



Hospitalisation for systemic lupus erythematosus associates with an increased risk of mortality in Australian patients from 1980 to 2014: a longitudinal, population-level, data linkage, cohort study

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ABSTRACT

Objective Mortality rates for patients with SLE have not been reported in Australia. This study determined the association between a hospitalisation for SLE with mortality.

Methods Population-level cohort study of patients with SLE (n=21 12; 25 710 person-years) and general population comparators (controls) (n=21, 120; 280 637 person-years) identified from hospital records contained within the WA Rheumatic Disease Epidemiological Registry from 1980 to 2013. SLE was identified by ICD-9-CM: 695.4, 710.0, ICD-10-AM: L93.0, M32.0. Controls were nearest matched (10:1) for age, sex, Aboriginality and temporality. Using longitudinal linked health data, we assessed the association between a hospitalisation for SLE mortality and mortality with univariate and multivariate Cox proportional hazards and competing risks regression models.

Results At timezero, patients with SLE were similar in age (43.96 years), with higher representation of females (85.1% vs 83.4%, p=0.038), Aboriginal Australians (7.8% vs 6.0%) and smokers (20.5% vs 13.2%). Before study entry, patients with SLE (mean lookback 9 years) had higher comorbidity accrual (Charlson Comorbidity Index ≥ 1 item (42.0% vs 20.5%)), especially cardiovascular disease (CVD) (44.7% vs 21.0%) and nephritis (16.4% vs 0.5%), all p<0.001. During follow-up (mean 12.5 years), 548 (26.0%) patients with SLE and 2450 (11.6%) comparators died. A hospitalisation for SLE increased the unadjusted (HR 2.42, 95% CI 2.20 to 2.65) and multivariate-adjusted risk of mortality (aHR 2.03, 95% CI 1.84 to 2.23), which reduced from 1980 to 1999 (aHR 1.42) to 2000–2014 (aHR 1.27). Females (aHR 2.11), Aboriginal Australians (aHR 3.32), socioeconomically disadvantaged (aHR 2.49), and those <40 years old (aHR 7.46) were most vulnerable. At death, patients with SLE had a higher burden of infection (aHR 4.38), CVD (aHR 2.09) and renal disease (aHR 3.43), all p<0.001.

Conclusions A hospitalisation for SLE associated with an increased risk of mortality over the 1980–2014

Key messages

What is already known about this subject?

► Patients with SLE experience premature mortality compared with the general population. However, there are no population-level studies on the risk of mortality in patients with SLE in Australia, and information on Aboriginal Australians with SLE is scarce.

What does this study add?

► Hospitalisation for SLE increased the risk of mortality relative to general population comparators in Western Australia from 1980 to 2014.
► The highest mortality risk was seen in patients with SLE under 40 years of age, the socioeconomically disadvantaged, and Aboriginal Australians.
► Patients with SLE carry substantially more comorbidity at the time of hospitalisation and death compared with general population comparators.

How might this impact on clinical practice or future developments?

► Beyond the attempt to manage the increased risk of premature mortality after a hospitalisation for SLE, clinicians should be particularly mindful about managing comorbidity and modifiable risk factors, such as smoking, alcohol consumption and obesity, to improve survival in this patient population. Special attention should be given to patients with SLE under 40 years of age, the socioeconomically disadvantaged, and Aboriginal Australians.

period compared with the general population. The risk was especially high in younger (<40 years old), socioeconomically disadvantaged and Aboriginal Australians.

INTRODUCTION

SLE is a chronic inflammatory autoimmune disease where a variety of organ complications, which often require intensive and/or long-term use of immunosuppressive medication, contribute to an increased risk of premature mortality.¹ During the 10 years from 1970 to 1979, a large multinational cohort study reported a standardised mortality rate (SMR) of 4.9 for patients with SLE compared with the general population.² A 2014 meta-analysis showed that the increased meta-SMR for patients with SLE compared with the general population had reduced, but remained elevated (meta-SMR of 3).³ Recent data from the UK demonstrated that this life-expectancy gap had improved for patients with SLE, up until 2000, but the overall increased risk of mortality was unchanged thereafter to 2014.^{4,5}

Australian data on mortality in SLE are limited to single-centred, retrospective studies of high-risk groups.^{6–8} These studies showed increased mortality among those with lupus nephritis,⁹ as well as Aboriginal Australians treated in either metropolitan (n=6) or regional centres, including the Northern Territory of Australia (n=22; mortality rate (MR) 90.4) and Central Australia (n=18; MR 18).^{8,10,11} This is the first Australian study, using whole-population longitudinal linked health data, to investigate all-cause mortality and the underlying and contributing causes of death in a cohort of patients with SLE from 1980 to 2014.

METHODS

This whole-of-population cohort study used data linked by the Western Australian Data Linkage System, which uses probabilistic matching (99.7% accuracy) to identify individuals across administrative health datasets.¹² The Western Australian Rheumatic Disease Epidemiological Registry (WARDER) includes all private and public hospital separations (emergency department presentations, inpatient episodes, including same-day interventions and admissions, as well as cancer notifications and death notifications) statewide for over 200 000 patients with rheumatic disease conditions and another 200 000 non-exposed general population comparators (free from the conditions defined in online supplemental table 1). The WARDER comprises information linked from the Hospital Morbidity Data Collection (HMDC, from 1970), WA Cancer Registry (from 1982) and the Death Register (from 1969) and the Emergency Department Data Collection (from 2002). Since the 1970s, the HMDC has recorded the primary and (up to 20) co-diagnoses and the primary and (up to 10) secondary procedure codes for each hospital-level in-patient separation using the International Statistical Classification of Diseases and Related Health Problems (ICD) 9th,^{13,14} ICD 10th revision¹⁵ or the Australian Classification of Health Interventions codes.¹⁶ The linkage of the WARDER dataset was done on 1 February 2017.

Within participants of the WARDER, aged 0–80 years, hospitalisations for SLE were identified in the HMDC between 1 January 1980 and 31 December 2013 by ICD-9-CM: 695.4 and 710.0, and ICD-10-AM: M32.0, M32.1, M32.8, M32.9, L93.0, L93.1 and L93.2. In 2013, Ward reported that administrative data were valid in the identification of rare diseases and suitable for producing epidemiological estimates.¹⁷ In addition, in administrative or claims data, having at least one ICD-9-CM code of SLE (ICD-9: 694.4 and 710) had a positive predictive value of 70%–96%.¹⁸ Internationally, 89% to 93% of patients with SLE meeting classification criteria are hospitalised during their disease course.^{19,20} Given that the HMDC captures same-day drug infusions (although not the specific drug types) and procedures, at a minimum our cohort would represent patients with SLE with moderate-to-severe disease.

Patients with SLE (n=2111) were propensity score matched (1:10) to 22 110 controls free of rheumatic disease conditions. Timezero (study entry) was defined as the index hospitalisation for SLE and a random hospitalisation in the non-exposed comparators. Patients with SLE and controls were matched for the year of the index (first ever) hospital contact, year of timezero, age at timezero, gender and Aboriginality. Aboriginality, captured via self-identification during hospital admissions, is over 90% accurate; thus, to reduce the likelihood of under-reporting, we defined Aboriginality as the presence of an 'Aboriginality' flag being present for at least 25% of all hospital admissions since 1980. Socio-economic status was proxied using the Socio-economic Indices for Areas (SEIFA)–Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD).²¹ Available for hospitalisation since 2006, IRSAD scores are calculated from 5-yearly census data and then divided into quintiles based on residential postcode (quintile 1—most disadvantaged through to quintile 5—most advantaged).²¹ Comorbidities, modifiable risk factors (smoking, harmful alcohol use and obesity) and intravenous/intramuscular corticosteroid administration were identified in the HMDC with the ICD codes defined in online supplemental table 2.

All-cause and cause-specific mortality was determined from the Death Register which contains demographic information related to the individual and coded death certificate data using information in Parts 1 and 2 of the death certificate, or all diagnosis text fields from the death certificate. The Death Register data included the contributing causes of death data from 1980. ICD codes were used for diagnoses in the HMDC and contributing causes of death in the WA Death registry. Contributing causes of death were defined according to the Australian Institute of Health and Welfare's *Multiple causes of death: An analysis of all natural and selected chronic disease causes of death 1997–2007*, and further defined based on the most prevalent diseases per category.²²

Statistical analysis

Results are presented as a mean with SD, median with IQR or frequency and proportion. Between-group differences were assessed with the t-test, Mann-Whitney U test, χ^2 test and ORs with 95% CIs as appropriate. To mitigate the likelihood of incurring an immortal time bias, a maximum of 20 person-years were calculated from timezero to the date of the death event or relevant exit date, for example, 31 December 2014. We determined the association between a hospitalisation for SLE and 20-year all-cause mortality with univariate and multivariate Cox proportional hazards regression models. Sub-group and period-specific (overall, 1980–1999 and 2000–2014) analysis looked at the association between a hospitalisation for SLE and 20-year mortality within, males, non-Indigenous Australians, Aboriginal Australians, age groups (<40, 40–49, 50–59, 60–69 and ≥ 70 years of age) and socioeconomic status (quintiles). The association between a hospitalisation for SLE and 1-year, 3-year, and 5-year risk of mortality was also conducted. A multiple causes of death analysis was done with competing risks regression to determine the burden of contributing causes of death.²² The multivariate models for overall mortality risk were adjusted for age,² gender, Aboriginality, prevalent number of Charlson Comorbidity Items (0=no CCI items, 1=1–2 CCI items, 2=3 or more CCI items).²³ Period-specific multivariate models were adjusted for age, age,² gender, Aboriginality and CCI categories. No significant interactions were found in an effect modification analysis of prevalent clinical thromboembolic events, alcohol consumption, smoking, obesity, prevalent hypothyroidism, prevalent hypertension, prevalent diabetes, dyslipidaemia and the requirement of intravenous/intramuscular (IV/IM) corticosteroids ever, all $p > 0.10$. Within patients with SLE, we assessed whether the risk of mortality was higher in sub-groups with prevalent thromboembolic events, other rheumatic diseases and nephritis. Direct standardisation included the calculation of standardised mortality rates (SMRs) using the reference population data from the 2011 Census data for WA from the Australian Bureau of Statistics.²⁴ Expected deaths were estimated at yearly intervals using the Stata *stsvs ado* program and the Ederer II method.²⁵ The statistical analysis including Cox proportional hazards, competing risks regression and the direct standardisation was done using Stata V.16.1.

RESULTS

Patients hospitalised for SLE were similar for age (43.96 years) and socioeconomic status, with a marginally higher representation of (85.1% vs 83.4% female, $p = 0.038$) and Aboriginal Australians (OR 1.32, 95% CI 1.11 to 1.56). Those hospitalised for SLE were more likely to have any CCI item (OR 2.81, 95% CI 2.56 to 3.08), but had equivalent median CCI scores (2 vs 2, $p = 0.160$) as well as higher odds of having thromboembolic events, hypertension, dyslipidaemia, hypothyroidism, and nephritis and proteinuria. Patients with SLE were more likely to have a history

of harmful alcohol consumption, smoking and obesity (table 1).

Association between a hospitalisation for SLE with the risk of mortality

A total of 548 (26.0%) deaths occurred in the SLE cohort compared with 2450 in controls (11.6%). At the time of death, patients with SLE were on average 11.5 years younger (64.6 vs 76.05 years, $p < 0.001$), died earlier after hospitalisation (6.85 vs 7.43 years of follow-up, $p < 0.001$), and were more likely to die in hospital (71.5% vs 55.0%, $p < 0.001$) or on arrival to hospital (1.1% vs 0.9%, $p < 0.001$) (figure 1). Overall, a hospitalisation for SLE associated with an increased risk of all-cause mortality compared with general population comparators in the unadjusted (HR 2.42, 95% CI 2.20 to 2.65; $p < 0.001$) and multivariate-adjusted (aHR 2.03, 95% CI 1.84 to 2.23; $p < 0.001$) models from 1980 to 2014. This increased risk of mortality following a hospitalisation for SLE was seen in the 1980–1999 period (aHR 1.42, 95% CI 1.20 to 1.70; $p < 0.001$), and while reduced in the 2000–2014 period, it remained higher than the comparators (aHR 1.27, 95% CI 1.11 to 1.45; $p < 0.001$) (table 2).

Relative to comparators, a hospitalisation for SLE associated with a higher risk of all-cause mortality in female rather than male patients. Furthermore, in the 1980–1999 period, a hospitalisation for male SLE was not associated with survival (aHR 1.07, 95% CI 0.76 to 1.51; $p = 0.697$). Aboriginal Australians hospitalised for SLE had substantially higher (age-adjusted and sex-adjusted) risk of mortality throughout the study period; however, this association was attenuated in the fully adjusted modelling. While significant improvements were seen across the 1980–1999 (aHR 4.65) to 2000–2014 (aHR 2.63) period, Aboriginal Australians hospitalised for SLE remained among the most vulnerable patients, although this was due to a greater influence of comorbidity and modifiable risk factors on premature mortality. While patients with SLE had increased risk of mortality across all age groups, the risk was especially high in patients under 40 years of age. In addition, we demonstrated that SLE associated with a high risk of mortality within 1 to 5 years post-hospitalisation. Furthermore, a hospitalisation for SLE associated with an increased risk of mortality across all socioeconomic quintiles, with the highest risk seen in those at the most disadvantage (Q1: aHR 2.49) (table 2).

Effect modification of the association between a hospitalisation for SLE and the risk of mortality was evident for prevalent thromboembolic events, harmful alcohol use, smoking status, hypertension, hypothyroidism, dyslipidaemia, diabetes and IV/IM corticosteroid requirement, but not obesity (table 3).

Within hospitalised patients with SLE, prevalent hospitalisation for another rheumatic disease, antiphospholipid syndrome (ever) or thromboembolic events had no influence on survival. Yet, those hospitalised for nephritis and/or haemato-proteinuria during the lookback period

Table 1 Cohort characteristics at study entry

	SLE	Comparators	OR (95% CI)
Participants, n	2111	21 110	
Lookback time, mean±SD	9.25±8.57	9.03±9.42	–
Follow-up time, mean±SD	13.69±9.10	16.00±10.12	–
Demographics			
Age, mean±SD	43.96±17.74	43.54±19.65	–
Males, n (%)	314 (14.9)	3512 (16.6)	–
Females, n (%)	1797 (85.1)	17 598 (83.4)	–
Aboriginality, n (%)	165 (7.8)	1275 (6.0)	1.32 (1.11 to 1.56)
SEIFA (IRSAD) quintiles, n=data available			
Quintile 1 – most disadvantaged, n (%)	206 (12.9)	2045 (12.0)	Reference
Quintile 2, n (%)	204 (12.8)	2411 (14.1)	0.84 (0.69 to 1.03)
Quintile 3, n (%)	282 (17.7)	3055 (17.9)	0.92 (0.76 to 1.11)
Quintile 4, n (%)	472 (29.6)	5050 (29.6)	0.93 (0.78 to 1.10)
Quintile 5 – most advantaged, n (%)	431 (27.0)	4490 (26.3)	0.95 (0.80 to 1.13)
Modifiable risk factors			
Harmful alcohol use, n (%)	83 (3.9)	467 (2.2)	1.81 (1.43 to 2.30)
Obesity, n (%)	133 (6.3)	604 (2.9)	2.28 (1.88 to 2.77)
Smoking status, n (%)	432 (20.5)	2782 (13.2)	1.70 (1.51 to 1.90)
Comorbidity at timezero			
Cardiovascular disease, n (%)	943 (44.7)	4425 (21.0)	3.04 (2.78 to 3.34)
Acute myocardial infarction, n (%)	78 (3.7)	416 (2.0)	1.91 (1.49 to 2.44)
Congestive heart failure, n (%)	119 (5.6)	339 (1.6)	3.66 (2.96 to 4.53)
Thromboembolic events, n (%)	245 (11.6)	498 (2.4)	3.87 (2.64 to 5.66)
Peripheral vascular disease, n (%)	71 (3.4)	196 (0.9)	4.08 (2.14 to 7.79)
Cerebrovascular disease, n (%)	125 (5.9)	427 (2.0)	2.81 (1.78 to 4.43)
Antiphospholipid autoantibodies ever, n (%)	80 (3.8%)	9 (0.0%)	92.4 (46.3 to 184.2)
Hypertension, n (%)	388 (18.4)	1743 (8.3)	2.50 (2.21 to 2.82)
Dyslipidaemia, n (%)	85 (4.0)	540 (2.6)	1.60 (1.27 to 2.02)
Dementia, n (%)	9 (0.4)	110 (0.5)	0.82 (0.41 to 1.62)
Chronic pulmonary disease, n (%)	277 (13.1)	1236 (5.9)	2.43 (2.11 to 2.79)
Rheumatic disease (excluding SLE), n (%)	211 (10.0)	0 (0.0)	–
Osteoporosis (OP), n (%)	41 (1.9)	61 (0.3)	6.87 (4.61 to 10.23)
OP with fracture, n (%)	13 (0.6)	19 (0.1)	7.00 (3.45 to 14.18)
Peptic ulcer, n (%)	103 (4.9)	380 (1.8)	2.80 (2.24 to 3.50)
Mild liver disease, n (%)	87 (4.1)	193 (0.9)	4.66 (3.60 to 6.03)
Moderate or severe liver disease, n (%)	16 (0.8)	33 (0.2)	4.88 (2.68 to 8.88)
Diabetes (any), n (%)	131 (6.2)	914 (4.3)	1.46 (1.21 to 1.77)
Diabetes without complications, n (%)	123 (5.8)	769 (3.6)	1.64 (1.35 to 1.99)
Diabetes with complications, n (%)	50 (2.4)	392 (1.9)	1.28 (0.95 to 1.73)
Hypothyroidism, n (%)	90 (4.3)	199 (0.9)	4.68 (3.63 to 6.03)
Hemi/paraplegia, n (%)	49 (2.3)	166 (0.8)	3.00 (2.17 to 4.14)
Renal disease (as per Quan <i>et al</i> ²³), n (%)	136 (6.4)	155 (0.7)	9.31 (7.36 to 11.77)
Nephritis and proteinuria, n (%)	346 (16.4)	112 (0.5)	35.75 (29.54 to 45.73)
Malignancy, n (%)	122 (5.8)	1569 (7.4)	0.76 (0.63 to 0.92)
Patient had a metastatic solid tumour, n (%)	24 (1.1)	468 (2.2)	0.51 (0.34 to 0.77)

Continued

Table 1 Continued

	SLE	Comparators	OR (95% CI)
Patient had a AIDS/HIV, n (%)	<5 (0.0)	<5 (0.0)	3.33 (0.35 to 32.07)
Charlson Comorbidity Index (CCI), any item, n (%)	886 (42)	4322 (20.5)	2.81 (2.56 to 3.08)
CCI score, median (IQR)	2 (1, 3)	2 (1, 3)	–
0 items, n (%)	1225 (58.0)	16788 (79.5)	Reference
1–2 items, n (%)	716 (33.9)	3750 (17.8)	2.62 (2.37 to 2.89)
>2 items, n (%)	170 (8.1)	572 (2.7)	4.07 (3.40 to 4.88)
Hospitalisations for other rheumatic disease conditions			
Rheumatoid arthritis, n (%)	149 (7.1)	0 (0.0)	–
Polymyalgia rheumatica, n (%)	102 (4.8)	0 (0.0)	–
Sicca symptoms, n (%)	49 (2.3)	0 (0.0)	–
Raynaud's phenomenon, n (%)	52 (2.5)	0 (0.0)	–
Myositis (excluding infective), n (%)	44 (2.1)	0 (0.0)	–
Vasculopathies, n (%)	44 (2.1)	0 (0.0)	–
Scleroderma, n (%)	23 (1.1)	0 (0.0)	–
Gout, n (%)	36 (1.7)	0 (0.0)	–
Other connective tissue diseases, n (%)	82 (3.9)	0 (0.0)	–
Medication use			
IV/IM steroids, n (%)	246 (11.7)	197 (0.9)	14.00 (11.54 to 16.99)
Adverse reaction to IV/IM steroids, n (%)	0 (0.0)	<5 (1.0)	–

Bolded cells were statistically significantly different between patients with SLE and comparators.

"<5" displayed to maintain participant confidentiality

IV/IM, intravenous/intramuscular.

increased the risk of all-cause mortality (aHR 1.43, 95% CI 1.13 to 1.80; $p=0.004$) (online supplemental table 3).

Direct standardisation

Hospital-based comparators had similar survival compared with the estimated resident population of Western Australia in 2011²⁴ (figure 2A). Compared with the background population of Western Australia, patients with SLE had an increased age-adjusted and sex-adjusted standardised mortality rate ratio (SMR) from 1980 to 2014 (SMR 2.29, 95% CI 2.12 to 2.47; $p<0.001$) (figure 2B) as well as an increased 5-year rolling SMR. Compared with the general population, a hospitalisation for SLE associated with an increased SMR at 1 year, 1–5 years, 5–10 years, 10–15 years and >15 years post-hospitalisation (online supplemental table 4).

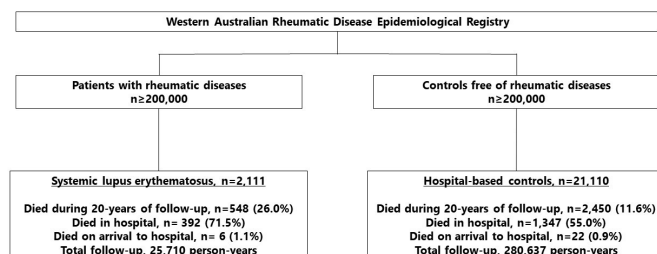


Figure 1 Study flowchart.

Underlying and contributing causes of death in patients hospitalised for SLE compared with general population comparators

Competing risks regression models determined the relative contribution of conditions captured on the death certificate between those with a hospitalisation for SLE and comparators. A hospitalisation for SLE associated with an increased risk of death from infection (aHR 4.38), cardiovascular disease (aHR 2.09), cerebrovascular disease (aHR 1.39), peripheral vascular disease (aHR 2.64), respiratory disease (aHR 2.26), renal disease (aHR 3.42), and gastrointestinal and/or hepatic disease (aHR 2.27). In addition, SLE increased the risk of mortality related to malignancies of the lymphatic and hematopoietic tissues (aHR 1.91); cytopenias, including anaemia (aHR 5.83), haemolytic anaemia and thrombocytopenia; as well as neurological disease, endocrine and metabolic diseases (excluding diabetes), skin and subcutaneous disease, and mental health and behavioural disorders, including intentional self-harm (table 4).

DISCUSSION

This population-level longitudinal cohort study from Western Australia demonstrated that an index hospitalisation in patients with SLE was independently associated with an increased (aHR 2.03) risk of premature

Table 2 All-cause mortality, stratified by demographics, study period and time since study entry

	SLE		Controls		HR (95% CI)	Adjusted HR (95% CI)
	N	py	N	py		
Overall	548	25 710	2450	280 637	2.42 (2.20 to 2.65)	2.03 (1.84 to 2.23) *
1980–1999	236	9045	781	113 450	3.62 (3.13 to 4.19)	1.42 (1.20 to 1.70) †
2000–2014	312	16 663	1669	167 157	1.88 (1.67 to 2.12)	1.27 (1.11 to 1.45) †
Males	126	3471	642	42 568	2.37 (1.96 to 2.87)	1.88 (1.54 to 2.29) †
1980–1999	55	1290	237	17 324	2.90 (2.16 to 3.90)	1.07 (0.76 to 1.51) †
2000–2014	71	2180	405	24 240	2.02 (1.57 to 2.60)	1.37 (1.04 to 1.81) †
Females	422	22 239	1808	238 068	2.48 (2.23 to 2.76)	2.11 (1.89 to 2.35) †
1980–1999	181	7754	544	96 126	3.97 (3.36 to 4.70)	1.60 (1.30 to 1.96) †
2000–2014	241	14 482	1267	141 917	1.88 (1.63 to 2.15)	1.26 (1.08 to 1.47) †
Non-Indigenous	494	24 018	2231	263 126	2.41 (2.18 to 2.66)	1.99 (1.80 to 2.21) †
1980–1999	213	8545	711	105 208	3.55 (3.04 to 4.13)	1.40 (1.17 to 1.69) †
2000–2014	281	15 470	1520	157 890	1.89 (1.67 to 2.15)	1.26 (1.09 to 1.45) †
Indigenous Australians	54	1691	219	17 511	2.40 (1.78 to 3.23)	3.32 (2.45 to 4.49) ‡
1980–1999	23	499	70	8242	4.65 (2.88 to 7.49)	4.65 (2.87 to 7.52) §
2000–2014	31	1192	149	9267	1.63 (1.11 to 2.40)	2.63 (1.78 to 3.90) §
Age groups						
<40	89	13 175	91	166 209	12.09 (9.02 to 16.20)	7.46 (5.41 to 10.28) †
40–50	64	5182	100	39 560	4.95 (3.62 to 6.78)	2.83 (2.02 to 3.97) †
50–60	104	3480	221	30 105	4.05 (3.21 to 5.12)	2.57 (2.00 to 3.29) †
60–70	132	2385	620	24 519	2.21 (1.83 to 2.67)	1.82 (1.50 to 2.20) †
≥70	159	1489	1418	20 244	1.49 (1.26 to 1.75)	1.23 (1.04 to 1.46) †
Socioeconomic status #						
Quintile 1	32	2678	149	27 223	2.17 (1.48 to 3.18)	2.49 (1.67 to 3.73) †
Quintile 2	28	2644	159	31 691	2.13 (1.43 to 3.19)	1.79 (1.17 to 2.76) †
Quintile 3	35	3451	186	38 974	2.14 (1.49 to 3.07)	1.62 (1.09 to 2.42) †
Quintile 4	56	6188	359	65 195	1.66 (1.25 to 2.19)	1.60 (1.19 to 2.16) †
Quintile 5	81	5384	411	57 002	2.11 (1.66 to 2.68)	1.87 (1.46 to 2.39) †
Since study entry						
1 year	111	2035	454	20 791	2.48 (2.02 to 3.05)	1.63 (1.32 to 2.02) *
3 years	204	5855	781	60 309	2.67 (2.29 to 3.12)	1.85 (1.57 to 2.17) *
5 years	264	9312	1029	96 490	2.64 (2.31 to 3.02)	1.96 (1.70 to 2.25) *

Bolded HRs were statistically significant, $p < 0.05$.

*Adjusted for age², sex, Indigenous status, Charlson Comorbidity Index (CCI) categories, harmful alcohol consumption, obesity and smoking status.

†Adjusted for age, age², sex, Indigenous status, CCI categories, harmful alcohol consumption, obesity and smoking status.

‡Adjusted for age² and sex only.

§Adjusted for age, age² and sex only.

py, person-years.

mortality, compared with matched general population comparators over the 35 years since 1980. The risk of mortality was highest within 5 years of hospitalisation, with younger patients (<40 years of age), socioeconomically disadvantaged and Aboriginal Australians being particularly vulnerable. Prevalent thromboembolic disease, harmful alcohol use, smoking, hypothyroidism, hypertension, dyslipidaemia and requirement of IV/IM corticosteroids were found to be effect modifiers of the

association between a hospitalisation for SLE and premature mortality, and warrant further investigation. Within patients with SLE, the risk of mortality was higher with those with (lupus) nephritis. The presence of antiphospholipid syndrome, thromboembolic disease or other rheumatic disease conditions, including rheumatoid arthritis within patients hospitalised for SLE conferred no additional mortality risk.

Table 3 Effect modification between patients with SLE and hospital-based controls

	Patients with SLE		Controls		Cox proportional hazards
	Died	Person-years	Died	Person-years	aHR (95% CI) *
Prevalent thromboembolic events	95	2393	180	4289	1.32 (1.02 to 1.71)
No prevalent thromboembolic disease	453	23318	2270	276347	2.13 (1.92 to 2.37)
History of harmful alcohol use	33	698	127	4413	1.29 (0.88 to 1.91)
No history of harmful alcohol use	515	25013	2323	276224	2.06 (1.86 to 2.27)
History of smoking	131	3808	496	20309	1.69 (1.38 to 2.07)
No history of smoking	417	21902	1954	260328	2.09 (1.88 to 2.33)
History of obesity	63	1277	118	5501	1.97 (1.41 to 2.76)
No history of obesity	485	24433	2332	275136	2.03 (1.84 to 2.25)
Prevalent hypertension	194	3836	713	14902	1.47 (1.24 to 1.74)
Normotensive	354	21874	1737	265735	2.25 (2.00 to 2.54)
Prevalent hypothyroidism	40	1016	67	2041	1.47 (0.98 to 2.22)
Normal thyroid function	508	24694	2383	278596	2.05 (1.86 to 2.26)
Prevalent dyslipidaemia	45	577	191	4310	1.58 (1.13 to 2.22)
Normal lipid levels	503	25134	2259	276326	2.06 (1.86 to 2.27)
Prevalent diabetes	68	995	355	6467	1.26 (0.96 to 1.65)
Non-diabetic	480	24715	2095	274170	2.17 (1.95 to 2.40)
IV/IM corticosteroids ever	71	3420	30	2648	1.78 (1.13 to 2.78)
No IV/IM corticosteroids ever	477	22290	2420	277988	1.98 (1.79 to 2.19)

Bolded HRs were statistically significant, $p < 0.05$.

*Adjusted for age, sex, Aboriginality and Charlson Comorbidity Index categories. Interaction testing, all $p > 0.20$.

The age and gender distributions for patients with SLE in this study were comparable with other studies reporting on mortality in hospitalised^{19 26–28} and community-based (population-level) patients with SLE.⁴ For marginal differences in sex and Aboriginality at timezero, patients with SLE had accrued three times as much the comorbidity (CCI>0) during a similar (9 years) lookback period compared with general population comparators. Comorbidity accrual (CCI>0) in our study was similar to Kuo *et al.*²⁹ Our overall CCI scores were higher on a per-patient level (data not shown) than those reported a population study in the UK,⁵ which might represent a selection bias given that our sample was hospital ascertained, and patients were on average 15 years older than the typical onset of age of SLE. Beyond the CCI items, our data confirm the higher prevalence of a range of comorbidities, including cardiovascular disease, thromboembolic disease, hypothyroidism, hypertension, osteoporosis and dyslipidaemia experienced by patients with SLE.^{30–32} While the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) has not been validated for use in Australian administrative datasets, we think that the CCI has sufficient coverage of conditions captured in the SDI to produce robust and meaningful mortality estimates. Interestingly, the attenuation of the association between mortality in Aboriginal Australians with SLE with increasing categories of CCI suggests that a broader rather than SLE-specific comorbidity index is

better suited to population-level research and the generalisability of the findings, especially when discussing the health disparities between Aboriginal and non-Aboriginal Australians. In addition, patients with SLE had higher rates of smoking, harmful alcohol consumption and obesity compared with controls. While the prevalence of smoking was similar to Jorge *et al* (~30%),⁵ our alcohol and obesity exposures were much lower than other comparable studies.^{5 29} This most likely resulted from the identification of these exposures on discharge summaries (meaning the conditions required management during a hospitalisation), rather than from outpatient letters or primary care information systems. The latter are better suited to capture details, such as standard drinks per week, cigarettes smoked per day and accurate measures of anthropometry, including body mass index or measures of adiposity.^{5 29} Furthermore, our hospitalisation-level data representing either the acute exacerbation or ongoing management of moderate-to-severe SLE would explain the attenuation of the risk of mortality in the effect modification analysis. Collectively, our findings confirm that patients hospitalised for SLE have higher accrual of comorbidity and modifiable risk factors compared with demographically and temporally matched general population comparators. Furthermore, the increased prevalence of comorbidity and modifiable risk factors in this and other studies indicates that there is significant scope for medical and allied health services to improve the health outcomes and reduce the risk of

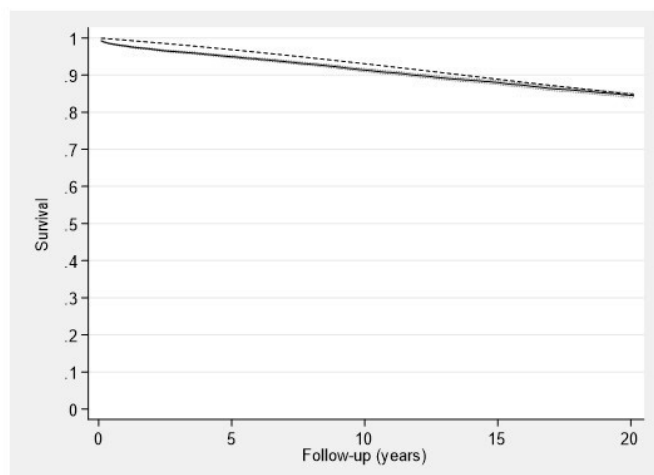


Figure 2a

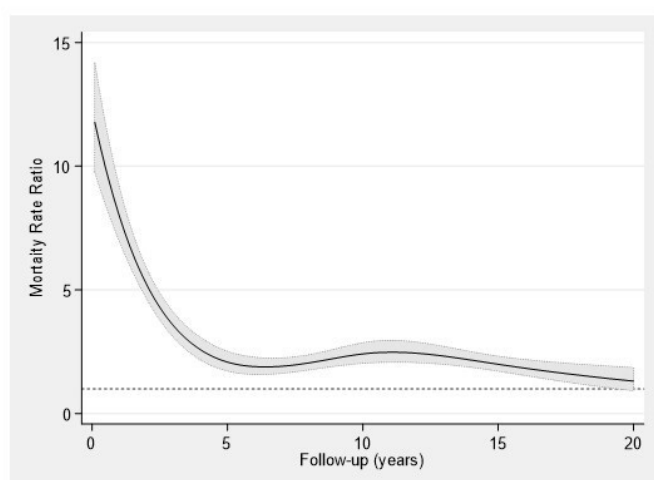


Figure 2b

Figure 2 (A) Comparing mortality rates of hospital-based general population comparators of the WARDER compared with the general population of Western Australia. Black line: observed survival with 95% CI (grey area) of WARDER comparators. Dotted line: expected survival of general population of Western Australia. (B) Mortality rate ratios of hospital-based patients with SLE compared with the general population of Western Australia. Black line: mortality rate ratio; grey area: 95% CI of mortality rate ratios.

premature mortality at or before the index hospitalisation for SLE.³³

Our data demonstrated that patients with SLE had increased risk of all-cause mortality (aHR 2.03, 95% CI 1.84 to 2.23; $p < 0.001$) compared with hospital-based controls, and to the general population of Western Australia (SMR 2.29, 95% CI 2.12 to 2.47; $p < 0.001$). The increased risk of mortality shown herein aligned with population-level findings from Hungary (aHR 2.75).³⁴ While our time-limited (1, 3 and 5 years since hospitalisation) findings were tempered compared with other studies (all, aHR > 4), we had included more confounding variables, which may partly explain the differences between the published estimates. While our SMR (2.29) was higher

than the community-based population-level data from the UK (MRR 1.67, 95% CI 1.43 to 1.94),⁴ our estimates were lower than the meta-SMR of 3 reported in a meta-analysis of observational studies,^{3 5 29} although our 5-year SMR from 1980 to 2015 was similar to previously published estimates. Ultimately, hospitalisation for SLE conferred an increased risk of mortality for up to 20 years when compared with general population comparators, and the background population of Western Australia.^{5 29 34 35}

After hospitalisation for SLE, female patients had an increased risk of mortality compared with controls, and this association remained significant, although reduced in the latter 2000–2014 period. These data aligned with Rees *et al* (1999–2012; MRR 1.64, 95% CI 1.43 to 1.94) who demonstrated increased mortality in female patients with SLE compared with the general population.⁴ We demonstrated that males with SLE had an increased risk of mortality compared with controls, which while being attenuated in the 1980–1999 period (due to a pronounced effect of CCI variable on the risk of mortality) regained significance in the 2000–2014 period (aHR 1.37, 95% CI 1.04 to 1.81). This aligned with the age-adjusted, sex-adjusted and region-adjusted MRR for male patients with SLE (1.80, 95% CI 1.37 to 1.96; $p < 0.001$) of Rees *et al*; however, our association was weaker due to our adjustment for comorbidity and modifiable risk factors. Underwriting the attenuation of the association between a hospitalisation for SLE with mortality in males by increasing CCI categories was an increased burden of comorbidity accrual in male patients with SLE compared with women at baseline (data not shown). These data confirm similarity to the accelerated comorbidity accrual seen in males, as shown for incident CVD in the general population,³⁶ combined with the increased prevalence of CVD risk factors shown herein and elsewhere.^{30 32} Taken together, our data would suggest that male and female patients with SLE have comparable mortality rates, although where differences do arise, it would most likely be related to a comorbidity effect rather than SLE-specific factors or the inherent sex bias of females with SLE.^{37–39}

We confirmed data from cohort and population-level studies that patients with SLE died more than 10 years earlier than non-exposed controls,^{4 28 40} and that patients with SLE have an increased likelihood and risk of mortality from across those < 40 up to 70 years of age.^{4 41–45} Similar to other studies, we also demonstrated significantly (aHR 7.46) increased risk of mortality in patients with SLE under 40 years of age.⁴ However, we also demonstrated that patients with SLE exhibit a bimodal pattern of mortality (figure 2B), in which early deaths relate to active (‘flaring’) disease and/or the higher incidence of infection, and later deaths related to increased atherosclerotic CVD, side effects of long-term treatment and comorbidity.⁴⁶

The Aboriginal population of Western Australia is approximately 3%; both Aboriginal Australians with (7.8%) and without SLE (6.0%) were over-represented in our study. The increased prevalence of SLE in Aboriginal

Table 4 Competing risks analysis of the association between a hospitalisation for SLE with causes of death from 1980 to 2014

	SLE n=2111	Hospital-based controls n=21 110	Adjusted HR (95% CI)
Certain infectious and parasitic diseases (A00–B99)	67 (3.2)	128 (0.6)	4.38 (3.15 to 6.09)
Septicaemia	48 (2.3)	102 (0.5)	3.95 (2.72 to 5.73)
Influenza and/or pneumonia (J00–J18)	49 (2.3)	225 (1.1)	2.16 (1.57 to 2.97)
Malignancy (C00–C97)	121 (5.7)	897 (4.2)	0.94 (0.76 to 1.15)
Digestive tract	27 (1.3)	263 (1.2)	0.76 (0.50 to 1.15)
Lung cancer	28 (1.3)	172 (0.8)	1.27 (0.84 to 1.95)
Lymphatic and hematopoietic tissues	17 (0.8)	76 (.4)	1.91 (1.10 to 3.31)
Breast	12 (0.6)	100 (0.5)	0.71 (0.38 to 1.31)
Skin cancer or melanoma	4 (0.2)	25 (0.1)	1.07 (0.36 to 3.17)
Central nervous system	4 (0.2)	31 (0.1)	0.94 (0.32 to 2.78)
Benign neoplasms (D00–D49)	8 (0.4)	28 (0.1)	2.54 (1.21 to 5.36)
Blood, blood-forming organs and/or immune related (D50–D89)	44 (2.1)	56 (.3)	6.47 (4.28 to 9.77)
Anaemias	21 (1.0)	33 (.2)	5.83 (3.39 to 10.04)
Endocrine, nutritional and metabolic diseases (E00–E90)	72 (3.4)	307 (1.5)	1.67 (1.27 to 2.20)
Diabetes	41 (1.9)	213 (1.0)	1.20 (0.85 to 1.69)
Mental and behavioural disorders (F00–F99)	39 (1.8)	280 (1.3)	1.42 (1.01 to 2.01)
Substance abuse disorders	13 (0.6)	67 (0.3)	1.74 (0.94 to 3.22)
Intentional self-harm	6 (0.3)	11 (0.1)	5.39 (1.90 to 15.28)
Diseases of the nervous system (G00–G99)	38 (1.8)	208 (1.0)	1.75 (1.23 to 2.49)
Dementia	23 (1.1)	278 (1.3)	0.89 (0.57 to 1.37)
Parkinson's	3 (.1)	30 (.1)	1.11 (0.33 to 3.80)
Cardiovascular disease (I00–I99)	268 (12.7)	1231 (5.8)	2.09 (1.79 to 2.45)
Congestive heart disease	116 (5.5)	604 (2.9)	1.80 (1.45 to 2.23)
Hypertensive disease	71 (3.4)	398 (1.9)	1.78 (1.36 to 2.32)
Heart failure	64 (3.0)	244 (1.2)	2.47 (1.85 to 3.29)
Cerebrovascular disease	53 (2.5)	349 (1.7)	1.39 (1.03 to 1.87)
Vascular disease	35 (1.7)	108 (0.5)	2.64 (1.78 to 3.91)
Arrhythmias	19 (0.9)	159 (0.8)	1.12 (0.69 to 1.83)
Respiratory system (J00–J99)	139 (6.6)	571 (2.7)	2.26 (1.85 to 2.76)
Chronic pulmonary disease	46 (2.2)	225 (1.1)	1.74 (1.26 to 2.40)
Respiratory failure	26 (1.2)	106 (0.5)	2.08 (1.33 to 3.25)
Diseases of the digestive system (K00–K93)	57 (2.7)	200 (0.9)	2.27 (1.67 to 3.08)
Chronic liver disease	23 (1.1)	58 (0.3)	2.56 (1.53 to 4.29)
Gastrointestinal bleeding	7 (0.3)	47 (0.2)	1.31 (0.59 to 2.94)
Diseases of the skin and subcutaneous system (L00–L99)	17 (0.8)	22 (0.1)	7.74 (3.93 to 15.25)
Musculoskeletal, connective tissue and subcutaneous diseases (M00–M99)	168 (8.0)	37 (0.2)	–
SLE	135 (6.4)	0 (0.0)	–
Diseases of the genitourinary system (N00–N99)	87 (4.1)	227 (1.1)	3.43 (2.64 to 4.46)
Renal failure	71 (3.4)	186 (0.9)	3.39 (2.54 to 4.51)
Renal or urinary tract infection	16 (0.8)	31 (0.1)	5.20 (2.85 to 9.50)

Competing risks Cox proportional HRs adjusted for age, sex, Aboriginality and Charlson Comorbidity Index (CCI) categories (CCI=0, CCI=1–2 or CCI>2).

Australians aligns with earlier reports of a twofold higher prevalence of SLE in Aboriginal Australians compared with non-Aboriginal Australian cohorts.^{7 8 47} Overall, Aboriginal patients with SLE had the highest age-adjusted and sex-adjusted risk of mortality (aHR 3.32). Yet the risk of mortality in non-Aboriginal Australians with SLE was similar to other studies.^{4 48} Our data mirror the literature, which indicates that ethnicity is an important determinant of SLE prevalence, severity and survival.⁴⁹ We showed that Aboriginal Australians remained the most vulnerable group in the 2000–2014 period (aHR 2.63). However, the association between a hospitalisation and mortality in Aboriginal Australians was attenuated in the fully adjusted model (data not shown). This finding mirrored the Australian Institute of Health and Welfare's data which showed that Aboriginal Australians die much earlier than non-Aboriginal Australians (MR 1.60),⁵⁰ and aligns with the long-established mortality gap between Aboriginal and non-Aboriginal Australians.^{51 52} While there are some differences between Aboriginal and non-Aboriginal patients with SLE with respect to the increased prevalence of anti-Smith autoantibodies,^{8 11} lupus nephritis^{7 9} and cytopenias⁸ as well as treatment-related factors (non-adherence or non-compliance),⁵³ environmental factors, such as ultraviolet radiation exposure (nationwide), and the prevalence of infection in remote or subtropical Northern regions,^{7 47} SLE was found to be an independent risk factor for mortality herein. Our findings suggest that accrual of comorbidity and modifiable risk factors are still the strongest determinants of premature mortality in Aboriginal Australians, beyond that of SLE.

We found that a hospitalisation for SLE increased the risk of mortality across all levels of socioeconomic status, with the highest risk in the most disadvantaged group (aHR 2.49). This finding confirms that survival in patients with SLE is impacted by low socioeconomic status, especially for ethnic minorities, such as African Americans.⁵⁴ The relative high risk of mortality across all SEIFA quintiles may reflect the composition of the IRSAD index, which takes into account household income, internet access, highest educational attainment, family status, unemployment, profession type (labour/managerial/professional), disability, cost of living and asset ownership (cars/home/rental properties). Taken together, a hospitalisation for SLE affects survival across all strata of society, with the most disadvantaged being the most vulnerable.

While patients with SLE are at increased risk of many comorbidities, we showed that prevalent rheumatic diseases occurred in 10.0% at timezero. This is lower than the 38% (n=229/600) reported by Lockshin *et al* data which included anti-phospholipid syndrome, rheumatoid arthritis, Sjögren's, thyroid disease and other rheumatic diseases. Within patients with SLE, we found that those with another rheumatic disease did not influence the risk of mortality. While the data on the outcomes of patients with SLE with another (overlapping) autoimmune condition are scarce, these fit with the data showing that the

mortality risk is still higher in patients with SLE⁵⁵ or patients with SLE-like features,⁵⁶ rather than other rheumatic diseases, such as rheumatoid arthritis, which has seen improved survival over time.⁵⁷ In addition, we found that patients with SLE with prevalent (lupus) nephritis, proteinuria and haematuria were at increased risk of mortality, which fits with the literature and highlights the long known concerns for renal involvement in SLE.⁵⁸ Furthermore, we found no difference in the mortality risk after a hospitalisation for SLE in those with antiphospholipid syndrome (APS) or prevalent thromboembolic events. Frodlund *et al*'s study showed that prevalent APS was linked to damage accrual.⁵⁹ We found that prevalent thromboembolic events (of which APS was prevalent in >30%) attenuated (was an effect modifier of) the association between a hospitalisation for SLE and mortality, which signifies that thromboembolic events influence survival. Taken together, this suggests that well-controlled APS may not increase the risk of mortality in patients with SLE in the absence of a clinical event. However, further studies are needed to determine the association between APS (substantiated with laboratory findings) and clinical thromboembolic events with premature mortality in patients with SLE.

With respect to the causes of death, we found that patients with SLE did not experience an increased risk of cancer-related deaths, which aligns with Yurkovich *et al* (meta-SMR 1.19, 95% CI 0.89 to 1.59).³ However, we found that patients with SLE had increased risk of mortality with malignancies of the lymphatic and hematopoietic tissues, which aligned with the literature about the increased risk of lymphoma in patients with autoimmune disease.^{60 61} Our data confirmed the increased likelihood and risk of a range of underlying causes of mortality in patients with SLE, in particular, infection, cardiovascular (CVD), respiratory⁶² and genitourinary (renal) diseases.³ In addition, patients with SLE had increased risk of mortality with leucopenia, thrombocytopenia and anaemias of chronic disease.⁶³ This fits with the data on the association of thrombocytopenia in SLE being associated with a worse prognosis and premature mortality.⁶⁴ Furthermore, we confirm the limited data which suggest that patients with SLE had increased likelihood and risk of mortality related to gastrointestinal disease,⁶⁵ hepatic disease, thyroid disorders, mental and behavioural disorders,^{66 67} neurological diseases⁶⁸ and osteoporosis.⁶⁹ Collectively, this demonstrates that patients with SLE have a higher burden of a wide range of comorbidities at the time of death.

The limitations of this study pertain to the identification of patients with SLE who required hospital services, that is, emergency department presentations and hospital admissions; this meant that we might not have captured those milder SLE cases who may have been managed in the community, outpatient or private practice settings, respectively. Furthermore, we were not able to ascertain whether our patients with SLE met classification criteria due to the lack laboratory data captured in the HMDC. However, this should not be

considered a major issue as another study showed that only a small number of patients with SLE went without hospitalisation over an 11-year period (6.2%, n=19/309).²⁰ Despite this potential selection bias, our mortality estimates were similar to a range of clinical, cohort and registry-based studies, and, despite the different health-care settings, we produced nearly identical estimates to those from a primary care setting.^{4 5 29} The relative strength and stability of our estimates are ensured by the ability to identify a large number of patients with SLE during a 35-year period, which allowed for an average of 9 years of lookback and 14 years of follow-up. Our SLE cohort of 2111 in the context of an average population of 2.1 million in Western Australia over the study period approximates the 1:1000 prevalence reported in other studies.⁷⁰ In addition, we ascertained complete mortality data from the WA Death Registry, which captures all death events in the state, ensuring that we accurately identified this outcome for all patients.

In conclusion, hospital-ascertained patients with SLE were at an increased risk of all-cause and cause-specific mortality compared with hospital-based controls and the general population of WA from 1980 to 2014. The risk of death was especially high for younger patients with SLE (<40 years of age), socioeconomically disadvantaged, Aboriginal Australians and those with prevalent nephritis. Critically, our findings show that for moderate-to-severe SLE, the risk of premature mortality remained throughout the 2000 to 2014 period.

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