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Multicentre retrospective cohort study assessing the incidence of serious infections in patients with lupus nephritis, compared with non-renal systemic lupus erythematosus

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To cite: Yates DJ, Mon SY, Oh Y, *et al*. Multicentre retrospective cohort study assessing the incidence of serious infections in patients with lupus nephritis, compared with non-renal systemic lupus erythematosus. *Lupus Science & Medicine* 2020;**7**:e000390. doi:10.1136/lupus-2020-000390

Received 6 February 2020
Revised 4 August 2020
Accepted 8 August 2020

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ABSTRACT

Objectives The incidence of serious infections is poorly defined in patients with lupus nephritis (LN). It is also unclear if LN influences risk of serious infections in a longitudinal analysis. The aim of this study was to determine the incidence of serious infections in patients with SLE and LN, compared with patients with SLE without LN.

Methods A multicentre retrospective cohort study was conducted. Patients with LN identified at two tertiary centres were matched where possible with age and gender-matched patients with SLE without LN.
Any infection requiring inpatient admission, occurring in the 6 months following index clinical visit, was considered serious. Cox regression was employed to investigate the association between risk of serious infection and LN status, and other relevant covariates.

Results A total of 173 patients were included within the analysis (n=87 LN, n=86 SLE only). A total of 9.2% (n=8) of patients with LN experienced at least one serious infection within the study period, compared with 5.8% (n=5) of patients without LN, equivalent to 19.5 and 12.0 infections per 100 patient-years with and without LN, respectively. Univariable and multivariable analyses found no significant increased risk of serious infection in patients with LN versus controls (HR 1.61; 95% CI 0.53 to 4.92 and adjusted HR (aHR) 0.91; 95% CI 0.27 to 3.06, respectively). Increased prednisone dose and modified SLE comorbidity index were strongly associated with serious infection (aHR (per 5 mg) 1.21; 95% CI 1.07 to 1.37; p=0.003 and aHR 1.13; 95% CI 1.02 to 1.25; p=0.018, respectively).

Conclusions In this cohort, adjusting for cofactors, the presence of LN alone does not appear to increase the risk of serious infections compared with patients with SLE without LN. However, increased prednisone dose at baseline visit and increasing comorbidity were independently associated with the incidence of serious infection.

INTRODUCTION

SLE is a systemic autoimmune condition associated with substantial mortality and morbidity. Perturbations in the immune system, including impaired neutrophil function, functional hyposplenia, impaired clearance of opsonised bacteria, reduced antibody response, genetic factors and deficiencies in mannose-binding lectin coupled with requirements for significant immunosuppression, predispose patients to serious infections.[1–9] Indeed, previous research has suggested patients with SLE are at a sixfold to sevenfold increased risk of serious infection, compared with the general population.[10]

Infections in patients with SLE are a significant cause of increased hospitalisation and mortality.[3 5–7] Research thus far has suggested that patients with SLE are at particular risk of serious bacterial infections,[11] in addition to viral, tuberculous, non-tuberculous mycobacterial and fungal infections.[11 12] Previous studies have suggested that infection risk is modulated by disease activity, male gender, glucocorticoid use and use of other immunosuppressant agents.[11 13]

Furthermore, lupus nephritis (LN) is a significant complication of SLE, and is itself associated with significant mortality and morbidity.[14] A recent retrospective study found high rates of hospitalised infections in patients with biopsy-proven LN, with 60.3% of patients being hospitalised for infection within 11 months of diagnosis and infection-related mortality occurring in 5.3% of patients.[7] A large population-based study found significantly higher rates of serious infections in an SLE with LN subgroup,[4] however it is unclear if this excess burden of infection is related to increased requirements for immunosuppression in this patient cohort, critical in improving renal survival and mortality,[15] or the presence of LN itself. Additionally, the

incidence and types of infections in patients with SLE and LN in an Australian cohort remain undefined.

Hence, the aim of this study was to determine the incidence of serious infections in patients with SLE without renal involvement, compared with age and gender-matched controls with LN in an Australian cohort, adjusting for relevant cofactors including immunosuppression and disease activity in a 6-month observational period.

METHODS

Study design and participants

A retrospective cohort study was performed at a metropolitan tertiary referral centre and a regional tertiary referral centre in Queensland, Australia. Ethical approval, including informed consent waiver, was granted for the study, in addition to local research governance approvals at both study centres.

Patients greater than or equal to 18 years of age with biopsy-proven, or with renal physician-diagnosed probable LN in the absence of biopsy were identified in clinical records as attending renal or rheumatology outpatient services, or as inpatients under either service. LN, in the absence of biopsy, was defined as SLE with proteinuria and renal impairment, as per previous research.[3] These patients were matched by age and gender, to controls attending rheumatology outpatient clinics with rheumatologist-diagnosed SLE identified in clinical records. Index clinical visit occurred between July 2009 and May 2016 and was selected according to earliest and most complete available patient record. Patients were excluded if an alternative cause for nephritis other than LN was identified in the patient record.

Serious infections

Serious infections were defined as infection of any type, necessitating inpatient admission for management occurring within six calendar months of follow-up following index clinical visit, with a 6-month follow-up period selected in accordance to other similar studies.[3] These were identified using clinical notes, in addition to microbiological, PCR and radiographic evidence of type and site. Infections of different pathogens, occurring at alternate sites and requiring inpatient therapy during the same admission, were included as new infections. Infections at the same site required ≥30 days separation between admissions to be included as recurrent events.

Patient characteristics

Baseline patient characteristic data were collected at index clinic review. Baseline renal function was defined by creatinine, estimated glomerular filtration rate, urea and, where available, urinary protein:creatinine ratio (PCR) and/or 24-hour urinary protein.

Lupus activity at initial study visit was defined retrospectively using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),[16–19] and a lupus-specific comorbidity index was also calculated for each patient; 2 (congestive heart failure+cerebrovascular accident+-diabetes+nephritis+chronic renal failure+pleuritis)+3 (AIDS+myocardial infarction+metastatic cancer+pericarditis)+4 (any malignancy+thrombocytopenia)+6 (peripheral vascular disease)+8 (severe liver disease).[20] Modified SLE comorbidity score was calculated using SLE-specific index—2 for patients with LN.

Baseline immunosuppression was identified at index visit. Prednisone dose at inclusion was assessed, in addition to administration of hydroxychloroquine, mycophenolate, cyclophosphamide (intravenous or oral), azathioprine, cyclosporine, methotrexate, leflunomide, rituximab or tacrolimus. Administration of *Pneumocystis jirovecii* pneumonia prophylaxis at index visit was also recorded.

Secondary outcome measures

In addition to serious infections, data related to mortality and other morbidity were collected. All-cause mortality during the follow-up period was identified, as was hospital length of stay due to any cause, in addition to length of any intensive care unit (ICU) admission.

Statistical analysis

Patient characteristics and outcomes were summarised according to LN or SLE groups using frequencies and percentage for categorical variables and mean (SD) or median (IQR) for continuous variables. Associations between LN status and patient characteristics were assessed using χ^2 or Fisher's exact test for categorical variables, and a Student's t-test or Mann-Whitney U test for continuous variables. ORs were estimated using a logistic regression model for hospital admission and death within 6 months.

Associations between risk of serious infection and specified variables were assessed using a univariable Cox regression analysis. For multivariable modelling, variables with fewer than 10% missing values and with $p<0.2$ in univariate analysis were included in the initial model, then covariates were sequentially eliminated if covariates were neither significant on basis of Wald test at 5% level, nor important confounders based on the change of a coefficient of LN status where >20% was used as an indicator of important change. Modified SLE-specific comorbidity index which was calculated by excluding LN was included in the multivariable model to avoid structural multicollinearity between SLE-specific comorbidity index and LN status. Proportional hazards assumptions were assessed using scaled Schoenfeld residuals. STATA V.15 was used for data analysis, and statistical significance level was set at 0.05.

RESULTS

A total of 87 patients with LN were identified in clinical records between July 2009 and May 2016. A total of 86 appropriate age and gender-matched controls were identified with SLE in the absence of LN over the same period (table 1).

Table 1 Baseline patient characteristics

	SLE only n=86	LN n=87	P value
Gender¶			0.007
Male	5 (6%)	17 (20%)	
Female	81 (94%)	70 (80%)	
Age (years),§ mean (SD)	42.9 (15.5)	39.8 (15.7)	0.20
Location¶			0.32
Metropolitan	49 (57%)	56 (64%)	
Regional	37 (43%)	31 (36%)	
AASTI status¶			0.64
Non-ATSI	78 (91%)	77 (89%)	
ATSI	8 (9%)	10 (11%)	
SLEDAI score*, median (IQR)	2 (0–4)	8 (4–16)	<0.001
SLE comorbidity index*, median (IQR)	0 (0–0)	2 (2–5)	<0.001
eGFR¶			0.002
≥90	50 (58%)	35 (40%)	
60	22 (26%)	18 (21%)	
30–59	5 (6%)	18 (21%)	
15–29	0 (0%)	7 (8%)	
<15	9 (10%)	9 (10%)	
Total number of immunosuppressant agents,*† median (IQR)	2.0 (1.0–2.0)	3.0 (2.0–3.0)	<0.001
Total number of immunosuppressant agents†¶			<0.001
0	10 (12%)	3 (3%)	
1	31 (36%)	7 (8%)	
2	30 (35%)	22 (25%)	
3+	15 (17%)	55 (63%)	
Prednisone (n=169)¶	37 (44%)	72 (85%)	<0.001
Prednisone (total daily dose or equivalent, mg),* median (IQR)	0.0 (0.0–5.0)	5.0 (3.0–15.0)	<0.001
Hydroxychloroquine¶	68 (79%)	69 (79%)	0.97
Mycophenolate¶	3 (3%)	45 (52%)	<0.001
Cyclophosphamide‡	3 (3%)	26 (30%)	<0.001
Azathioprine¶	9 (10%)	20 (23%)	0.027
Cyclosporine¶	0 (0%)	3 (3%)	0.25
Methotrexate¶	16 (19%)	6 (7%)	0.021
Leflunomide‡	3 (3%)	1 (1%)	0.37
Rituximab‡	0 (0%)	1 (1%)	1.00
Tacrolimus‡	0 (0%)	5 (6%)	0.059
Creatinine* (µmol/L, n=166), median (IQR)	64 (52–70)	78 (59–113)	<0.001
Urine protein:creatinine ratio* (n=118), median (IQR)	9 (3–16)	84 (16–302)	<0.001
Lupus duration* (years, n=165), median (IQR)	6.0 (1.9–14.7)	6.6 (1.7–12.6)	0.98
Lupus nephritis class			
Class I		1 (1%)	

Continued

Table 1 Continued

	SLE only n=86	LN n=87	P value
Class II		4 (5%)	
Class III		18 (21%)	
Class IV		33 (38%)	
Class V		11 (13%)	
Class III, class V		5 (6%)	
Class IV, class V		3 (3%)	
Unknown		12 (14%)	
Biopsy proven			
No		7 (8%)	
Yes		76 (87%)	
Unknown		4 (5%)	
Median time from biopsy to index visit (IQR) (years, n=76)		0.8 (0.1–5.9)	

*Mann-Whitney U test.
†Total number of immunosuppressant agents includes prednisone.
‡Fisher's exact test.
§Student t-test.
¶χ^2 test.
ATSI, Aboriginal and Torres Strait Islander; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Lupus activity was significantly higher in the LN cohort, with a median SLEDAI of 8 (IQR 4–16) vs 2 (IQR 0–4) in the SLE only group (p<0.001) (table 1). Lupus-specific comorbidity index was higher in the LN group versus the SLE only group; median 2 (IQR 2–5) vs 0 (IQR 0–0). Median time from lupus diagnosis to index clinical visit was similar between groups; 6.6 years (IQR 1.7–12.6) in LN vs 6.0 years (IQR 1.9–14.7) in SLE only (p=0.98) (table 1).

Median baseline serum creatinine was significantly higher in the LN cohort; 78 µmol/L (IQR 59–113) vs 64 µmol/L (IQR 52–70) (p<0.001). Median urine PCR was significantly higher in patients with LN versus patients with SLE only; 84 (IQR 16–302) vs 9 (IQR 3–16) (p<0.001) in the 118 patients where this was available at baseline visit (table 1).

Eighty-seven per cent of patients included within the LN cohort were biopsy proven, with 8% not biopsied due to the procedure being contraindicated and 5% with historically diagnosed LN, however no explicit record of biopsy being performed. A majority of patients were diagnosed with class IV LN (38%), followed by class III (21%) (table 1).

The total number of immunosuppressant agents at inclusion visit, including prednisone, was higher in the LN group versus SLE only. Three per cent of patients with LN vs 12% of patients with SLE only were receiving no immunosuppression at inclusion. Eight per cent of patients with LN vs 36% of patients with SLE were receiving one agent, 25% vs 35% were receiving two agents and 63% of patients with LN were receiving ≥3 agents at inclusion (p<0.001) (table 1).

Eighty-five per cent of patients with LN vs 44% of patients with SLE were receiving any dose of prednisone at inclusion. Median prednisone dose was higher in the LN group versus SLE only; 5.0 (IQR 3.0–15.0) vs 0.0 (IQR 0.0–5.0) (p<0.001). Significantly more patients with LN received either mycophenolate, cyclophosphamide or azathioprine. A majority of patients with either LN or SLE received hydroxychloroquine (79% vs 79%, p=0.97) (table 1).

Eight patients (9.2%) within the LN cohort were diagnosed with at least one serious infection during the study period, with two (2.3%) being diagnosed with two discrete infections (table 2). Within the SLE only group, five (5.8%) patients experienced a serious infection with a single patient (1.2%) being diagnosed with two discrete infections. Of these serious infections, a majority were bacterial. The incidence rate of serious infections in the LN cohort was 19.5 (95% CI 9.7 to 38.9) per 100 patient-years and 12.0 (95% CI 5.0 to 28.9) per 100 patient-years in the SLE only cohort (table 2).

The total number of hospital admissions, regardless of cause, was similar between groups; 27.6% in LN vs 19.8% in SLE only (p=0.23). Hospital length of stay was also similar; 4.0 days (IQR 1.5–11.5) vs 5.5 days (IQR 1.5–22.0) in SLE only groups (p=0.56) (table 3). There were two deaths within the follow-up period within both groups (2.3% in patients with SLE only, 2.3% in patients with LN, p=0.99) (table 3). Of these deaths, one in the SLE

Table 2 Incidence of serious infections by LN status

	SLE only n=86	LN n=87
Number of serious infections per person		
0	81 (94.2%)	79 (90.8%)
1	4 (4.7%)	6 (6.9%)
2	1 (1.2%)	2 (2.3%)
First serious infection	5 (5.8%)	8 (9.2%)
Infection site (n=13)		
Cystitis	0 (0%)	1 (13%)
Cellulitis	0 (0%)	2 (25%)
Gastroenteritis	0 (0%)	2 (25%)
Mucositis	0 (0%)	1 (13%)
Pelvic inflammatory disease	1 (20%)	0 (0%)
Pneumonia	3 (60%)	1 (13%)
Psoas abscess	1 (20%)	0 (0%)
Pyelonephritis	0 (0%)	1 (13%)
Infection type (n=13)		
Bacterial	4 (80%)	3 (38%)
Viral	0 (0%)	3 (38%)
Mycobacterial	1 (20%)	0 (0%)
Unknown	0 (0%)	2 (25%)
Identified pathogen (n=13)		
HSV1	0 (0%)	1 (13%)
Herpes zoster	0 (0%)	1 (13%)
Clostridium difficile	0 (0%)	1 (13%)
Mycobacterium tuberculosis complex	1 (20%)	0 (0%)
Neisseria gonorrhoeae	1 (20%)	0 (0%)
Norovirus	0 (0%)	1 (13%)
Stenotrophomonas maltophilia	1 (20%)	0 (0%)
Streptococcus pneumoniae	1 (20%)	0 (0%)
Streptococcus pyogenes	1 (20%)	0 (0%)
Unknown	0 (0%)	2 (25%)
No growth	0 (0%)	2 (25%)
Second serious infection	1 (1.2%)	2 (2.3%)
Infection site (n=3)		
Peritonitis	0 (0%)	1 (50%)
Pneumonia	0 (0%)	1 (50%)
Septic arthritis	1 (100%)	0 (0%)
Infection type (n=3)		
Bacterial	1 (100%)	2 (100%)
Identified pathogen (n=3)		
Pseudomonas aeruginosa	1 (100%)	0 (0%)
Staphylococcus epidermidis	0 (0%)	1 (50%)
Streptococcus pneumoniae	0 (0%)	1 (50%)

Data are presented as n (%).
HSV1, herpes simplex virus 1; LN, lupus nephritis.

only group was in the context of admission for *Stenotrophomonas maltophilia* pneumonia.

In univariable Cox regression analysis, LN status was not associated with increased risk of serious infection (HR 1.61; 95% CI 0.53 to 4.92; p=0.40) (table 4). Modified SLE comorbidity index score (excluding LN contribution), daily prednisone dose, serum creatinine and urine PCR were significantly associated with risk of infection (p<0.05 respectively). No significant association was identified between risk of infection and other factors.

Modified SLE comorbidity index score, daily prednisone dose, SLEDAI score, duration of SLE and number of immunosuppressant agents which had p values <0.2 in univariate analysis were included in the initial multivariable model. Urine PCR was not included due to large number of missing values. Of those, daily prednisone dose and modified SLE comorbidity index were identified as independent predictors. After adjusting for these factors, LN status was not associated with increased risk of infection (adjusted HR (aHR) 0.91; 95% CI 0.27 to 3.06; p=0.88). Only prednisone dose at inclusion (aHR 1.21; 95% CI 1.07 to 1.37, p=0.003) and modified SLE comorbidity index (aHR 1.13; 95% CI 1.02 to 1.25; p=0.018) were associated with an increased risk of serious infection on multivariable analysis (table 4).

Given the study included patients with LN at any time subsequent to diagnosis, an exploratory analysis was performed to assess risk of serious infection in patients ≤6 months post-diagnostic renal biopsy. Univariable analysis suggested that, compared with patients with SLE only, there was a higher risk of serious infection in patients with biopsy-proven LN (HR 1.86; 95% CI 0.61 to 5.67; p=0.28) and a significantly greater risk in patients with LN ≤6 months postdiagnostic renal biopsy (HR 3.72; 95% CI 1.08 to 12.85; p=0.038).

Exploratory analyses were also performed regarding individual immunosuppressant agents. Covariates including prednisone dose <5 or ≥5 mg, in addition to whether patients were receiving either cyclophosphamide or mycophenolate, were included within a further multivariable model. Of these covariates, prednisone and cyclophosphamide did not confer a significant increased risk of infection on univariable analysis; prednisone ≥5 mg

Table 3 Secondary outcomes by LN status

	SLE only n=86	LN n=87	OR (95% CI) (ref=SLE only)	P value
Hospital admission*	17 (19.8%)	24 (27.6%)	1.55 (0.76 to 3.14)	0.23
Hospital LoS (days, n=40)†	5.5 (1.5–22.0)	4.0 (1.5–11.5)		0.56
ICU admission*	1 (1.2%)	0 (0.0%)	ND	0.50
Death within 6 months F/U*	2 (2.3%)	2 (2.3%)	0.99 (0.14 to 7.18)	0.99

*Presented as n (%) and OR based on a binary logistic regression.
†Presented as median (IQR) and tested using Mann-Whitney U test.
F/U, follow-up; ICU, intensive care unit; LN, lupus nephritis; LoS, length of stay; ND, not determined due to zero event.

(HR 3.0; 95% CI 0.83 to 10.91; p=0.095) and cyclophosphamide (HR 0.91; 95% CI 0.2 to 4.11; p=0.90).

Mycophenolate was found to be associated with a greater risk of infection in the univariable model (HR 4.39; 95% CI 1.43 to 13.4; p=0.010), however this effect was not significant when adjusted for daily prednisone dose and SLE comorbidity index (aHR 2.62; 95% CI 0.78 to 8.83; p=0.12).

DISCUSSION

In this retrospective cohort study, significant rates of serious infections requiring hospitalisation occurred in patients with SLE and with LN in an Australian cohort. The incidence rate of 19.5 infections per 100 patient-years in the LN cohort is comparable to 23.9 infections per 100 patient-years determined by Feldman *et al*,[4] as was the incidence in non-renal lupus in the same study; 10.8 infections per 100 patient-years.

No statistically significant difference was detected in risk of serious infections between the patient groups based on univariable and multivariable Cox regression models. Analysis for incidence was not made in the largest contemporary study comparing both cohorts.[4] Nephritis was also not determined to be a significant cofactor in serious infection in an SLE cohort on multivariable regression in Ruiz-Irastorza *et al*'s research.[21] Furthermore, no statistically significant difference was detected in hospital admissions, hospital length of stay, ICU admission and death within the follow-up period.

Regarding the LN cohort, a recent study by Lim *et al*[7] found a significantly higher rate of infection in contrast to this study, with 27.0% of subjects with LN identified experiencing an infection within 6 months of diagnosis. The index event in Lim *et al*'s study, however, was diagnosis of LN, as opposed to at any stage during the disease course as in this study, with higher levels of immunosuppression expected within this time frame. Exploratory analysis of this cohort did identify significantly higher rates of serious infections in a subset of patients with LN ≤6 months from diagnostic biopsy. Furthermore, 94.2% of patients were receiving glucocorticoids in that study, compared with 85% of patients with LN in this cohort, however the median dose was not defined.

Another possible explanation for the lower rate of serious infection in the LN cohort may be the higher proportion of patients receiving hydroxychloroquine at index visit; only 48.2% of patients with LN who were hospitalised with infection in Lim *et al*'s study were receiving hydroxychloroquine.[7] Indeed, this difference was also noted in other populations, with only 54% of patients coprescribed mycophenolate and 54.5% of patients coprescribed azathioprine receiving hydroxychloroquine in a large, propensity-matched SLE cohort.[3] Only 45% of patients in a Chinese SLE cohort study were administered hydroxychloroquine.[5] Current evidence suggests that antimalarial administration in patients with SLE leads to significantly lower risk of serious infection,[10 22] with antimalarial administration an independent factor in reduced infection risk on multivariable regression,[21] a finding also mirrored in recent research by Feldman *et al*.[4]

While no relationship between the presence of LN and serious infection risk was found in this study, a significant association was found between prednisone dose and risk of serious infection. This relationship has been identified in several previous studies. Ruiz-Irastorza *et al* determined an OR=1.12 (95% CI 1.04 to 1.19) for steroid dose (mg/day). Corticosteroid use in general was also associated with an increased risk of infection in Gladman *et al*'s research, with OR=3.0 (95% CI 1.15 to 9.31). This association was also observed in multivariable modelling in both Ruiz-Irastorza's research and in this study. In further modelling, no significant relationship between cyclophosphamide administration and serious infections was found in in this research. However, on univariable analysis, increased risk with mycophenolate was determined, in partial agreement with Ruiz-Irastorza, who found a significant relationship between mycophenolate and cyclophosphamide on univariable analysis; however, this was not noted on further multivariable analysis for these cofactors in an SLE cohort.[21]

The significantly increased HR for infection identified on univariable analysis associated with serum creatinine and protein:creatinine ratio, coupled with the aforementioned relationship with prednisone dose, may also suggest that severity of LN, as opposed to class, is associated with increased risk of infection. Indeed, the positive relationship between increasing comorbidity index and risk of serious infection supports the assertion that overall disease SLE/LN severity contributes to infection risk.

Table 4 Univariable and multivariable Cox regression analysis

	Univariable model		Multivariable model			
			Initial model (n=155)		Final model (n=169)	
	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
LN status		0.40		0.91		0.88
No	1.00		1.00		1.00	
Yes	1.61 (0.53 to 4.92)		1.09 (0.25 to 4.79)		0.91 (0.27 to 3.06)	
Gender		0.76				
Male	1.00					
Female	0.79 (0.18 to 3.57)					
Age (years)	1.01 (0.97 to 1.04)	0.74				
ATSI status		0.73				
No	1.00					
Yes	0.70 (0.09 to 5.38)					
Location		0.60				
Metropolitan	1.00					
Regional	1.33 (0.45 to 3.97)					
SLE comorbidity index	1.12 (1.03 to 1.23)	0.008				
Modified SLE comorbidity index*	1.14 (1.04 to 1.24)	0.007	1.14 (0.97 to 1.33)	0.12	1.13 (1.02 to 1.25)	0.018
SLEDAI score	1.04 (0.99 to 1.09)	0.10	0.97 (0.89 to 1.06)	0.51		
Prednisone dosage (per 5 mg)	1.21 (1.08 to 1.36)	0.001	1.22 (1.05 to 1.42)	0.008	1.21 (1.07 to 1.37)	0.003
Creatinine (per 100 µmol/L)	1.22 (1.04 to 1.44)	0.015	1.16 (0.92 to 1.46)	0.21		
Urine protein:creatinine ratio† (n=118)	1.27 (1.05 to 1.55)	0.016				
Lupus duration (years)	0.93 (0.85 to 1.02)	0.13	0.93 (0.84 to 1.04)	0.20		
Number of immunosuppressant agents (continuous)‡	1.38 (0.91 to 2.11)	0.13	1.03 (0.54 to 1.98)	0.92		
Number of immunosuppressant agents‡		0.16				
<2	1.00					
2+	2.32 (0.71 to 7.54)					

*SLE comorbidity index score excluding LN contribution.
†Urine protein:creatinine ratio was not included in the multivariate model due to large number of missing values (n=55).
‡Number of immunosuppressant agents other than prednisone.
ATSI, Aboriginal and Torres Strait Islander; LN, lupus nephritis; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

Recent studies have demonstrated that reduced dose, or corticosteroid-free regimes are effective in the management of LN. An exploratory study by Zeher *et al*[23] suggested that mycophenolate with a reduced dose corticosteroid regime achieved similar complete renal response to a standard regime. Intravenous methylprednisolone combined with reduced dose oral prednisone produced similar complete renal remission rates when combined with cyclophosphamide.[24] Steroid-free cyclophosphamide regimes have also shown comparable rates of complete remission in observational data.[25] This, in addition to the association demonstrated in this study between steroid exposure and infection risk, underscores the importance of establishing further evidence for reduced dose steroid regimens in treating LN.

Limitations of this research include some differences in patient groups, which was the result of a minority of index LN subjects occurring in young, male patients with subsequent difficulty in matching to appropriate age and gender-matched controls. Furthermore, follow-up was

limited to 6 months after inclusion, which was selected in order to minimise variation between baseline characteristics at inclusion and at infection occurrence, however, may have led to possible underestimation of infection incidence between the treatment groups. The duration of time between renal biopsy and index visit may also have skewed the cohort towards patients with lower LN activity and hence lower overall levels of immunosuppression and infection risk. Additionally, some variation between prednisone dose at inclusion and actual dose at infection may have occurred, particularly if infection was identified during the induction phase of therapy for LN where rapid corticosteroid tapering occurs.

CONCLUSIONS

This retrospective cohort study demonstrated a significant incidence of serious infections in patients with SLE and with LN in an Australian context, with significant associated morbidity and mortality. Incidence rates in both groups appear similar to previously published research in international cohorts. LN itself does not appear to confer an increased risk of infection in patients with SLE, however increasing doses of prednisone and increasing comorbidity appear to be independently associated with increased risk of serious infection.

Contributors All authors made substantial contributions to the work in conception, design, and acquisition and analysis of data. All authors have approved the final version and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MS reports non-financial support from Pfizer, Roche, UCB, AbbVie, Janssen, Seqirus and Amgen outside the submitted work.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Obtained.

Ethics approval Ethical approval for this research was gained by Ethics Committees at Royal Brisbane and Women's Hospital (HREC/17/QRBW/28) and The Townsville Hospital (SSA/17/QTHS/139). A consent waiver was gained through both relevant ethics agencies given the observational nature of research, and the use of deidentified data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Deidentified data are available with reasonable request and pending approval of relevant ethics committees.

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