ORIGINAL ARTICLE

Tuberculosis remains a leading contributor to morbidity due to serious infections in Indian patients of SLE

Rudrarpan Chatterjee[1] · Sarit Sekhar Pattanaik[1] · Durga P. Misra[1] · Vikas Agarwal[1] · Able Lawrence[1] · Ramnath Misra[1] · Amita Aggarwal[1]

Abstract

Introduction Infections are a major cause of morbidity and mortality in systemic lupus erythematosus (SLE). We assessed the incidence and risk factors for major infections in SLE in India.

Methods A retrospective review of a cohort of 1354 patients of adult SLE (ACR 1997 criteria) seen between 2000 and 2021 at a single center was conducted. Serious infections (need for hospitalisation, prolonged intravenous antibiotics, disability, or death) were recorded. Cox regression was used to determine factors associated with serious infection and the effects of serious infection on survival and damage.

Results Among the 1354 patients (1258 females, mean age of 30.3 years, follow-up of 7127.89 person-years), there were 439 serious infections in 339 patients (61.6 per 1000 person-years follow-up). Bacterial infections ($N = 226$) were the most common infection followed by mycobacterial infections ($n = 81$), viral ($n = 35$), and then invasive fungal infections ($N = 13$). Mycobacterium tuberculosis was the single most common microbiologically confirmed organism with incidence of 1136.4/100,000 person-years with 72.8% of them being extrapulmonary. Infection free survival at 1 year and 5 years was 82.9% and 73.8%. There were 119 deaths with infection attributable mortality in 65 (54.6%). On multivariable Cox regression analysis, higher baseline activity (HR 1.02, 1.01–1.05), gastrointestinal involvement (HR 2.75, 1.65–4.69), current steroid dose (HR 1.65, 1.55–1.76), and average cumulative steroid dose per year (HR 1.007, 1.005–1.009) were associated with serious infection and higher albumin (HR 0.65, 0.56–0.76) was protective. Serious infections led to greater damage accrual (median SLICC damage index of 1 vs. 0) and mortality (HR was 18.2, 32.7 and 81.6 for the first, second, and third infections).

Conclusion Serious infections remain a major cause of mortality and damage accrual in SLE and higher disease activity, gastrointestinal involvement, hypoalbuminemia, current steroid dose, and cumulative steroid dose are the risk factors for it.

Key Points
• *Tuberculosis is still a major cause of morbidity in South Asian patients of SLE.*
• *Serious infections are associated with higher damage accrual and mortality in patients with SLE.*
• *Higher disease activity, gastrointestinal involvement, hypoalbuminemia, and current steroid dose were associated with increased risk of infection.*
• *This study provides data to enable specific recommendations for infection prevention in SLE for the South Asian region.*

Introduction

Systemic lupus erythematosus (SLE) is the prototypic autoimmune disease with chronic multisystem involvement. SLE predominantly affects young females and leads to significant morbidity and mortality. In the first decade of the disease, infections and disease activity are the leading causes of mortality in patients of SLE [1].

✉ Amita Aggarwal
aa.amita@gmail.com

1 Department of Clinical Immunology & Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

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The increased risk of infections in SLE arises from the underlying immune defects themselves like complement deficiency, impaired phagocyte function, T lymphocyte and B lymphocyte dysfunction, and immunoglobulin deficiency. In addition, immunosuppressive treatment given for the control of disease activity can lead to lymphopenia, leucopenia, neutrophil dysfunction, and other immune abnormalities [2–4].

Prevalence of serious infections in SLE ranges from 15.4 to 40% across different studies depending on the population studied and location of the study [5–8]. In a Canadian study, patients with SLE had an 82% higher risk of severe infection and had on average twice (rate ratio 2.07) the number of severe infections as compared to the general population [9].

Although overall mortality in SLE has improved over the last few decades with advances in immunosuppressive therapy, early mortality due to infections still persists with serious infection conferring a 22 times higher odds of mortality in the first year of disease [10]. Infection attributable mortality of 25% has been previously reported from a European cohort [5]. We have previously found serious infections to be a major cause of mortality in adult and juvenile onset SLE in the north Indian population [11, 12].

The profile of infections is expected to vary across different geographic regions as per the local epidemiology. Previous cohorts from Spain, Canada, and China have reported high prevalence of acute bacterial infections of the lungs and gastrointestinal and urinary tracts followed by viral infections whereas a multiethnic cohort form South Africa also reported an increased risk of tuberculosis (TB) in addition to bacterial infections [13–16]. Similarly, previous data from our center had TB as one of the important infections [12]. This implies that the preventive strategies need to be tailored according to the profile of infections prevalent in each region. The Asia Pacific League against Rheumatism (APLAR) has recently constituted a special interest group to formulate guidelines for infection prevention in the Asia Pacific region, and they found that there is paucity of data on the profile of major infections in South Asian patients of SLE [17].

Thus, this study was designed to determine the incidence as well as spectrum of serious infections in South Asian patients of SLE in North India and identify predictors of serious infection as well as their impact on patient outcomes.

Methods

We conducted a retrospective review of patients seen between 2000 and 2021 at a single rheumatology center in North India. Adult onset SLE patients with age of onset beyond 18 years, who fulfilled ACR 1997 classification criteria were included in the study. All patients were of South Asian ethnicity. Data were retrieved from hospital clinic files and the electronic health information system. Most patients in this center have follow-up visits every 3 months and at each visit clinical details, laboratory parameters (hemogram, renal function, liver functions, and urine analysis), and clinical SLEDAI scores are recorded.

In addition, detailed baseline data including demographics, organ involvement and disease activity (SLEDAI-2 K) was collected. During follow-up serious infections, corticosteroid use, background immunosuppression, complications, and disease outcomes were also recorded.

Outcomes

Serious infections

Any infection requiring hospitalization, inpatient IV antibiotic therapy, or resulting in disability of death was deemed to be serious [15]. Infections were identified based on the opinion of the treating rheumatologist with supportive evidence of microbiological confirmation by culture from the affected tissue, evidence of recent serological response to a pathogen, isolation of pathogen by polymerase chain reaction (PCR), or radiological evidence of infection. Due to the pandemic nature of the disease, COVID infections and its sequelae were excluded from the study.

Opportunistic infections

Any infection with *Mycobacterium tuberculosis*, nontuberculous mycobacteria, viral infections (*Herpes simplex, Herpes zoster*, and *Cytomegalovirus*), and invasive fungal infections (*Candida* species, *Aspergillus*, *Mucormycosis*, *Histoplasma*, and *Pneumocystic jiroveci*).

Mortality

All inpatient deaths were recorded from the hospital information system. Data on outpatient deaths were available as communicated by the patient's relatives in the hospital clinic files.

Morbidity

The SLICC damage index was calculated at the last follow-up visit for all patients.

Ethics

The study was approved by the institutional ethics committee. Due to the retrospective nature, the ethics committee approved a waiver of informed consent (IEC code no. 2021–30-DM-EXP-36).

Statistics

Baseline data were expressed as median (IQR) for numerical variables and number (percentage) for categorical data. Data were analyzed using parametric student's *T* test for continuous variables. The Chi-squared test or Fischer's exact test was used for categorical variables. Factors predicting serious infection as determined from the univariate analysis and other biologically plausible variables were used to fit Cox proportional hazards models for multivariate analysis. If missing data was less than 10% of the total, we did not impute the missing values and used the data as is for multivariate analysis. Three separate models were fit. The first was a Cox proportional hazards model with time to first serious infection as the dependent variable. As there were a number of patients who had recurrent serious infections, a second model was fit as per the Anderson–Gill modification of Cox regression for recurrent timed events which accounted for all serious infections in the cohort [18]. A third multistate Cox regression model was fit with time to mortality as the dependent variable and the transition from baseline to 1st infection, 1st to 2nd infection, and 2nd to 3rd infection as the dependent variable. Hazard ratios were obtained for each transition [19]. Kaplan–Meier survival analysis was used to plot serious infection-free survival. Poisson regression with non-lupus-related admissions as the dependent variable and duration of follow-up as the offset was used to determine the rate ratio for admissions in those with serious infections compared to those without.

Results

Demographics and clinical characteristics

A total of 1354 patients were included in the study of whom 1258 were females (female: male = 13: 1). The mean age at presentation was 30.32 ± 9.42 years with a median follow up duration of 3.41 (1.02–8.01) years and a total follow-up of 7127.89 person-years. Briefly, at presentation clinical manifestations were as follows: fever (1004, 74.2%), mucocutaneous (941, 69.5%), arthritis (831, 62.9%), myositis (120, 8.9%), hematological (578, 42.7%), serositis (218, 16.1%), nephritis (656, 48.4%), respiratory (34, 2.5%), cardiovascular (42, 3.1%), neuropsychiatric (142, 10.5%), gastrointestinal (30, 2.2%), vasculitis (65, 4.8%), and secondary anti-phospholipid antibody syndrome (APS) (114, 8.4%). The median SLEDAI-2 K score at presentation was 11 (8–16). Four percent of patients were diabetic.

Profile of infections

A total of 439 major infections occurred in 339 (25.03% of the cohort) individuals at a rate of 61.6 serious infections per 1000 person-years of follow-up. Recurrent infections occurred in 86 (6.35%) patients. Of the recurrent cases, 70 had two infections, 15 had 3 infections, and a single patient had 4 serious infections. There was no microbiological diagnosis in 88 (20.04%) cases. The probability of developing a second serious infection was 20.64%, and the probability of developing a third serious infection in those with previous serious infections was 21.42%. The most common infections were bacterial (308, 70.15%) followed by viral (35, 7.97%) and then fungal (13, 2.96%) with many patients developing more than 1 microbiologically proven serious infection (Tables 1 and 2).

Opportunistic infections

Amongst the serious infections, *Mycobacterium tuberculosis* was the most common and was seen in 81 patients. The incidence rate of TB was 1136.4 per 100,000 person-years. Most cases (59, 72.8%) were extrapulmonary. One patient had non-tubercular mycobacterial infection-associated skin infection (Table 1). There were 40 more opportunistic infections. Among these, reactivation of CMV (11, 27.5%) was the most common followed by multidermatomal Herpes zoster (HZ) reactivation and HZ encephalitis (10, 25%), invasive candidiasis (5, 12.5%), cryptococcal meningitis (5, 12.5%), disseminated histoplasmosis (2, 5%), and 1 (2.5%) each of *Aspergillus flavus* pneumonia, central nervous system toxoplasmosis, and chronic diarrhoea due to *Giardia lamblia*. Eight (20%) of these patients died: 2 patients with cryptococcal meningitis, 1 each with Aspergillus pneumonia, Candidial sepsis, Herpes simplex oesophagitism and chronic giardiasis, and 2 patients with complications arising out of disseminated zoster reactivation.

Univariate analysis of predictors of infections

Serious infections were significantly associated with male gender, higher SLEDAI-2 K score at baseline, fever, myositis, nephritis, gastrointestinal involvement, and neuropsychiatric lupus (NPSLE) as initial disease manifestation (Table 3). Baseline laboratory parameters associated with serious infections were low albumin, low absolute lymphocyte count (ALC), low platelets, high anti-dsDNA antibody levels, and low C3 and C4 levels. They were also on higher daily steroid (prednisolone) doses, had cyclophosphamide as background immunosuppression, and had received higher cumulative steroid doses per year until the time of infection.

Table 1 Profile of serious bacterial infections

Organism and clinical syndrome	N	Incidence rate (per 100,000 person-years)
Bacterial infections:		
Mycobacterium tuberculosis	81	1136.4
Lung[*] (22), disseminated (11), central nervous system (10), lymph node (9), abdomen (8), joint (8), spine (3), pleural effusion (2), pericarditis (2), hepatitis (2), skin (1), abscess (1), osteomyelitis (1), tenosynovitis (1)		
Mycobacterium abscessus	1	
Eschericia coli	51	715.5
Sepsis (20), pyelonephritis (14), cystitis[θ] (7), pneumonia (6), spontaneous bacterial peritonitis (2), abscess (2)		
Staphylococcus aureus	65	911.9
Abscess (30), pneumonia (12), sepsis (11), cellulitis (7), meningitis (2), brain abscess (1), muscle (1), osteomyelitis (1)		
Methicillin-resistant Staphylococcus aureus	7	98.2
Abscess (4), sepsis (2), lung (1)		
Streptococcus pneumoniae	20	280.6
Sepsis (8), pneumonia (7), urinary tract infection (2), meningitis (1), brain abscess (1), abscess (1)		
Klebsiella pneumoniae	29	406.9
Lung[δ] (19), urinary tract infection (5), sepsis[δ] (3), pyelonephritis (1), abscess (1)		
Pseudomonas aeruginosa	29	406.9
Lung (12), sepsis (9), abscess (4), urinary tract infection (4)		
Enterococcus faecalis	7	98.2
Urinary tract infection (4), sepsis (2), abscess (1)		
Salmonella Typhi/Paratyphi	3	42.1
Acinetobacter baumannii	9	126.2
Pneumonia (4), urinary tract infection (3), abscess (1), apontaneous bacterial peritonitis (1)		
Proteus mirabilis	1	14
Abscess (1)		
Listeria monocytogenes	1	14
Meningitis (1)		
Nocardia	4	56.1
Brain abscess (2), disseminated (1), lung abscess (1)		
No microbiological confirmation:	88	
Pneumonia (62), sepsis (21), CSOM (3), ASOM (1), liver abscess (1)		

[*]1 multidrug-resistant tuberculosis

[θ]2 extended spectrum beta lactamase (ESBL) strains

[δ]2 and 1 ESBL strains, respectively

Infections are represented here as a rate per 100,000 person-years and are not mutually exclusive: there were patients with more than 1 serious infection

Multivariate analysis of predictors of infection

On fitting a Cox proportional hazards regression model for time to the first serious infection, higher baseline SLEDAI-2 K score (HR 1.03, 1.01–1.05), gastrointestinal involvement (HR 2.75, 1.65–4.99), daily steroid dose per 10 mg increment (HR 1.65, 1.55–1.76), and average cumulative steroid dose per year (HR 1.007, 1.005–1.009) predicted serious infections whereas higher albumin levels (HR 0.65, 0.56–0.76) were protective (Model 1, Table 4). Using the Anderson–Gill modified Cox regression model for time to serious infection and taking into account recurrent serious infections, the same parameters were found to be associated (Model 2, Table 4). Absolute lymphocyte count, dsDNA, C3, and C4 were not included in the final models as they are a part of the SLEDAI-2 K scores.

Time trend of serious infections

The average number of infections for the entire cohort increased from 9.9 per year for the decade from 2000 to 2009 to 23.7 per year for the decade from 2010 to 2019. However, the incidence density per person-year follow-up remained stable across the study period (Supplementary Fig. 1).

Table 2 Profile of serious non bacterial infections

Organism and clinical syndrome	N	Incidence rate (per 100,000 person-years)
Viral infections:		
Cytomegalovirus	11	154.3
Gastrointestinal tract (4), hepatitis (2), disseminated (2), lung (2), encephalitis (1)		
Herpes zoster	10	140.3
Multidermatomal (9), encephalitis (1)		
Herpes simplex	1	14
Esophagitis (1)		
Hepatitis C	5	70.15
Hepatitis B	2	28.1
Dengue	2	28.1
H1N1 influenza	3	42.1
Parvovirus	1	14
Fungal infections:		
Candida	5	70.1
Oesophagitis (3), sepsis (1), pyelonephritis (1)		
Cryptococcus neoformans	5	70.1
Meningitis (5)		
Histoplasma	2	28.1
Disseminated (2)		
Aspergillus flavus	1	14
Lung (2)		
Parasitic infections:	4	14 each
Toxoplasma (1), neurocysticercus (1), *Giardia lambia* (1), *Plasmodium falciparum* (1)		

Infections are represented here as a rate per 100,000 person-years and are not mutually exclusive: there were patients with more than 1 serious infection

Health care utilization

Median total admissions were higher in those with serious infection (3, IQR 2–6) compared to those without (1, IQR 0–2) (Table 3).

Excluding admissions related to lupus disease activity, those with a major infection were more likely to require recurrent admissions with a rate ratio of 2.34 (95% CI 2.01–2.68) compared to those without. The rate of infection-specific hospitalization was 52.3 per 1000 person-years.

Outcomes

A serious infection ever in the disease course was associated with greater damage. The median SLICC damage index was 1 (IQR 0–2) in those with an infection and 0 (IQR 0–0) in those without. This difference was statistically significant.

The survival free from serious infections at 1 year, 5 years, and 10 years was 82.9% (95% CI 80.8–85), 73.8% (95% CI 71.1–76.6), and 65.2% (95% CI 61.7–68.9), respectively (Fig. 1a). Any serious infection ever in the disease course predisposed to higher mortality (Fig. 1b).

One hundred and nineteen patients succumbed to illness. The hazard ratio for mortality increased progressively with each serious infection and was 18.2, 32.7, and 81.6 for the first, second, and third serious infections, respectively (Model 3, Table 4). Infection attributable mortality occurred in 65 (54.6%) patients.

Discussion

The most common infections in this single-center study were bacterial followed by viral and fungal. Mycobacterial infections were the most common opportunistic infection, and a significant number were extrapulmonary. Higher disease activity at baseline, presence of gastrointestinal disease, lower baseline albumin levels, higher daily steroid dose, and cumulative steroid dose predicted serious infections on follow-up. Serious infection led to more damage and mortality increased with each episode of infection.

Gram-negative bacterial infections cumulatively exceeded Gram-positive infections. However, *Staphylococcus aureus* was the most common bacterial infection in our cohort and a large majority of these were skin infections. This is similar to previous cohorts from South Africa and Australia (Table 4) [16, 20]. The prevalence of *Staphylococcus aureus* colonization has been reported to be 50% in patients with active cutaneous lupus [21]. This may explain the high rates of skin infections in our cohort. *Staphylococcus aureus* has been hypothesized to have a causal role in the induction of autoimmunity as well as systemic flares of glomerulonephritis in lupus-prone mice by activating the IL17 family cytokines and Th17 cells [22]. *Streptococcus pneumoniae* was the other predominant Gram-positive organism isolated. The incidence of *Streptococcus pneumoniae* in our cohort was similar to previous reports from Europe (280/100,000 person-years versus 201–236/100000 person-years) [23, 24]. *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were the other commonly isolated Gram-negative bacteria. This is similar to data from China and Mexico (Table 1) [10, 25].

Mycobacterium tuberculosis was the most common infection in our cohort with a predominance of extrapulmonary forms. Although this is partly expected due to the endemic nature of tuberculosis in India, it is still much higher than the background incidence of tuberculosis of 188 (95% CI 129–257) per 100,000 person-years in the Indian population last reported in 2021 [26]. The proportion of extrapulmonary cases in this study was much higher at 72.8% as

Table 3 Univariate analysis of predictors of serious infection

Covariate	Infection ($n=339$)	No infection ($n=1015$)	Effect size (RR, 95% CI)
Demographics:			
Age at onset (yrs)	29 (23–36)	28 (23–35)	-
Male gender	36 (10.6%)	60 (5.9%)	1.21 (1.04–1.42)
Baseline features:			
SLEDAI-2 K*	14 (10–18)	10 (6–15.75)	-
Fever	279 (82.3%)	725 (71.42%)	1.15 (1.08–1.22)
Myositis	41 (12.09%)	70 (68.9%)	1.15 (1.01–1.32)
Nephritis	209 (61.65%)	447 (43.23%)	1.19 (1.12–1.27)
GI	16 (4.72%)	14 (13.8%)	1.62 (1.10–2.38)
NPSLE	48 (14.16%)	949.26	1.15 (1.02–1.30)
Laboratory parameters:			
Albumin* (mg/dl)	3 (2.4–3.6)	3.5 (2.9–4)	-
Diabetes	19 (5.6%)	36 (3.55%)	1.15 (0.95–1.40)
DsDNA* (IU)	180 (60.3–300)	142.2 (33–272.2)	-
Complement 3* (mg/dl)	50.9 (30–80.25)	65.05 (39–101.75)	-
Complement 4* (mg/dl)	10 (6–19)	12 (6.2–21)	-
ALC* (/cumm)	1298 (850–1891)	1484 (1012–2088)	-
Platelets* ($\times 10^5$/cumm)	1.62 (1.03–2.4)	1.83 (1.27–2.54)	-
Treatment:			
Daily steroid (prednisolone) dose* (mg)	15 (7.5–40)	5 (0–7.5)	-
Average cumulative steroid (prednisolone) dose* (g/year)	4.07 (1.89–14.31)	1.82 (1.01–2.66)	-
Cyclophosphamide use	64 (18.88%)	56 (5.52%)	1.66 (1.37–2.02)
Total admissions	3 (2–6)	1 (0–2)	-

ALC, absolute lymphocyte count

*Significant by the Wilcoxon signed rank test

Table 4 Cox proportional hazards models for the predictors of major infection (models 1 and 2) and for risk of death from major infection (model 3)

Model 1			Model 2			Model 3		
Covariates	HR	95% CI	Covariate	HR	95%CI	Covariates	HR	95% CI
Male sex	1.2	0.82–1.75	Male sex	1.34	0.93–1.95	Infection 1	18.2	11.8–28.1
Fever	1.04	0.78–1.4	Fever	1.03	0.80–1.33	Infection 1:2	32.7	16.9–63.01
Myositis	1.05	0.74–1.51	Myositis	1.05	0.77–1.43	Infection 2:3	81.6	29.9–222.7
Nephritis	0.98	0.74–1.3	Nephritis	1.002	0.78–1.3			
GI*	2.75	1.65–4.59	GI*	2.07	1.09–3.96			
NPSLE	1.07	0.78–1.5	NPSLE	1.22	0.9–1.67			
SLEDAI*	1.02	1.01–1.05	SLEDAI	1.03	1.01–1.05			
Daily steroid dose* (/10 mg)	1.65	1.55–1.76	Daily steroid dose* (/10 mg)	1.43	1.36–1.51			
Average cumulative steroid dose*	1.007	1.005–1.009	Average cumulative steroid dose*	1.002	1.001–1.004			
Albumin*	0.65	0.56–0.76	Albumin*	0.83	0.71–0.96			
Cyclophosphamide use	1.16	0.85–1.6	Cyclophosphamide use	1.21	0.92–1.61			

*Significantly associated with risk of serious infection on follow up

Model 1, Cox proportional hazard model for 1st serious infection; *Model 2*, Anderson Gill modified Cox proportional hazard model for recurring serious infections; *Model 3*, multistate Cox proportional hazard model for mortality with every infection; *GI*, gastrointestinal manifestations

Fig. 1 **A** The Kaplan–Meier survival curve depicts time to first serious infection with the numbers at risk. **B** The Kaplan–Meier survival curve shows the overall survival difference between those with any serious infection ever compared to those with no serious infection in the disease course
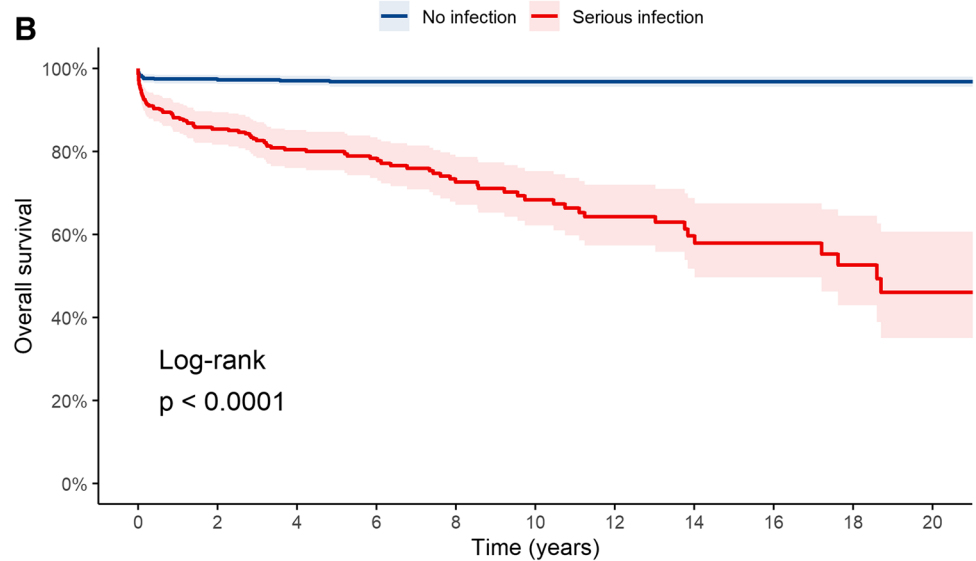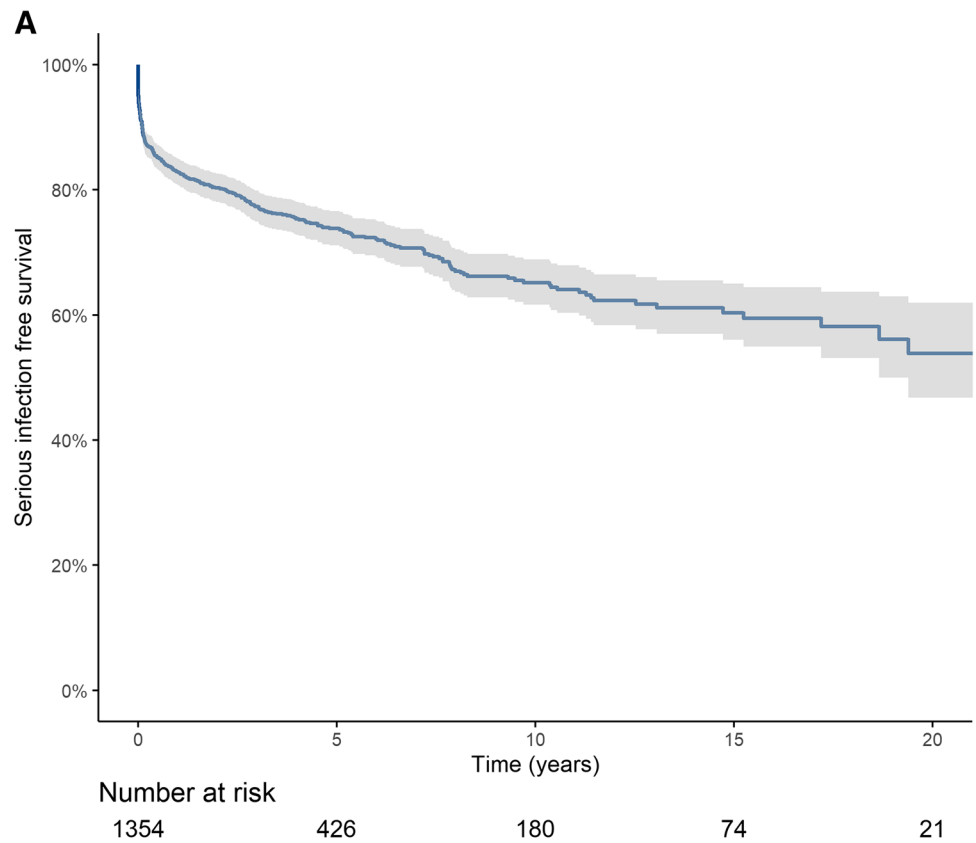
compared to 12.5–67% across multiple studies [27–34]. Studies from Southeast Asia report higher prevalence as compared to studies from other regions with Hong Kong reporting a prevalence of 67% for extrapulmonary tuberculosis [30]. Of the autoimmune rheumatic diseases receiving long term steroids, SLE was associated with the highest rate of reactivation of tuberculosis in a prior study (2.22 per 100 recruited cases/year) [35]. Though BCG vaccination is thought to reduce extrapulmonary TB especially meningitis but in patients with SLE the underlying immune deficiency may result in disseminated and extrapulmonary disease.

Recently, antibodies to interferon alpha have been associated with and excess risk of developing tuberculosis over other infections in SLE [36]. This could be a useful screening tool to identify those suited for latent TB prophylaxis. In a seminal study from West India, all patients of SLE at diagnosis expected to be on steroid therapy were initiated on isoniazid (INH) prophylaxis for 1 year and further followed up for 1 year [37]. Tuberculosis developed in 1 patient in the first month of therapy and another in the 2nd year in the follow-up period. Compared to historic controls from the same institute, the incidence of tuberculosis declined from 11 to 2% in newly diagnosed SLE patients. A randomized controlled trial from China found no incident cases of tuberculosis in the group assigned to TB prophylaxis with either rifampicin alone or rifampicin with ethambutol for 1 year compared to 11% in those treated with standard of care immunosuppression alone [38]. Thus, TB prophylaxis, with newer regimens merits, is further studied in a clinical trial especially in TB endemic countries of Asia.

Cytomegalovirus (CMV) reactivation was the most common viral infection in our patients followed by Herpes zoster. CMV infection has not been frequently reported in previous cohorts of lupus. A multicenter study from Japan found a prevalence of 2.04% (151 cases out of 7377 hospitalized patients) in autoimmune diseases [39]. The highest prevalence was in SLE and CMV reactivation led to mortality in about a third of patients. A high index of suspicion is warranted for diagnosis as presentation may often mimic SLE disease flare. Cryptococcal meningitis was the most common invasive fungal infection in our cohort. Cryptococcal meningitis has been reported to be the cause in 25% all cases of invasive fungal infections in SLE [40]. Higher disease activity and higher corticosteroid dose predispose to this often fatal complication [41].

Higher disease activity at baseline as measured by SLE-DAI-2 K, hypoalbuminemia, gastrointestinal involvement at baseline, cumulative steroid dose prior to infection, and daily steroid dose at the time of infection were associated with increased risk of serious infection in our cohort. Lower albumin could reflect greater inflammation at baseline or the effect of poor nutrition. Gastrointestinal involvement at baseline was also a significant predictor of mortality in our

cohort [12]. Till date, a single prediction model developed from the Spanish multicenter RELESSER cohort has undergone external validation for prediction of serious infection with mixed results (predictive accuracy at baseline 63% and at the time of infection 79%) [15, 42]. This model included age at diagnosis (≥ 46 years), male sex, Latin–American ancestry, current steroid dose (≥ 10 mg), previous hospitalization, and previous serious infection. Most of these factors also predicted infection in our cohort. Other factors associated with serious infection across studies include serositis, renal involvement, anemia, thrombocytopenia, hypoproteinemia, hypoalbuminemia, low C3, and the presence of diabetes (Table 5) [5, 10, 15, 16, 20, 25, 43]. Increasing daily corticosteroid dose and immunosuppressants such as cyclophosphamide, mycophenolate mofetil, and rituximab were also predictors of infection whereas cumulative use of hydroxychloroquine was protective [15, 44, 45]. Our models found a 65% increase in serious infections for every 10-mg increase in corticosteroid dose whereas adjusted for the steroid dose, the use of cyclophosphamide no longer conferred any additional risk. A recent study from Japan showed a higher risk of infection (hazard ratio of 6.8) with doses as low as 5–7.5 mg prednisone per day [46]. Higher daily corticosteroid use is a consistent factor across all studies, and thus, attempt should be made to use minimum dose for a minimum period of time [47, 48].

In our cohort, patients with serious infections were likely to have excess hospitalization of 2.34 times compared to those without. SLE is a chronic disease that requires lifelong therapy. Hospitalization significantly adds to the economic burden of the disease and accounts for the largest component of direct cost varying from 25 to 30% across studies [49, 50]. In addition to the direct costs of hospitalization, significant economic burden also arises out of loss of work and economic loss with caregivers reporting 12.8% reduction in paid work time in the USA [51]. In a developing low middle-income country like India, with greater vocational uncertainty, this impact is expected to be greater though there is a lack of data in this regard.

The SLICC damage index at last follow-up was higher in patients with infections in our cohort, and this is consistent with prior studies [15, 52]. Serious infections also predisposed to death in our cohort with each successive infection resulting in a further increase in mortality risk. Infection attributable mortality accounted for more than half of the deaths that occurred. This is similar to the long term outcomes from a UK cohort with infections as the leading cause of death at 31.7% [48]. Infection attributable mortality ranged from 23 to 26% in a Spanish cohort which also corresponded to a threefold increase over the general population (25% versus 8%) [53]. Infections also conferred a hazard ratio for mortality of 2.79 on long-term follow-up of the Hopkins lupus cohort from the USA [54]. Infection-related

Table 5 Comparison of previous studies on serious infections from different regions of the world

	Country	Design	Number of patients	Median follow-up	Serious infections, n (%)	Most common infections	Predictors
Goldblatt et al. [5]	UK	Cohort	104	5 years	16 (15.4%)	Pneumonia (no organism isolated) (10) *S. pneumoniae* (2) *S. aureus* (2) *E. coli* (2)	Recent change in immunosuppression
Dubula et al. [16]	South Africa	Cohort	167	1.75 years	84 (50.3%)	*S. aureus* (15) *E. coli* (12) *M. tuberculosis* (8) *K. pneumoniae* (8) *P. aeruginosa* (5) NTM (3)	Serositis Seizures
Merayo-Chalico et al [25]	Mexico	Case control	167	7.8 years	89	*E. coli* (16%) *E. faecalis* (11%) *S. pneumoniae* (6%) *S. aureus* (6%) *P. aeruginosa* (6%) *K. pneumoniae* (4%) *M. tuberculosis* (4%)	Lymphopenia Prednisolone use Low C3
Rua-figueroa et al. [15]	Spain	Cohort	3658	10 years	705 (19.3%)	Bacterial (51.9%) Unknown (30.4%) Viral (11.9%) Mycobacterial (3.5%) Fungal (2.3%)	Age at diagnosis Male sex Hispanic ethnicity Steroids > 10 mg/day Hospitalization Severity Katz index Previous infection
Wang et al. [10]	China	Cohort	494	2.8 years	69 (14%)	*K. pneumoniae* (8) *P. aeruginosa* (7) *S. pneumoniae* (5)	SLEDAI > 10 Lymphocyte count < 800/cumm Creatinine > 1.18 mg/dl
Ko et al. [20]	Australia	Cohort	346	6.6 years	86 (24.8%)	*S. aureus* (10) *E. coli* (9) *E. faecalis* (4) Streptococcus (3) Varicella (3)	SLEDAI High disease activity state SLICC damage index Cyclophosphamide

mortality is the leading cause of excess mortality in SLE as per analysis of a large insurance database in Hungary [55]. In a recent meta-analysis, infection attributable standardized mortality ratio (SMR) in SLE was 4.98 compared to all cause SMR of 3.14 [56]. Nearly a century on from the discovery of the first antibiotic, the prevention and treatment of infections remain an unmet need of care in SLE.

The strength of the present study is its large numbers, data of incidence, and spectrum of infections in SLE from a South Asian cohort which has been lacking in the past. The limitations include the retrospective nature of the study and a survivorship bias in the cohort as evidenced by the greater loss to follow-up seen in the group without serious infection. The other major limitation is patients lost to follow-up cases

have been censored in the survival analysis as we could not contact all patients to determine present status.

We also did not have data on damage prior to serious infection and this could be a potential confounder for the higher damage scores at the end of follow-up in those with serious infections.

Conclusion

Serious infections remain a major cause of mortality and damage accrual in SLE. The profile of infections is different in South Asian patients with a predominance of tuberculosis especially extrapulmonary forms. Higher disease activity at

baseline, gastrointestinal involvement, hypoalbuminemia, higher current steroid dose, and cumulative steroid dose increase the chances of serious infections.

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Data availability The original data will be available on request sent by email to the corresponding author.

Declarations

Disclosures None.

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