, glucocorticoids, and immunosuppressant exposure[2]. As a result, the contribution of both disease activity and damage leading toward further damage and mortality in SLE is increasingly recognized by physicians treating SLE.

Despite the important relative contributions of disease activity and damage toward SLE outcomes, clinical assessment of patients varies among rheumatologists. Formalized assessments with the use of validated outcome measures of disease activity and damage are largely

performed in tertiary care centers that are systematically collecting SLE outcomes for research. A practice pattern survey of Canadian rheumatologists revealed that most were not formally evaluating disease activity or damage using standardized metrics [e.g., validated disease activity instruments such as the SLE Disease Activity Index (SLEDAI)][3]. This is in contrast to other rheumatic diseases such as rheumatoid arthritis (RA) or spondyloarthritis (SpA), in which validated composite measures of disease activity have been integrated more commonly into clinical practice to facilitate treat-to-target care and medication reimbursement.

Recommending regular performance of validated measures of SLE disease activity and damage in clinical practice is complicated because of many factors including appropriateness in the clinic setting and rheumatologists' familiarity with available instruments. Moreover, the association between the measured constructs in these validated measures and the important physician-driven outcomes of mortality and damage in the short term and long term require analysis. Therefore, the goal of this systematic literature review was to collect existing evidence for the effect of disease activity and damage when measured with validated metrics on mortality and damage in patients with SLE. This summary of evidence will inform upcoming Canadian recommendations for the assessment of SLE using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.

MATERIALS AND METHODS

A survey of 175 Canadian rheumatologists to evaluate practice patterns for the diagnosis, monitoring, and treatment of patients with SLE was completed in 2012 and served as the basis for future Canadian SLE recommendations[3]. The question of disease activity/damage evaluation as part of patient assessment/monitoring over time arose from this survey, serving as the basis for this systematic literature review. Patient-reported outcomes (PRO) were not included in this analysis owing to the heterogeneity of outcome measures, and difficulties applying this in a clinical context, knowing that PRO and disease activity/damage are independent domains in the assessment of SLE and in general not associated with disease activity/damage. Moreover, disease flares were discussed but not included in the measured outcomes because of the difficulties in finding homogeneous definitions among studies.

Search strategy. The effects of disease activity and damage, using validated metrics, on the outcomes of damage accrual [measured by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and mortality were assessed. A list of candidate disease activity and damage measures was identified by the group through the American College of Physicians[4] Journal Club, UptoDate, and existing systematic reviews on the subject. A final list of candidate measures of disease activity/damage was circulated and discussed by teleconference by the group and submitted to the librarian (TC) as part of the search criteria. Relevant articles were identified by searching OVID Medline (1946 to July 2016), OVID Embase (1974 to July 2016), and the Cochrane Library (inception to July 2016). Conference abstracts retrieved from Embase were also reviewed. The search strategy was broad to address 2 PICO (population, intervention, comparison, outcome), the first relating to validation studies for disease activity and damage measures (not the subject of this review). The second PICO and focus of this review evaluated the following: population = SLE; intervention = disease activity and damage scores; comparison = self; outcome(s) = worse disease activity, damage, and mortality.

Terms were searched as keywords and/or subject headings as appropriate (Supplementary Data 1, available with the online version of this article) and duplicate references were removed within RefWorks. Studies were limited to those involving humans, and exclusions included non-English abstracts, case reports, editorials, and review articles. Bibliographies of review and guideline articles were hand-searched for articles meeting the inclusion criteria. The dataset from this search was used to inform GRADE recommendations for SLE assessment and monitoring in Canada. Ethics approval was not required because this was a systematic literature review.

Data collection and analysis. Title/abstract screening was performed by 2 reviewers (SOK/AB) and full paper review divided among SOK/JM/ZT/NT/JP/ZA/AB. Disagreements at the title screening and full paper level were discussed and consensus reached. A prespecified Excel spreadsheet for inclusion/exclusion criteria and data extraction was created to reduce data extraction error. Data extraction included publication information (year/author), study site(s), study design, patient population, sample size, outcome measure(s) used (e.g., specific disease activity or damage measure), comparator measures, and outcomes assessed [mortality, damage (free text for specific damage data)].

Data analyses included descriptive statistics. Mortality and damage outcomes were pooled using a DerSimonian Laird random effects model when enough data were available for studies using validated disease activity and damage measures (BV). The statistical heterogeneity was assessed with the I^2 test statistic with the following interpretations: 25–49% low heterogeneity; 50–74% moderate, and ≥ 75% high heterogeneity[5]. Pooled relative risks (RR) and OR with 95% CI comparing dead versus surviving patients with higher disease activity and damage were also calculated. Data from cohorts with multiple studies were included only once. Study quality was assessed using the Newcastle-Ottawa scale for observational studies[6].

RESULTS

We identified 816 papers for full review. Fifty-three met the specific inclusion criteria for mortality and damage outcomes from high disease activity or damage scores after removing 33 for evaluating PRO (e.g., the Medical Outcomes Study Short Form-36 questionnaire, fatigue). These were the most common reasons for data exclusion: (1) not meeting the inclusion criteria (664 articles); (2) not being in English (18 articles); (3) being reviews (14 articles); and (4) involving rheumatic diseases other than SLE (14 articles). Thirty articles described outcomes related to disease activity measures [British Isles Lupus Assessment Group (BILAG), SLEDAI, European Consensus Lupus Activity Measure (ECLAM), and SLE Activity Measure (SLAM)] and 23 related to damage measures (SDI and Brief Index of Lupus Damage; Figure 1)[7].

Disease activity outcome measures. Four different disease activity measures were evaluated (Table 1[8-61]) including the BILAG index, the SLEDAI and its derivations [SLEDAI-2K, Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI, Mexican SLEDAI], with 30 studies in total. The majority (23) of studies were prospective, 9 were retrospective, 1 study was from a randomized control trial, 1 from an SLE clinical trials registry, and 2 were observational cohorts not otherwise specified. Higher mortality was noted in 6 studies[14,22,23,35,37,38] evaluating the effect of higher SLEDAI scores at baseline or over time (weight-adjusted HR
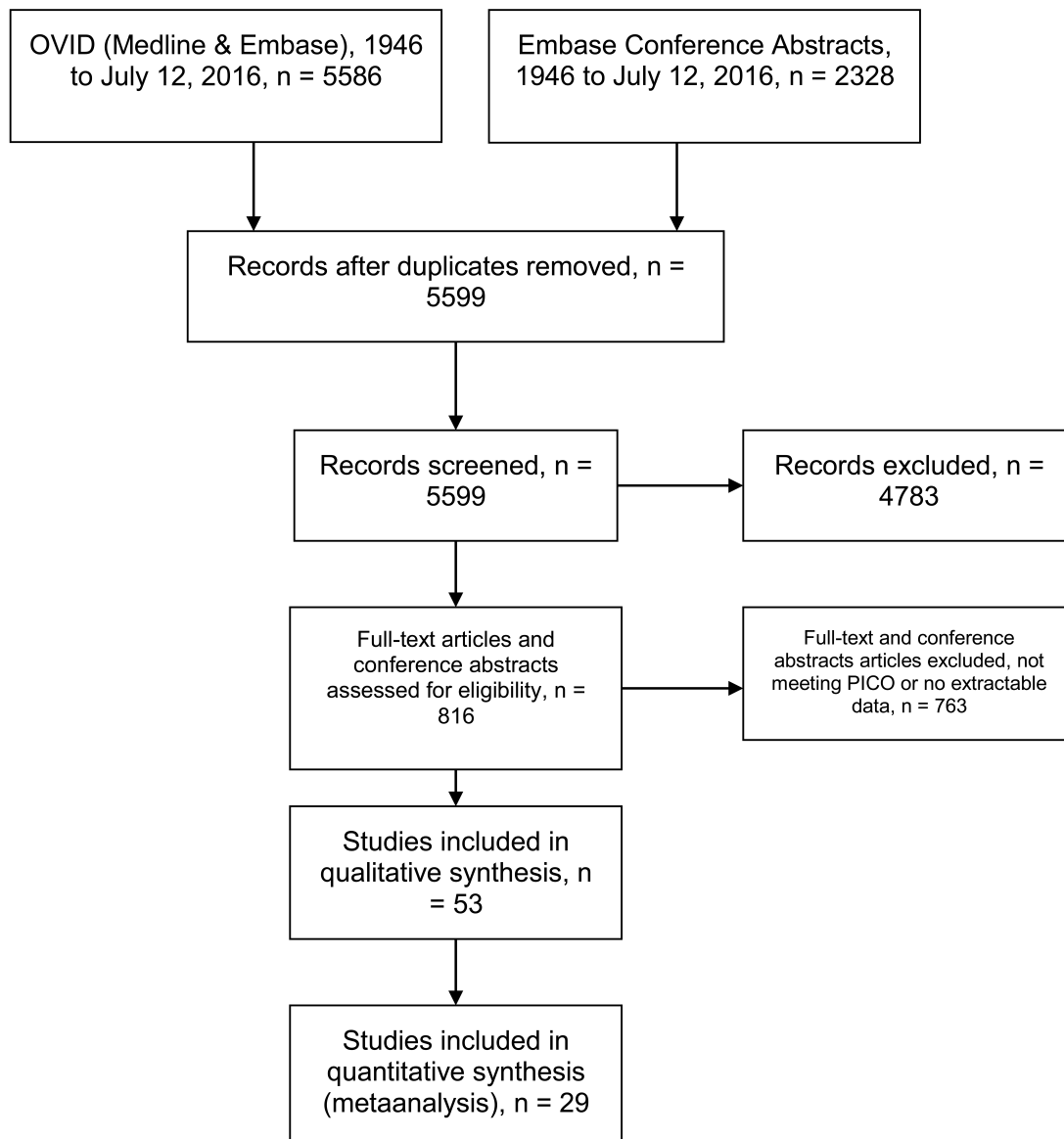
Figure 1. PRISMA diagram for systematic literature review and metaanalysis. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; PICO: population, intervention, comparison, outcome. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PLoS Med 2009;6(7):e1000097. Distributed under the terms of the Creative Commons Attribution License.

1.14, 95% CI 1.06–1.22; Figure 2). Sensitivity analyses evaluating the effect of higher baseline SLEDAI and higher time-adjusted SLEDAI [e.g., adjusted mean SLEDAI (AMS)] on mortality demonstrated a greater but not statistically significant mortality risk, with HR of 1.13 (95% CI 0.99–1.28) for baseline SLEDAI[35,37,38] and HR 1.19 (95% CI 0.99–1.43) for time-adjusted SLEDAI (data not shown)[14,20,21,22,23].

A greater risk of mortality was found in patients with SLE with over 10 years of followup[14,22,23,38] (HR 1.13, 95% CI 1.06–1.21) compared to those with < 10 years of follow-up[35,37] in a sensitivity analysis (HR 1.98, 95% CI 0.53–7.49). Although increasing age is a significant risk factor for

mortality, the majority of these patients were young adults, in whom the relative contribution of age to death is less significant. Three studies (Figure 2) demonstrated higher SLEDAI scores in dead versus living patients with SLE[29,32,39], and the odds of mortality were greater (OR 1.13, 95% CI 1.06–1.22) in SLE patients with higher SLEDAI disease activity[25].

Higher disease activity scores were also associated with greater damage in patients with SLE (Figure 3). Three studies[18,24,25] demonstrated greater damage in patients with higher SLEDAI scores at baseline with OR 1.08 (95% CI 1.03–1.12; Figure 3). Four studies[14,15,21,30] demonstrated

Table 1. Characteristics of all studies evaluating relationship between SLE disease activity and damage measures on the outcomes of mortality and damage accrual.

Study (Composite Measure)	N	Design	Population	Outcome	Study Details	Newcastle-Ottawa Quality Rating (no. stars)
BILAG (British Isles Lupus Assessment Group score for disease activity; BILAG or BILAG 2004)						Low risk of bias*
Furie, 2009[8]	321	RCT	Adult, phase II RCT (retrospective application of the SRI).	Non-renal morbidity	Belimumab treatment resulted in a statistically larger percentage of responders than treatment with placebo	
Hay, 1993[9]	353	Prospective observational cohort	Adult, multicentered, England. Median disease duration 9.5 yrs (range 0–58).	Non-renal morbidity	Validation of the BILAG Index (interrater, criterion, construct validity)	6
Lopez, 2012[10]	350	Prospective observational cohort	Adult, SLE clinic, London, UK. Median disease duration (at T_0) 6 yrs (0–34).	Mortality, renal morbidity, damage	Mean total BILAG score associated with mortality, new organ damage and CV/pulmonary or musculoskeletal damage. Pre-existing SDI = independent predictor of mortality and further organ damage.	8
Stoll, 2000[11]	141	Prospective observational cohort	Adult, SLE outpatient clinic. Mean disease duration 10.2 yrs (SD 6.3).	Damage	Total damage score (OR 1.46, 95% CI 1.04–2.05) and health perception (OR 0.96, 95% CI 0.93–0.99) at inclusion predicted damage at 3 yrs	6
Stoll, 2004[12]	141	Prospective observational cohort	Adult, SLE clinic. Mean disease duration 10.2 yrs (SD 6.3). Same clinic as reference 10.	Mortality, damage	Multiple logistic regression analysis showed that high total disease activity over entire study period predicted death and increase in damage (p < 0.001); replacement of total BILAG score by average number of A-flares predicted accrual of damage during study period (p = 0.004)	6
SLEDAI (SLE Disease Activity Index), SELENA-SLEDAI, SLEDAI-2K, Mexican SLEDAI, Adjusted Mean SLEDAI (AMS), Weight-adjusted SLEDAI (WAS)						
Bandeira, 2006[13]	357	Retrospective observational cohort	Pediatric, consecutive patients 1988–2000 in 3 sites (2 Italy, 1 Brazil). Followed for ≥ 3 yrs within 12 mos of diagnosis.	Damage (SDI)	Patients accruing new damage over 3 yrs had greater frequency of severe disease flare. Damage accrual associated with severe disease flares.	8
Becker-Merok, 2006[14]	86	Prospective observational cohort	Adult, Tromso (Norwegian) Lupus Cohort. Mean disease duration 11.9 yrs (0.5–38).	Mortality, damage (SDI)	SDI scores higher in 37 nonsurvivors (23.4%; SDI 2.1) vs survivors (SDI 0.9; p < 0.05); damage accrual linear in first decade of disease; only independent predictor for SDI ≥ 3 was WAS score > 3 (HR 2.34, 95% CI 1.1–4.9); age > 40 yrs at diagnosis (HR 5.6, 95% CI 2.4–12.7) and WAS > 3 (HR 2.4, 95% CI 1.2–4.0) = significant predictors of death	8
Bruce, 2015[15]	1722	Prospective observational inception cohort	Adult, SLICC Cohort Study. Enrolled within 15 mos of diagnosis.	Damage, mortality	SDI ≥ 1 at enrollments associated with worsening of SDI (vs those with SDI 0; p < 0.01); SLEDAI-2K score associated with damage development and progression. SDI associated with HR 1.46 (95% CI 1.18–1.81) for mortality.	8
Clowse, 2013[16]	1478	Multiple clinical trials in SLE	LCTC Lupus Data Registry. Mean disease duration: SLE with damage accrual = 16.8 yrs vs stable damage = 12.17 yrs.	Damage	Baseline SLEDAI ≥ 10 associated with increase in SDI (RR 3.66, 95% CI 1.96–6.84). MVA showed only baseline SDI and SLEDAI predict damage accrual	8
Feng, 2011[17]	1956	Retrospective observational cohort	Adult, medical records of hospitalized SLE patients in China (15 hospitals). Median age disease onset: 30 yrs.	Mortality	SLEDAI > 8 at discharge independent predictor of mortality (HR 1.64, 95% CI 1.12–2.42; p = 0.012)	7
Gilboe, 2001[18]	93	Prospective observational cohort	Adult, Norwegian hospital SLE patients. Baseline 1995 and followup 2 yrs later; mean disease duration 6.1 (0–31) yrs.	Damage	Baseline SLEDAI OR 1.14 (1.00–1.28, p = 0.04) and SDI OR 1.52 (1.02–2.27, p = 0.04) for change in organ damage	8

Table 1. Continued.

Study (Composite Measure)	N	Design	Population	Outcome	Study Details	Newcastle-Ottawa Quality Rating (no. stars)
Hill, 2011[19]	1168	Prospective observational cohort	Adult, Hopkins cohort. Disease duration 6 yrs; 12-mo observation period.	Damage (SDI), death	AMS predicted death: HR 1.23 (95% CI 1.14–1.33), new onset renal damage: HR 1.24 (95% CI 1.08–1.42), new onset CV disease: HR 1.18 (95% CI 1.08–1.30); not predictor of new onset overall damage (HR 1.05, 95% CI 1.00–1.11)	7
Ibanez, 2005/2006/2007[20,21,22,‡]	575	Prospective observational cohort	Adult, Toronto Lupus Cohort. Disease duration last clinic visit 10.6 ≥ 8.1 yrs, 1970–2002.	Mortality, damage	AMS (HR 1.16, p < 0.0001) and age at diagnosis (HR 1.05, p < 0.0001) predicted survival: AMS (HR 1.06, p < 0.0001), age at diagnosis (HR 1.02, p < 0.0004), and disease duration (HR 1.05, p < 0.0001) predicted damage	8
Liang, 2010[23]	43	Retrospective observational cohort, patients receiving PD	Adult, 6 patients < 20 yrs old, Taiwan. Duration of PD 39.7 ± 22.4 mos.	Mortality	Pre-dialysis non-renal SDI and non-renal SLEDAI ≠ predict mortality in univariate Cox regression analysis. No difference in SDI scores between the dead and living groups.	6
Lilleby, 2005[24]	71	Retrospective observational cohort, and cross-sectional	Juvenile. Mean disease duration 10.8 ± 8.2 yrs.	Damage, mortality	4 died with higher last SDI score vs those who lived (3.3 vs 1.3, p = 0.012); increasing SDI not associated with SLEDAI in MVA	6‡
Lin, 2012[25]	158	Retrospective observational cohort	Adult, West China Hospital. Mean disease duration 63.86 ± 48.17 mos.	Mortality, damage	SLEDAI at diagnosis associated with survival in late-onset SLE (50 yrs+); OR 1.091 (1.030–1.155, p = 0.003)	7
Mikdashi, 2004[26]	130	Prospective observational cohort	Adult, University of Maryland Lupus Cohort. Mean disease duration: NP 0 = 7.2 (2.6–11.8) yrs vs NP > 1 = 8.5 (3.4–13.6) yrs	NP damage	SLEDAI independent predictor of significant NP damage	7
Mok, 2003[27]	242	Prospective observational cohort	Adult, Hospital, Hong Kong. Mean disease duration 75.3 ± 79 mos; 3 yrs followup.	Mortality, damage	Increase in SDI scores from baseline predictive of mortality OR 1.47 per 1 point, 95% CI 1.03–2.11, p = 0.04. No. major disease flares and current/past CYC treatment independently predicted damage accrual over 3 yrs.	7
Mok, 2006[28]	282	Prospective observational cohort	Adult, possible pediatric, hospital, Hong Kong. Mean followup 6.7 yrs.	Mortality, NP damage (SDI)	SLEDAI at diagnosis, cum non-NP damage, + antiphospholipid antibodies, ever use of methylprednisolone independently predicted NP damage in MVA; logistic regression did not confirm association between early or cumulative NP damage and mortality	8
Nossent, 1993[29]	68	Prospective observational cohort	Adult, possible pediatric; in/outpatients, hospital, Caribbean. Mean followup 38 (± 33) mos.	Mortality, disease exacerbations	High persistent disease activity (weighted average of SLEDAI scores > 10) independently associated with decreased survival	6
Nossent, 2010[30]	200	Prospective inception cohort	Adult, possible pediatric, multicenter European study. New-onset SLE. Followed for 5 yrs.	Disease damage (SDI)	MVA showed that persistent disease activity (average annual SLEDAI) predicted damage accrual (SDI ≥ 1)	8
Petri, 2012[31]	2054	Prospective observational cohort	Adult, Hopkins cohort. Mean age at diagnosis 33 yrs; mean followup 6.4 yrs.	Damage (SDI)	SDI increased by 0.13 per year; higher disease activity associated with more damage during followup; however, effect of disease activity lost in MVA	7
Pons-Estel, 2004 (SLEDAI/Mexican SLEDAI)[32]	1214	Prospective, observational cohort	Adult/pediatric, GLADEL cohort. Median disease duration 32 mos.	Mortality	Max mean SLEDAI/Mexican SLEDAI and SDI were significantly higher in dead (34 pts) vs living (1180 pts); mortality predicted in stepwise logistic regression model including SDI (≥ 1 vs 0; OR 2.8, 1.2–6.4)	8

Keeling, et al: Metrics of SLE disease activity

5

Table 1. Continued.

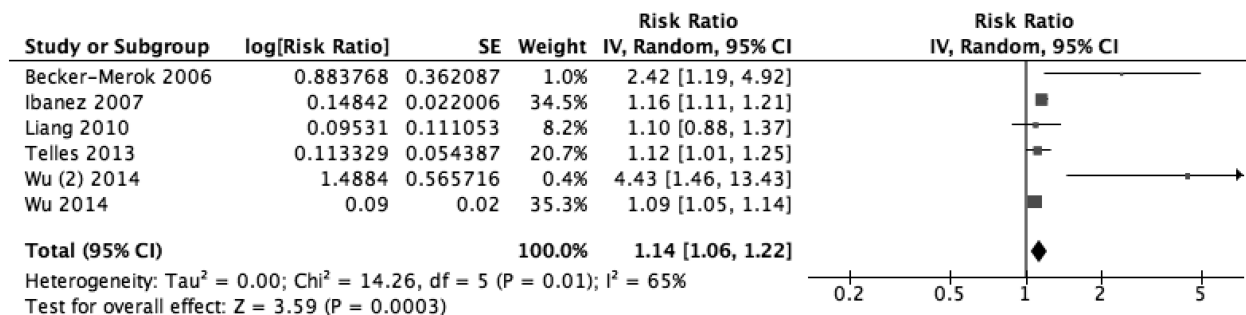| Study (Composite Measure)	N	Design	Population	Outcome	Study Details	Newcastle-Ottawa Quality Rating (no. stars)
Ramirez Gomez 2008 (SLEDAI/Mexican SLEDAI)[33]	1214	Prospective observational cohort	Pediatric and adult GLADEL cohort. Mean followup: pediatric 1.7 (0.8–2.9) yrs; adults 1.6 (0.8–2.7) yrs.	Mortality	Death in first 5 yrs: disease activity and infection. Children had higher disease activity scores (p = 0.001); adults had greater disease damage (p = 0.02).	8
Suarez-Larios, 2013 (Mexican SLEDAI)[34]	56	Retrospective observational cohort	Pediatric, ICU medical records, Mexico City (Jan 1999–Dec 2008).	Mortality	Mortality associated with high SLEDAI score; main cause of death = infection	7
Telles, 2013[35]	179	Prospective observational cohort	Adult, Brazil outpatient clinic (2006). Median disease duration at T_0 8.2 (4.3–12.4) yrs.	Mortality	Higher modified SLEDAI-2K (HR 1.12, 95% CI 1.01–1.25; p = 0.040) and SDI (HR 1.57, 95% CI 1.23–2.01; p < 0.001) among dead than survivors; initial SDI ≥ 3 significantly increased risk of death (log rank: p < 0.001)	8
Uziel, 2007[36]	102	Retrospective observational cohort	Pediatric, Israeli Pediatric Rheumatology Internet Registry (1987–2003).	Damage	Initial SLEDAI predicted development of late damage, while no other factors were predictive; 51% had minimum 5 yrs followup	8
Wu, 2014[37]	665	Prospective observational cohort	Adult, Chinese hospital SLE admissions (Jan 2006–Dec 2009).	Mortality	MVA with confounder adjustments found that male sex, older age at onset, high SLEDAI scores at time of diagnosis were independent risk factors for all-cause mortality	8
Wu, 2014[38]	104	Prospective observational cohort	Pediatric, tertiary care center, Taiwan, fulfilling ACR criteria and had renal biopsy (Jan 1999–Dec 2011).	Worsening renal function	PLN patients with poorer outcomes; prognostic factors = high baseline SLEDAI-2K (> 20; HR 6.76, p = 0.002), baseline GFR < 60 ml/min/m² (HR 3.88, p = 0.022); early responder (HR 0.19, p = 0.013)	8
Zonana-Nacah, 2007[39]	41	Observational cohort (not specified)	Hospitalized SLE patients in Mexico between 2004 and 2006. Mean followup 9.7 ± 6 mos.	Mortality	16 (39%) died; they had significantly higher SLEDAI (p = 0.004) and SLICC (p = 0.03) scores	8
SLAM (SLE Activity Measure)						
Alarcon, 2001[40]	258	Prospective observational cohort	Adult, met ACR criteria, 5 years or less.	Mortality	SLAM at enrollment OR 1.09 (1.01–1.17, p = 0.0194) and SDI (first computed) OR 1.45 (1.19–1.91, p = 0.0094) predictors of mortality in MVA	6
Karlson, 1997[41]	200	Retrospective observational cohort	Adult, 5-center, multiple insurance. Disease duration < 7 yrs.	Organ damage (SDI), SF-36	MVA showed that greater SLAM at diagnosis associated with greater damage; greater damage at diagnosis associated with greater damage	5
Nieves-Plaza, 2011[42]	61	Retrospective observational cohort	Adult, University of Puerto Rico.	Renal disease progression	SLAM-R and SDI scores did not predict a decline in GFR. SLAM score > 8 related to renal deterioration (HR 1.55, 95% CI 0.39–3.6).	5
Peschken, 2009[43]	1416	Prospective observational cohort	Adult, pediatric, Canadian (1000 Faces). Mean disease duration 12 ± 10 yrs.	Damage	MVA confirmed association of SLAM-R as independent predictor of damage accumulation in addition to low income, disease duration, age, CYC and prednisone ever	7
Toloza, 2004[44]	158	Prospective observational cohort	Adult, LUMINA median followup 24 (5–112) mos.	Time to initial damage	Higher SLAM scores were independent predictors of shorter time to initial damage in MVA (HR 1.09, 95% CI 1.04–1.15)	8
ECLAM (European Consensus Lupus Activity Measurement Index)						
Shariati-Sarabi, 2013[45]	71	Inception cohort, first renal symptoms	Adult, Iranian Medical Center (2005–2011). Mean disease duration 1 mo–15 yrs.	Damage (SDI)	SLEDAI-2K significantly associated with ECLAM results in correlation analyses (r = 0.827, p < 0.001); SDI significantly related to SLEDAI-2K and ECLAM (r = 0.699, p < 0.001)	5

Table 1. Continued.

Study (Composite Measure)	N	Design	Population	Outcome	Study Details	Newcastle-Ottawa Quality Rating (no. stars)
Systemic Lupus International Collaborating Clinics (SLICC) ACR Damage Index (SDI)						
Alarcon, 2004[46]	352	Prospective observational cohort	Adult, LUMINA cohort. Mean disease duration 18.3 (16.2) mos.	Damage	SLAM score ($p < 0.0001$) and prior SDI ($p < 0.0001$) associated with damage accrual in MVA	8
Appenzeller, 2005[47]	55	Retrospective observational cohort	Pediatric SLE cohort Brazil. Mean disease duration 4.8 (4.7) yrs.	Mortality	Male sex, infection, and nephritis independently associated with death in MVA; SDI did not influence survival	8
Bruce, 2015[15]	1722	Prospective observational inception cohort	Adult, SLICC Cohort Study.	Damage, mortality	See SLEDAI section	8
Cardoso, 2008[48]	105	Prospective observational cohort	Adult, consecutive patients meeting ACR class criteria. Median followup 6.3 yrs.	Mortality	Initial and final SDI ≥ 3 = independent predictors of mortality; HR 3.0 (95% CI 1.1–8.2) and 4.7 (95% CI 1.6–14.5); damage accrual during followup strongest predictor of death (HR 5.1, 95% CI 2.0–13.0)	8
Chambers, 2009[49]	232	Retrospective observational cohort	Adult, outpatient SLE clinic. Minimum 10 yrs followup.	Mortality	Increase in damage score associated with higher risk of death overall; for every 1-point increase in damage score, the patient was 1.32-times more likely to die; HR 1.32 (95% CI 1.09, 1.60; p < 0.005). Adjusted HR (adjusted for age at SLE onset) is 1.40 (1.14, 1.72).	8
Clowse, 2013[16]	1478	Multiple clinical trials	LCTC Lupus Data Registry.	Damage	See SLEDAI section	8
Danila, 2009[50]	635	Prospective observational cohort	Adult, LUMINA cohort. Mean disease duration 5.7 (3.7) yrs.	Mortality	Excluding poverty from MVA, renal domain of SDI was independently associated with shorter time to death (HR 1.65; 95% CI 1.03–2.66)	8
Gilboe, 2001[18]	93	Prospective observational cohort	Adult, Norwegian hospital SLE patients.	Damage	Study details in SLEDAI section	8
Gladman, 2000[5]	1297	Prospective observational cohort	Adult, SLICC patients. Mean age at diagnosis 32 (3–93) yrs.	Mortality	Patients who died had higher SDI scores early in their course (1.56) vs patients who remained alive (0.99; p = 0.0003)	8
Liang, 2010[23]	43	Retrospective observational cohort, PD patients	Adult, 6 patients < 20 yrs old.	Mortality	Study details in SLEDAI section	6
Lilleby, 2005[24]	71	Retrospective observational cohort, cross-sectional	Pediatric, Norwegian hospital.	Mortality	Study details in SLEDAI section	7[‡]
Lopez, 2012[10]	350	Prospective observational cohort	Adult, SLE clinic, London, UK.	Mortality, renal morbidity, damage	Study details in SLEDAI section	8
Mak, 2007[52]	149	Retrospective observational cohort	Adult/pediatric (1991–2003).	Renal damage (renal SDI)	Late-onset (≥ 50 yrs) SLE patients accrued more renal damage but not significantly associated with age after MVA	6
Manger, 2002[53]	338	Prospective observational cohort	Adult, University of Erlangen-Nuremberg. Median disease duration 7.8 yrs.	Mortality	Increase of ≥ 2 points of SDI from first to third yr of disease associated with mortality (RR 7.7, 3.3–18.6, p < 0.0001)	8
Mok 2013, 2014 (2 studies)[54,55,56 †]	694, 747, 756	Prospective observational cohort	Adult/pediatric, outpatient, Hong Kong (1995–2011); mean followup since diagnosis 9.6 ± 7.3 yrs.	Mortality, damage (SDI)	Age- and sex-adjusted HR of mortality in SLE patients are 2.23 (1.29, 3.85) with renal disease, 3.59 (2.20, 5.87) with renal damage, and 9.20 (4.92,17.2) with endstage renal disease; Cox regression revealed that early damage associated with adjusted HR 6.49 (95% CI 3.84–11, p < 0.001)	8

Table 1. Continued.

Study (Composite Measure)	N	Design	Population	Outcome	Study Details	Newcastle-Ottawa Quality Rating (no. stars)
Nived, 2002[57]	80	Prospective observational cohort	Adult SLE patients in Orup, Sweden (diagnosed 1981–91).	Mortality	5-yr SDI of ≥ 2 increased mortality risk by 3.4 (1.5–14.4)	8
Pons-Estel, 2004, (Mexican SLEDAI)[32]	1214	Prospective observational cohort	Adults/pediatric GLADEL cohort.	Mortality	See SLEDAI section	8
Rabbani, 2010[58]	198	Prospective observational cohort	Adult/pediatric, Aga Khan University Hospital, followed for 10 yrs.	Mortality	1-yr postdiagnosis mean renal damage score was significant predictor of death within 10 yrs of diagnosis	8
Rahman, 2001[59]	263	Prospective observational cohort	Adult, University of Toronto Lupus Clinic. Within 1 year of diagnosis prior to 1988; 10-year followup or death.	Mortality	Renal damage (p = 0.013) and trend to CV disease (p = 0.056) seen more often in SLE patients who died within 10 yrs (p = 0.013) than living patients; early damage associated with greater mortality after 10 yrs of followup	8
Stoll, 1996[60]	80	Retrospective, inceptional cohort	Adult, Switzerland. Within 10 yrs of diagnosis.	Mortality, damage	1 yr post-diagnosis mean renal damage score predicted endstage renal failure and mean pulmonary damage score significantly predicted death within 10 yrs of diagnosis	6
Telles, 2013[35]	179	Prospective observational cohort	Adult, Brazil SLE outpatient clinic.	Mortality	Study details in SLEDAI section	8
Zonana-Nacah, 2007[39]	41	Observational cohort (not specified)	Hospitalized SLE patients in Mexico.	Mortality	Study details in SLEDAI section	8
BILD (Brief Index of Lupus Damage)						
Katz, 2014[61]	958	Observational cohort (not specified)	Adult, UCSF Lupus Outcomes Study. Mean disease duration 16 ± 9 yrs.	Mortality	Higher risk of death with BILD scores of 2 (HR 6.1, 95% CI 1.3–30.0) and ≥ 3 (HR 10.8, 95% CI 2.5–46.2)	8

* Cochrane Risk of Bias tool used to assess quality of RCT[62]. † Three publications from same cohort, reported once. ‡ Adjusted version of Newcastle-Ottawa Scale for cross-sectional studies. SLE: systemic lupus erythematosus; RCT: randomized controlled trial; SRI: SLE Responder Index; CV: cardiovascular; LCTC: Lupus Clinical Trials Consortium Inc.; MVA: multivariate analysis; PD: peritoneal dialysis; NP: neuropsychiatric; cum: cumulative; CYC: cyclophosphamide; PLN: pediatric lupus nephritis; GLADEL: Grupo Latinoamericano de Estudio del Lupus; ICU: intensive care unit; ACR: American College of Rheumatology; GFR: glomerular filtration rate; SF-36: Medical Outcomes Study Short Form-36 questionnaire; LUMINA: Lupus in Minority; NAture vs Nurture cohort; UCSF: University of California at San Francisco; SELENA: Safety of Estrogens in Lupus Erythematosus National Assessment; SLAM-R: SLAM-Revised.

HR for risk of mortality with higher scores at baseline and over time.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Becker-Merok 2006	0.883768	0.362087	1.0%	2.42 [1.19, 4.92]
Ibanez 2007	0.14842	0.022006	34.5%	1.16 [1.11, 1.21]
Liang 2010	0.09531	0.111053	8.2%	1.10 [0.88, 1.37]
Telles 2013	0.113329	0.054387	20.7%	1.12 [1.01, 1.25]
Wu (2) 2014	1.4884	0.565716	0.4%	4.43 [1.46, 13.43]
Wu 2014	0.09	0.02	35.3%	1.09 [1.05, 1.14]
Total (95% CI)			**100.0%**	**1.14 [1.06, 1.22]**

Heterogeneity: Tau² = 0.00; Chi² = 14.26, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 3.59 (P = 0.0003)

Mean difference between dead and living SLE patients with higher SLEDAI scores.

Study or Subgroup	Dead Mean	SD	Total	Alive Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Nossent 1993	15	9	22	8	9	46	40.3%	7.00 [2.43, 11.57]
Pons-Estel 2004	19.6	13.3	34	13	8.1	1180	41.7%	6.60 [2.11, 11.09]
Zonana-Nacach 2007	23	12	16	15	9	25	17.9%	8.00 [1.14, 14.86]
Total (95% CI)			**72**			**1251**	**100.0%**	**7.01 [4.11, 9.92]**

Heterogeneity: Tau² = 0.00; Chi² = 0.11, df = 2 (P = 0.95); I² = 0%
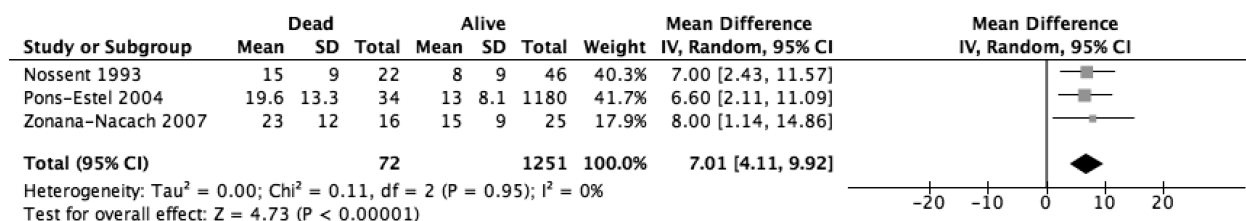Test for overall effect: Z = 4.73 (P < 0.00001)

Figure 2. Forest plots depicting the risk of mortality with higher SLEDAI scores. SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.
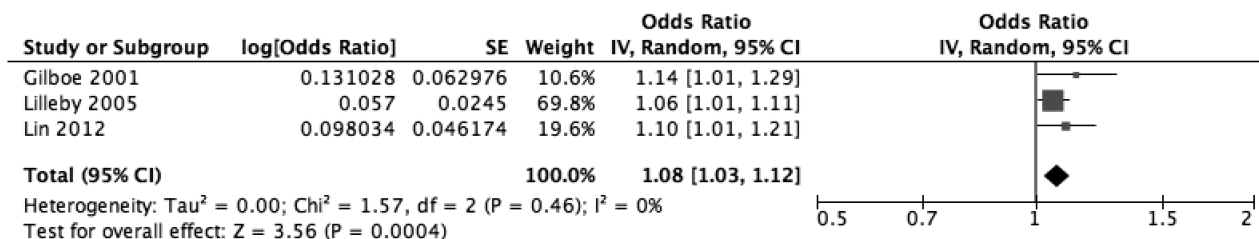
greater risk of damage in patients with higher SLEDAI scores over time with HR 1.18 (95% CI 1.02–1.37). A sensitivity analysis evaluating 2 inception cohorts[15,30] identified an HR of 1.23 (95% CI 1.15–1.32) for damage accrual associated with higher SLEDAI over time. Higher SLEDAI scores appeared to affect neuropsychiatric damage in 2 studies[26,28] (Figure 3). Stoll, *et al*[12] demonstrated that worse BILAG scores increased the odds of damage (OR 1.62, 95% CI 1.22–2.16), while Lopez, *et al*[10] also found a greater risk of damage with worse BILAG scores. Three studies[41,43,46] demonstrated the effect of worse SLAM scores on damage (HR 1.06, 95% CI 1.04–1.08; Figure 3). Toloza, *et al*[44] demonstrated a significant difference in the SLAM scores of SLE patients with damage versus those without damage.

Many other studies could not be combined to produce meaningful metaanalyses; however, those studies that involve pediatric and adult SLE international cohorts in both outpatient and hospital settings do support the association between higher disease activity (using SLEDAI, Mexican SLEDAI, BILAG, SLAM, or ECLAM) and the outcomes of mortality and damage accrual, respectively (Table 1). For example, in the Hopkins Lupus Cohort, AMS was a significant independent predictor of mortality (HR 1.23, 95% CI 1.14–1.33)[19]. Hospitalized Chinese patients with SLE had a higher mortality (HR 1.64) when discharged with a SLEDAI > 8[17], while a higher SLEDAI at diagnosis for a retrospective Chinese cohort of late-onset SLE (50 yrs or older) was an
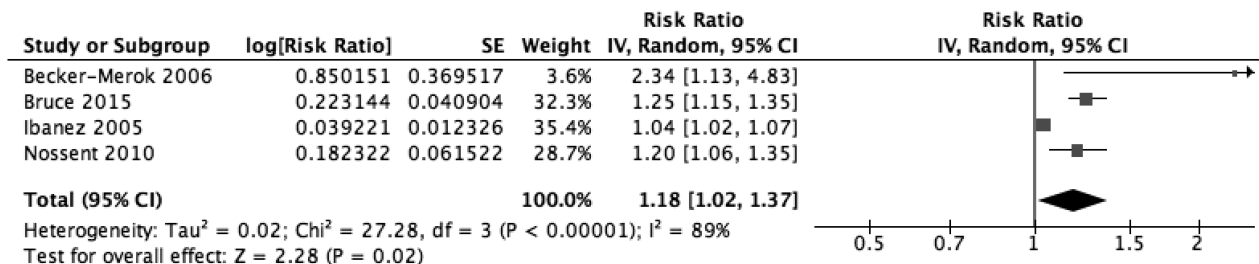
independent predictor of mortality (OR 1.091, p = 0.003)[25]. In confirming that the SDI score increased by 0.13 per year, Petri, *et al* also demonstrated that damage risk was greater for patients with higher disease activity (SELENA-SLEDAI); however, this association was not significant after adjusting for corticosteroid use[31].

SLE damage measures. The majority of studies evaluating the effect of damage on mortality and further damage involved the SDI (22 studies), with 14 prospective and 6 retrospective observational cohorts, 1 clinical trial registry, and 2 observational studies not otherwise specified. Specifically, 7 studies[10,15,35,48,49,55,59] found a significant effect on mortality with worse damage as measured by the SDI either at baseline or over time (HR 1.44, 95% CI 1.29–1.61; Figure 4). Sensitivity analyses were performed evaluating the effect on mortality of damage (measured by the SDI) at baseline and over time and confirmed HR of 1.35 (95% CI 1.25–1.46) and 1.57 (95% CI 1.29– 2.11), respectively (data not shown). Four studies[23,32,39,51] demonstrated worse SDI in dead versus living patients; however, the data were statistically insignificant (Figure 4). Although this was not statistically significant, the sample size and the heterogeneity of the included studies (as demonstrated by I² = 44%) could have affected these results. In addition, 2 studies[18,46] independently demonstrated greater odds of early damage in patients with baseline damage (worse SDI scores); however, the statistical effect was lost in the metaanalysis (OR 1.20,
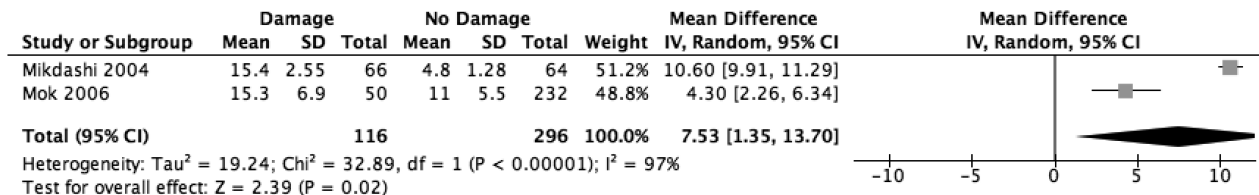
OR for accruing damage based on the SLEDAI at baseline.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Gilboe 2001	0.131028	0.062976	10.6%	1.14 [1.01, 1.29]
Lilleby 2005	0.057	0.0245	69.8%	1.06 [1.01, 1.11]
Lin 2012	0.098034	0.046174	19.6%	1.10 [1.01, 1.21]
Total (95% CI)			100.0%	1.08 [1.03, 1.12]

Heterogeneity: Tau² = 0.00; Chi² = 1.57, df = 2 (P = 0.46); I² = 0%
Test for overall effect: Z = 3.56 (P = 0.0004)

HR measuring the effect of the SLEDAI over time on the outcome of damage accrual.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
Becker–Merok 2006	0.850151	0.369517	3.6%	2.34 [1.13, 4.83]
Bruce 2015	0.223144	0.040904	32.3%	1.25 [1.15, 1.35]
Ibanez 2005	0.039221	0.012326	35.4%	1.04 [1.02, 1.07]
Nossent 2010	0.182322	0.061522	28.7%	1.20 [1.06, 1.35]
Total (95% CI)			100.0%	1.18 [1.02, 1.37]

Heterogeneity: Tau² = 0.02; Chi² = 27.28, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 2.28 (P = 0.02)

OR for neuropsychiatric damage based on the SLEDAI score.

Study or Subgroup	Damage Mean	SD	Total	No Damage Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Mikdashi 2004	15.4	2.55	66	4.8	1.28	64	51.2%	10.60 [9.91, 11.29]
Mok 2006	15.3	6.9	50	11	5.5	232	48.8%	4.30 [2.26, 6.34]
Total (95% CI)			116			296	100.0%	7.53 [1.35, 13.70]

Heterogeneity: Tau² = 19.24; Chi² = 32.89, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.39 (P = 0.02)

OR for damage accrual based on the SLAM score.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Alarcon 2003	0.0705	0.0129	44.6%	1.07 [1.05, 1.10]
Karlson 1997	0.05	0.0182	22.4%	1.05 [1.01, 1.09]
Peschken 2009	0.049	0.015	33.0%	1.05 [1.02, 1.08]
Total (95% CI)			100.0%	1.06 [1.04, 1.08]

Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 2 (P = 0.48); I² = 0%
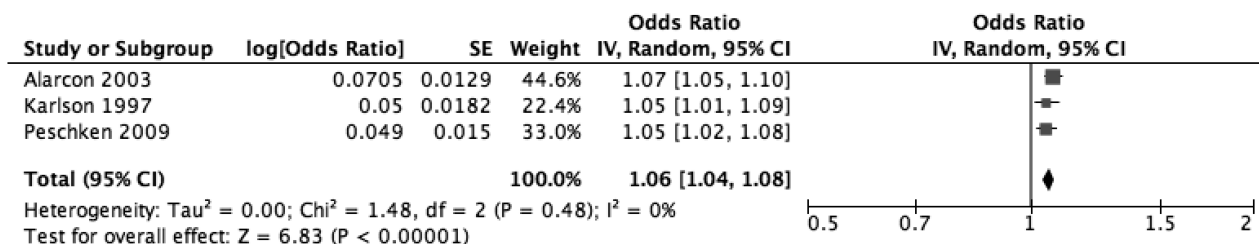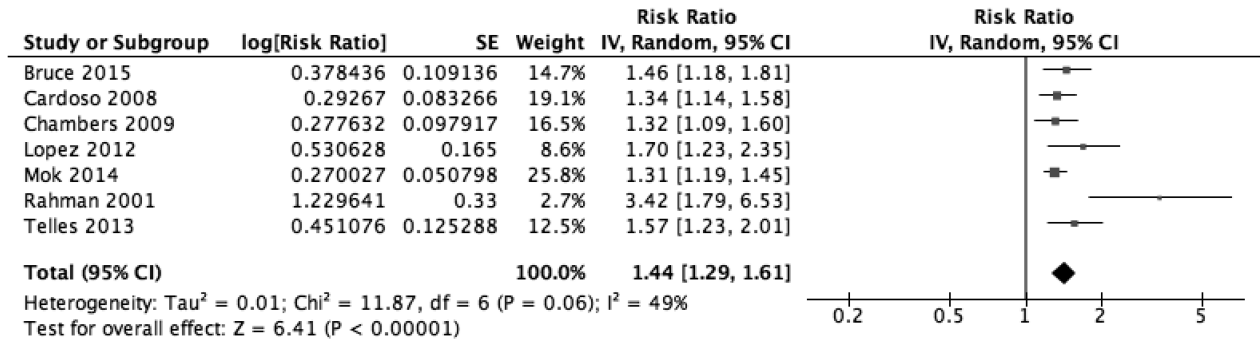Test for overall effect: Z = 6.83 (P < 0.00001)

Figure 3. Forest plots depicting risk of damage accrual (measured by the SDI) with higher SLEDAI, BILAG, and SLAM scores. SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; BILAG: British Isles Lupus Assessment Group; SLAM: SLE Activity Measure.

95% CI 0.87–1.66) owing to high heterogeneity (I^2 = 66%; Figure 5). Possible causes included different population sources and small sample sizes (e.g., the LUMINA cohort with 352 patients versus a Norwegian hospital SLE cohort with 93 patients), and different sample sizes.

Several other studies evaluated the effect of disease damage (measured by the SDI) on mortality and damage accrual, with varying results (Table 1). For example, Appenzeller, *et al* found that SDI scores did not influence survival in a pediatric SLE cohort from Brazil[47], while the

Risk of mortality (HR) with higher damage scores as measured by the SDI.

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Bruce 2015	0.378436	0.109136	14.7%	1.46 [1.18, 1.81]	
Cardoso 2008	0.29267	0.083266	19.1%	1.34 [1.14, 1.58]	
Chambers 2009	0.277632	0.097917	16.5%	1.32 [1.09, 1.60]	
Lopez 2012	0.530628	0.165	8.6%	1.70 [1.23, 2.35]	
Mok 2014	0.270027	0.050798	25.8%	1.31 [1.19, 1.45]	
Rahman 2001	1.229641	0.33	2.7%	3.42 [1.79, 6.53]	
Telles 2013	0.451076	0.125288	12.5%	1.57 [1.23, 2.01]	
Total (95% CI)			**100.0%**	**1.44 [1.29, 1.61]**	

Heterogeneity: Tau² = 0.01; Chi² = 11.87, df = 6 (P = 0.06); I² = 49%
Test for overall effect: Z = 6.41 (P < 0.00001)

Difference of past damage (measured by the SDI) between dead and living patients with SLE.

Study or Subgroup	Dead Mean	SD	Total	Alive Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Gladman 2000	1.56	1.5	99	0.99	1.5	1198	48.6%	0.57 [0.26, 0.88]	
Liang 2010	4.63	2.07	8	4.04	1.37	30	11.2%	0.59 [−0.93, 2.11]	
Pons-Estel 2004	2.1	2.6	34	0.54	1	1180	24.0%	1.56 [0.68, 2.44]	
Zonana-Nacach 2007	2.9	2.1	16	1.6	1.5	25	16.2%	1.30 [0.11, 2.49]	
Total (95% CI)			**157**			**2433**	**100.0%**	**0.93 [0.36, 1.49]**	

Heterogeneity: Tau² = 0.15; Chi² = 5.39, df = 3 (P = 0.15); I² = 44%
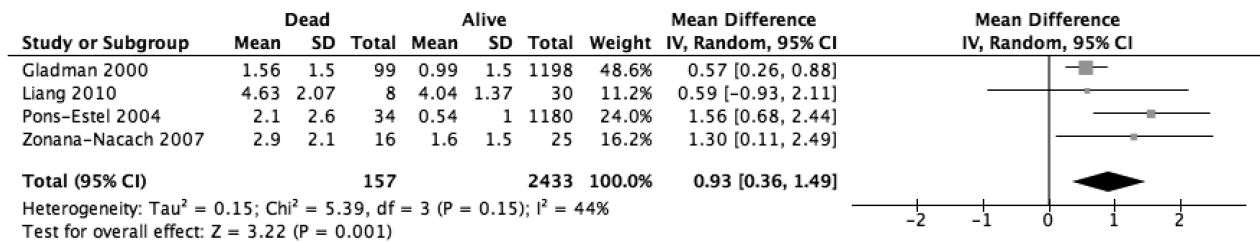Test for overall effect: Z = 3.22 (P = 0.001)

Figure 4. Forest plots associating damage with mortality in patients with SLE. SLE: systemic lupus erythematosus; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

Risk of damage from earlier damage.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
Alarcon 2003	0.0687	0.01428	66.9%	1.07 [1.04, 1.10]	
Gilboe 2001	0.41871	0.20408	33.1%	1.52 [1.02, 2.27]	
Total (95% CI)			**100.0%**	**1.20 [0.87, 1.66]**	

Heterogeneity: Tau² = 0.04; Chi² = 2.93, df = 1 (P = 0.09); I² = 66%
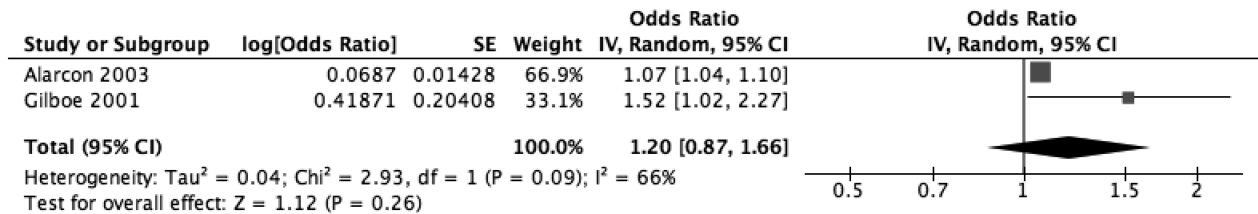Test for overall effect: Z = 1.12 (P = 0.26)

Figure 5. Forest plots depicting risk of damage (SDI) from past damage. SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

last measured SDI scores were higher in dead versus living pediatric patients with SLE in a Norwegian cohort[24]. A Swedish prospective inception cohort found that the SDI at 5 years postdiagnosis was predictive of survival and mortality up to a median of 7 years of followup[57], while the Erlangen cohort from Nuremberg[53] confirmed that an increase of 2 or more points of SDI from the first to the third year of disease was prognostic for mortality (RR 7.7, p < 0.0001). Renal damage at 1 year was predictive of death within 10 years of diagnosis in a Pakistani SLE cohort[58].

DISCUSSION

This systematic review suggests that disease activity and damage, as measured through various validated outcome measures, is overall associated with increased mortality and damage accrual. In particular, the effect of several different disease activity scores on the risk of mortality and damage accrual was consistently significant across the metaanalyses and largely confirmed by the independent studies. Overall, the risks of mortality and damage accrual were significantly higher with higher damage scores at baseline and over time, a result also supported by several individual studies. These

results likely confirm what many SLE physicians have seen or demonstrated in their clinical practice and/or research settings. The multiple observational cohort studies suggest that disease activity and damage beget more damage and death. Therefore, physicians involved in SLE care should consider proper evaluation of disease activity and damage through a formalized method such as any of the disease activity and damage indices evaluated in our study (Supplementary Table 1, available with the online version of this article).

However, several issues arise from this systematic literature review that complicate this assumption. Despite identifying over 50 studies, the ability to evaluate the various outcome measures and pool studies for metaanalyses was challenging and limited largely to descriptive reporting. Reasons include the significant heterogeneity between cohorts and the objectives of each study, and differences in how and when specific outcome measures might have been collected in a particular cohort. Cohort descriptions varied in their detail, often with a wide range of disease activity or damage at baseline and followup. This may partially explain the variability in significant results when evaluating the effect of disease damage on mortality and damage accrual in the metaanalyses. Moreover, studies conflicted regarding the effect of damage on further damage accrual and even when comparing dead versus living patients based on differences in past damage. The effect of glucocorticoids and how they were analyzed in the studies may have contributed to varying effects of disease activity and damage on mortality and damage accrual. Great difficulty arose in separating out adult versus pediatric SLE, although attempts were made to include both in this review.

Regarding the completed metaanalyses, statistical heterogeneity (computed with I^2) and heterogeneity in the characteristics of the studied cohorts were consistent challenges, reflecting among other things the unequal weight among studies within the analysis. For example, when evaluating the effect of higher disease activity scores on mortality, the combined studies included multiple international cohorts from China, Brazil, Europe, and Canada, and included hospitalized and outpatient groups and combined pediatric and adult patients, which may imply differences in SLE phenotypes and therefore disease severity.

This review was not meant to evaluate the validation and comparability of disease activity and damage metrics. However, it demonstrated that consistency and comparability exist across different metrics in evaluating for important outcomes in SLE. The choice of which measure to use will be influenced by many factors. Some important examples include feasibility in the clinical setting (e.g., time, paper vs electronic records, language used) to familiarity of clinic staff with a particular measure. Many components of the SLE disease activity and damage metrics are recorded in a good medical history and physical examination, which should be standard for SLE patients with the potential for multisystem disease. Moreover, adoption of standardized disease activity measures has already become integrated into rheumatology clinics beyond academic settings (e.g., the 28-joint count Disease Activity Score in RA, the Bath Ankylosing Spondylitis Disease Activity Score in SpA). The studies in our review were never designed to answer our specific PICO search strategy, and this likely contributed to the great heterogeneity seen in the results. Nevertheless, qualitatively the results of different studies based on different metrics of disease activity and damage, along with the results of the metaanalysis and the sensitivity analyses, were concordant. Clearly the results highlighted the effect of disease activity (at baseline and/or over time) on damage and mortality, and the effect of damage on mortality and further accrual of damage over time. A multicenter study to answer these questions with greater consistency in the metrics used to measure disease activity and damage would assist in addressing this more directly. Moreover, such a study might address how specific disease activity scores might be used in clinical practice, and what targets are appropriate in identifying low disease activity or remitted states, as is well-recognized in the defined disease activity score targets for RA.

This systematic literature review was conducted to inform a broader set of recommendations for the assessment of patients with SLE in Canada, focusing specifically on what to perform in the monitoring of our patients. This review confirmed that increased disease activity and damage, measured by validated metrics, were associated with further damage and increased mortality. This body of evidence was generated from studies using validated measures of disease activity and damage at baseline and on followup. Thus, it would be helpful to use validated metrics in the assessment and monitoring of SLE. The use of validated metrics enables scientists, trialists, industry people, and policy makers to qualify and evaluate the implication of a specific construct on other outcomes. When deciding on the use of a specific metric, one should consider its administrative (time, scoring, complexity) and cost burden, and the preparedness and skill of the assessor on the selected metric. Measurement of a health state (disease activity, damage) is essential in daily practice and research[63], and Lord Kelvin stated, "when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot, your knowledge is of a meager and unsatisfactory kind[64]."

The results will be included as part of the evidence-to-decision table in upcoming recommendations, which will incorporate other important domains that must be considered when developing recommendations according to GRADE.

ONLINE SUPPLEMENT
Supplementary material accompanies the online version of this article.

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