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Combining C reactive protein and serum albumin to predict 90-day mortality in systemic lupus erythematosus with serious community-acquired infections

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ABSTRACT

Objective Serious infections in SLE are common and have emerged as the major cause of death. However, effective methods to identify poor prognosis are still lacking. Therefore, we aimed to determine the predictive value of C reactive protein (CRP) plus albumin (ALB) in SLE with serious infections.

Methods From May 2015 to December 2018, consecutive patients with SLE presenting with serious infections in our emergency department were prospectively recruited. Serum CRP and ALB were measured within 24 hours of admission. The outcome was defined as mortality rate at 90 days. A CRP plus ALB score (2–6) was assigned based on the CRP and ALB concentrations. We performed univariate and multivariate regression analyses to detect the independent effects of CRP plus ALB on 90-day mortality (all-cause and infection-related). Subgroup analyses were used to show the effects stratified by lupus nephritis.

Results A total of 150 patients were included, and the all-cause 90-day mortality rate was 38% (n=57), 41 of which was infection-related. The predominant infection sites were pulmonary (79.3%) and bloodstream infection (20.7%). Serum CRP and ALB levels were significantly different in non-surviving patients compared with those in surviving patients (p=0.002 and p<0.001, respectively). In the fully adjusted logistic regression model, the CRP plus ALB score was associated with decreased 90-day survival (adjusted OR 1.52; 95% CI 1.08 to 2.13; p=0.017).

Conclusions CRP plus ALB was associated with the risk of all-cause and infection-related 90-day mortality in SLE with serious infections. Although this finding requires further verification, the two parameters may be useful for predicting poor outcomes in such patients.

Key messages

What is already known about this subject?

- Serious infections in SLE are common and have become one of the leading causes of morbidity and mortality.
- Identification of patients with SLE at high risk of death with severe infections is important for improving prognosis and optimising healthcare resource utilisation.

What does this study add?

- We constructed a score combined by C reactive protein (CRP) and serum albumin (ALB) to predict 90-day all-cause and infection-related mortality.
- We found that the CRP plus ALB score was associated with poor prognosis in patients with SLE with serious infections regardless of whether lupus nephritis was diagnosed.

How might this impact on clinical practice or future developments?

- CRP and ALB are readily available in the emergency department and both in combination may be useful in identifying patients with SLE with serious infections with worse survival.

INTRODUCTION

SLE is a multiorgan-involved autoimmune disease; both SLE itself and immunosuppression therapy predispose patients to infection susceptibility.[1] Various infection types, including bacterial, fungal, viral and parasitic, are associated with multiple emergency visits. Serious infectious diseases are recognised as the primary cause of morbidity and mortality in patients with SLE[2] and account for 13%–37% of hospitalisations.[2 3] The well-known prognostic factors for predicting poor outcomes include diabetes,[4] lupus nephritis (LN),[5] high-dose prednisolone[6] and immunosuppressive medications.[7] Identifying patients at a higher risk of death is important for improving prognosis and optimising healthcare resource utilisation. Furthermore, serum biomarkers, including peripheral lymphocyte subsets, the neutrophil-to-lymphocyte ratio and interferon-γ, have shown a certain

potential for risk discrimination. However, these clinical data also displayed poor performance in predicting patients' prognosis.[8–10] Hence, there remains a need for more precise parameters to predict poor outcomes. C reactive protein (CRP) and albumin (ALB) are frequently used as indices that reflect the activity of inflammatory conditions. Kim *et al* reported that CRP had high sensitivity and specificity compared with procalcitonin and S100A8/A9 in SLE with serious infections[11 12] as well as a good clinical prognostic value for patients with central nervous system infections and sepsis.[12–14] Frequently, acute inflammation can result in a decrease in serum ALB, regardless of the nutritional status of patients.[15 16] In SLE or sepsis infections, hypoproteinaemia has a high incidence and is known to be associated with poor prognosis and mortality.[17 18]

Recently, CRP combined with ALB has been identified as a promising marker of inflammation.[19 20] More specifically, the notable performance of CRP plus ALB has been observed in septic and critically ill patients.[21 22] However, these studies excluded patients with autoimmune diseases, and few other studies have investigated the association between CRP plus ALB with mortality in patients with SLE. Therefore, the present work aimed to evaluate the efficacy of CRP plus ALB for predicting mortality risk in patients with SLE with serious infections.

MATERIALS AND METHODS

Study design and setting

This work was a prospective study conducted between May 2015 and December 2018. A total of 174 consecutive patients with SLE who underwent emergency admission with infections at the Shanghai Jiao Tong University of Medicine affiliated with Renji Hospital South Campus were enrolled. Finally, 150 patients were eligible based on the following criteria: diagnosis of SLE according to the 1997 American College of Rheumatology classification criteria[23] and complications with a serious infection. The exclusion criteria were as follows: (i) age <18 years, (ii) patients receiving ALB infusion, (iii) patients with chronic liver disease, defined as the presence of portal hypertension, cirrhosis, hepatic ascites, variceal bleeding or hepatic encephalopathy, (iv) incomplete medical records and those lost to follow-up, (v) hospital-acquired infection (patients with SLE with serious infections attended the emergency department, which typically represented the clinical features of community-acquired infections), (vi) patients with malignant tumours, (vii) other causes of hypoalbuminaemia (eg, overt malnutrition, protein-losing gastroenteropathy, significant haemorrhages, exudative losses or surgical drains). Patients were followed up for 90 days after enrolment by reviewing their medical records and/or conducting telephone interviews. Written informed consent was obtained from all subjects prior to enrolment in the study.

Data collection

Data were collected from electronic medical records using a standardised collection form. Baseline data after admission emergency, including demographics, comorbidities, clinical and laboratory characteristics, site of infection, microbiological test results, medication history, CRP and ALB values were analysed. The outcome variable was all-cause and infection-related mortality assessed at 90 days after patient recruitment.

According to prognosis, the patients were classified as survival or non-survival. The SLE Disease Active Index (SLEDAI) 2000 was used to evaluate disease activity at baseline. To better understand clinical activity, the modified SLEDAI (m-SLEDAI) was calculated with complement and double-stranded DNA component removed. Organ damage of SLE is assessed by the Systemic Lupus International Collaborating Clinics (SLICC) damage score, a validated instrument consisting of 41 items that measure irreversible organ damage not caused by active inflammation in 12 organ systems. Assessment of the severity of serious infections in patients with SLE was performed using the quick Sequential Organ Failure Assessment (qSOFA) within the first 24 hours of emergency department admission. For patients with repeated admissions, if they were simply excluded from analysis, it could reduce the possibility of double-counting. However, excluded patients readmitting to a hospital for any reason were more prone to adverse outcomes, including death. Therefore, to avoid this misinterpretation we used the cumulative average of CRP and ALB of multiple admission measurements. During the study period, 12 patients had a total of 27 repeat admissions.

Laboratory parameters

Blood samples were obtained at the emergency department. The concentrations of ALB in serum were analysed using an automatic biochemical analyzer (AU5800; Beckman Coulter, Brea, California, USA) with a normal range of 35–55 g/L. CRP levels were measured using the rapid immunoanalysis method with a normal range of 0–8 mg/L. CRP level measured in our hospital's laboratory department had a detectable range of 0–200 mg/L. When CRP level was outside this range, above the upper reference value, the result for CRP measurement was expressed as >200 mg/L (14 values). Due to a ceiling effect of the detection, CRP and ALB concentration was converted to a categorical variable and constituted a score of CRP plus ALB.

A CRP plus ALB score value (range: 2–6) was assigned based on the CRP and ALB concentrations (score=1 if CRP ≤50 mg/L or ALB ≥30 g/L; score=2 if 50 mg/L <CRP ≤ 150 mg/L or 25 g/L <ALB < 30 g/L; score=3 if CRP >150 mg/L or ALB ≤25 g/L). For example, CRP=80 mg/L is rated as 2 score and ALB=23 g/L is rated as 3 score. The two scores are summed to produce a CRP plus ALB score of 5.

Definitions

Serious infections were defined as a deep infection for bacterial infection (cellulitis, endocarditis, pneumonia,

pyelonephritis, septic arthritis, osteomyelitis and bacteraemia), mycobacterial infections (tuberculosis and non-tuberculous mycobacteria), fungal infections (cryptococcosis, aspergillosis, histoplasmosis and pneumocytosis) and viral infections (cytomegalovirus, influenza, herpes zoster, varicella-zoster, Epstein-Barr meningitis and encephalitis).[24] When it was difficult to differentiate between infection and lupus activity in patients with negative culture tests, treatment response to antimicrobial therapy was considered by the assigned physician to confirm the infection diagnosis. Interpretation of microbiological results and judgement of contamination were performed together with medical microbiologists and physicians.

Statistical analysis

Categorical variables are expressed as numbers and percentages. Continuous variables are presented as means±SD for data with normal distributions and median (IQR) for non-normally distributed data. One-way analyses of variance, Kruskal-Wallis H tests and χ^2 tests were used to determine whether any statistical differences existed between groups, with distribution and data type used to select the appropriate statistical tests.

A three-step process was conducted to select covariates for multivariable adjustment: (1) we selected the covariates as potential confounders based on previous literature; (2) univariate analysis for 90-day mortality was conducted using a binary logistic model; (3) for multivariate analysis, we included variables that were significant in the univariate analysis at the p<0.01 significance level to identify independent factors as adjusting variables.

Three multivariate regression models were established to evaluate the associations between CRP plus ALB and 90-day mortality: model 1, no covariates were adjusted; model 2, only adjusted for age and gender and model 3, model 2+other covariates for which p<0.05 based on the multivariate analyses. We used two different methods to test for association, one using categorical variables and one using continuous variables, and calculated the p value for trend.

Finally, we conducted a subgroup analysis stratified by the presence of LN to assess whether the effect of CRP plus ALB differed between subgroups. All analyses were conducted using the R statistical package (http://www.r-project.org) and Empower Stats software (www.empowerstats.com; X&Y Solutions, Boston, Massachusetts, USA).

RESULTS

Figure 1 shows the flow chart of the study. In total, 174 patients with SLE admitted to the hospital, and 150 patients were included in the final cohort. The mean age of the patients was 43 years, 91.3% were women and the mean SLE disease duration was 4 years. Ultimately, 57 deaths occurred (38% of the study population) during the 90 days follow-up period, including 16 patients who died of non-infection-related causes. Causes of death in these cases were: gastrointestinal tract perforation and bleeding (n=6), renal failure (n=3), cerebral bleeding (n=3), hemophagocytic syndrome (n=2), liver failure (n=1) and malignant arrhythmia (n=1). Except for stroke (p=0.012), underlying medical conditions, including diabetes mellitus, chronic kidney disease, hypertension, etc, were similar between both groups. Neuropsychiatric lupus was more pronounced in deceased patients (16 (28.6%) vs 13 (14%); p=0.029); however, there was no difference in the mortality rate among interstitial lung disease, LN and pulmonary hypertension cases. Deceased patients had higher rates of mycophenolate mofetil use (33.3% vs 16.1%, p=0.015) compared with survivors. More frequent use of hydroxychloroquine (HCQ) occurred in living patients (58 vs 25), whereas patients with a history of immunosuppressant use in the past 6 months displayed the opposite trend. In addition, we found that the levels of CRP and blood urea nitrogen (BUN) were more than twice as high in non-survivors compared with survivors, and serum ALB concentration differed approximately 5 g/L between the groups (23.3 vs 28.2 g/L). The demographic, clinical and laboratory characteristics of the patients at baseline and at the end of the study period are presented in table 1.

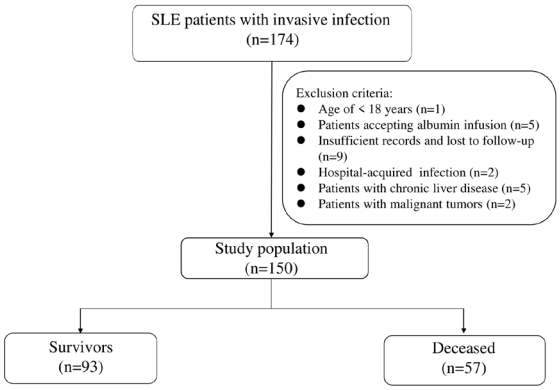

Figure 1 Flow chart of study population selection and outcomes.

Table 2 shows the distribution characteristics of the infection sites and pathogens. Pulmonary infection was the most common site of infection (79.3%), followed by bloodstream infection (20.7%). The top three pathogens isolated in pulmonary infection were *Candida* spp (n=27), *Aspergillus* (n=15) and *Klebsiella pneumoniae* (n=11). Ten patients developed central nervous system infection, the key causes of which were *Cryptococcus neoformans* (n=3), *Mycobacterium tuberculosis bacillus* (n=3) and four of unknown causes. Among the bacterial infections, the most frequently identified species was *Staphylococcus aureus*, with over half of the patients infected via the bloodstream. Additionally, in this study, 10 cases with cytomegalovirus, 7 cases with *Pneumocystis jirovecii* and 3 cases with *Nocard's bacillus* were diagnosed.

Table 1 Baseline characteristics and final measurements separated according to patient survival

Characteristics	All cohort (n=150)	Survivors (n=93)	Deceased (n=57)	P value
Demographic				
Age (year), mean (SD)	42.99 (14.26)	41.86 (13.51)	45.36 (14.98)	0.144
Gender, female, n (%)	137 (91.33)	84 (90.32)	53 (92.98)	0.574
Disease duration of SLE (year)	4.00 (0.50–10.00)	4.00 (0.50–10.00)	4.50 (0.90–12.25)	0.815
Disease duration of infection (day)	10.00 (4.00–15.00)	10.00 (4.00–16.00)	7.50 (4.00–14.25)	0.891
Laboratory findings				
Leucocyte count ($\times10^9$/L)	6.71 (3.85–9.18)	6.11 (3.69–7.96)	8.28 (5.19–11.50)	0.003
Lymphocyte count ($\times10^9$/L)	0.55 (0.34–0.91)	0.64 (0.42–1.03)	0.47 (0.30–0.71)	0.004
C reactive protein (mg/L)	46.73 (10.22–100.88)	28.43 (6.17–72.97)	59.36 (29.58–120.97)	0.002
Procalcitonin (ng/mL)	0.37 (0.13–1.43)	0.28 (0.10–0.95)	0.83 (0.19–2.57)	0.002
ESR (mm/hour), mean (SD)	54.52 (37.58)	58.08 (37.16)	48.61 (37.87)	0.159
Albumin (g/L)	26.70 (22.02–30.87)	28.20 (23.80–32.60)	23.30 (20.40–28.10)	<0.001
C3 (g/L)	0.63 (0.45–0.95)	0.64 (0.48–0.98)	0.62 (0.44–0.90)	0.711
C4 (g/L)	0.17 (0.08–0.26)	0.17 (0.08–0.26)	0.17 (0.08–0.23)	0.910
SCR (μmol/L)	78.00 (47.50–142.75)	68.00 (46.00–113.00)	98.00 (53.50–219.75)	0.026
BUN (mmol/L)	8.60 (5.69–17.77)	6.80 (5.10–14.30)	15.58 (7.98–26.86)	<0.001
LAC (mmol/L), mean (SD)	2.18 (1.18)	1.99 (0.99)	2.47 (1.37)	0.015
BNP ≥400 pg/mL, n (%)	46 (30.67)	28 (31.82)	18 (31.58)	0.976
SLEDAI score	8.00 (4.00–12.00)	7.00 (4.00–11.00)	9.00 (5.50–13.50)	0.044
m-SLEDAI score	6.00 (2.00–9.00)	5.00 (2.00–8.00)	8.00 (2.00–10.75)	0.041
qSOFA score	0.00 (0.00–1.00)	0.00 (0.00–1.00)	1.00 (0.00–1.00)	<0.001
SLICC damage score, mean (SD)	2.95 (2.51)	2.62 (2.35)	3.47 (2.69)	0.047
Comorbidity, n (%)				
Congestive heart failure	21 (14.00)	14 (15.05)	7 (12.50)	0.664
Diabetes mellitus	26 (17.33)	14 (15.05)	12 (21.43)	0.321
Chronic kidney disease*	49 (32.67)	27 (29.03)	22 (39.29)	0.197
Stroke	11 (7.33)	3 (3.23)	8 (14.29)	0.012
Hypertension	32 (21.48)	18 (19.35)	14 (25.00)	0.416
COPD	11 (7.33)	7 (7.53)	4 (7.02)	0.908
SLE organ system involvement†, n (%)				
Lupus nephritis	86 (57.33)	49 (52.69)	37 (66.07)	0.109
Neuropsychiatric lupus	29 (19.33)	13 (13.98)	16 (28.57)	0.029
Interstitial lung disease	19 (12.67)	12 (12.90)	7 (12.50)	0.943
Pulmonary hypertension	27 (18.00)	17 (18.28)	10 (17.86)	0.948
Musculoskeletal and skin	50 (33.33)	32 (34.41)	18 (31.58)	0.721
Cytopenia	77 (51.33)	50 (53.76)	27 (47.37)	0.447
Serositis	56 (37.33)	40 (43.01	16 (28.07)	0.066
Infection site, n (%)				
Pulmonary infection	119 (79.33)	71 (76.34)	48 (84.21)	0.248
Bloodstream infection	31 (20.67)	14 (15.05)	17 (29.82)	0.030
Central nervous system infection	10 (6.67)	6 (6.45)	4 (7.02)	0.893
Gastrointestinal infection	6 (4.00)	3 (3.23)	3 (5.26)	0.537
Urinary tract infection	6 (4.00)	3 (3.23)	3 (5.26)	0.537
Osteoarticular infection	6 (4.00)	5 (5.38)	1 (1.75)	0.272
Pelvic infection	6 (4.00)	4 (4.30)	2 (3.51)	0.810

Continued

Table 1 Continued

Characteristics	All cohort (n=150)	Survivors (n=93)	Deceased (n=57)	P value
Medication history‡, n (%)				
Maximum prednisone-equivalent dose ≥60 mg/day	97 (66.44)	51 (56.67)	46 (83.64)	<0.001
≥250 mg/day	42 (28.77)	24 (26.67)	18 (32.14)	0.477
≥500 mg/day	24 (16.44)	13 (14.44)	11 (19.64)	0.410
Immunosuppressant§	88 (58.67)	50 (53.76)	38 (67.86)	0.090
Hydroxychloroquine	83 (55.33)	58 (62.37)	25 (43.86)	0.027
Methotrexate	8 (5.33)	6 (6.45)	2 (3.51)	0.711
Azathioprine	6 (4.00)	4 (4.30)	2 (3.51)	0.810
Cyclophosphamide	30 (20.00)	18 (19.35)	12 (21.05)	0.801
Mycophenolate mofetil	34 (22.67)	15 (16.13)	19 (33.33)	0.015
Ciclosporin	19 (12.67)	8 (8.60)	11 (19.30)	0.056
Rituximab	10 (6.67)	6 (6.45)	4 (7.02)	0.893

Data are presented as median (IQR) unless otherwise noted.
*Chronic kidney disease was defined as serum creatinine measurements above the upper reference value over a 3-month or greater period.
†Organ involvement in SLE was representative of the current status at inclusion.
‡The usage of these drugs was assessed from inclusion in the study to the past 6 months.
§Immunosuppressant use was identified as treatment with any of methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, ciclosporin and rituximab.
BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary diseas; ESR, erythrocyte sedimentation rate; LAC, lactate; m-SLEDAI, modified SLE Disease Activity Index; qSOFA, quick Sequential Organ Failure Assessment; SCR, serum creatinine; SLICC, Systemic Lupus International Collaborating Clinics.

A score that ranged from 2 to 6 was calculated based on the levels of CRP plus ALB. A score of 4 comprised the highest proportion of patients (26%) and a score of 6 held the lowest proportion (6.7%). The mortality rate for each score, which ranged from 21.6% to 62.5%, is shown in figure 2. Patients with a score of 6 accounted for the second-highest mortality rate (50%). We have provided a table of the total number and mortality rates of the integration for different combinations of CRP plus ALB scores (table 3).

The univariate analyses (table 4) showed that BUN level (p<0.001), leucocyte count (p=0.003), bloodstream infection (p=0.008), maximum prednisone-equivalent dose in the past ≥60 mg/day (p=0.002) and qSOFA (p<0.001) were associated with 90-day mortality. In the multivariate analyses, only BUN (OR 1.06; 95% CI 1.02 to

Table 2 The characteristics of distribution of infection sites and pathogens

Infection sites*	Pathogens†
Pulmonary infection (n=119)	*Candida* spp (27) *Aspergillus* (15) *Klebsiella pneumoniae* (11) *Staphylococcus* (10) *Cytomegalovirus* (10) *Escherichia coli* (9) *Pneumocystis jirovecii* (7) *Pseudomonas aeruginosa* (5) *Cryptococcus neoformans* (4) *Tuberculous bacillus* (3) *Nocard's bacillus* (3) *Epstein-Barr virus* (2)
Bloodstream infection (n=31)	*Staphylococcus* (9) *K. pneumoniae* (7) *E. coli* (5) *Candida* (5) *P. aeruginosa* (2)
Central nervous system infection (n=10)	*C. neoformans* (3) *T. bacillus* (3)
Gastrointestinal infection (n=8)	*Candida* (2) *K. pneumoniae* (1) *P. aeruginosa* (1) *E. coli* (1) *Enterobacter cloacae* (1)
Kidney infection (n=7)	*E. coli* (5) *K, pneumoniae* (1) *Enterococcus faecium* (1)
Osteoarticular infection (n=5)	*Staphylococcus* (2) *Streptococcus constellatus* (1) *E. faecium* (1) *Fusarium solani* (1)
Pelvic infection (n=4)	*P. aeruginosa* (2) *Staphylococcus* (1) *T. bacillus* (1)
Infective endocarditis (n=3)	*Staphylococcus* (3)

*Infection sites totals exceed the number of patients because mixed infections were detected in some.
†Pathogens from the infection sites were not all determined in this study.

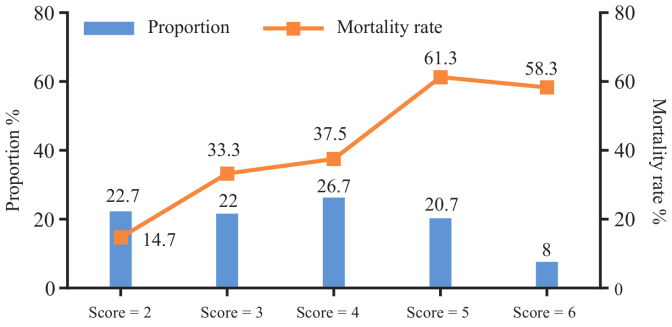

Figure 2 Proportion of population and mortality rate for each C reactive protein plus albumin score group.

1.10; p=0.006), bloodstream infection (OR 3.68; 95% CI 1.23 to 11.05; p=0.020), maximum prednisone-equivalent dose in the past ≥60 mg/day (OR 3.40; 95% CI 1.25 to 9.23; p=0.016) and qSOFA (OR 3.06; 95% CI 1.45 to 6.45; p=0.003) remained significantly predictive of the outcome. The results based on multivariate analyses are presented in table 4.

As shown in table 5, we constructed three models: model 1 contained the univariate analysis, model 2 was adjusted for age and gender and model 3 was adjusted for model 2 as well as the covariates presented in table 4. CRP plus ALB score as a continuous variable had an independent effect on models 1 and 2 (OR 1.77; 95% CI 1.32 to 2.38 and OR 1.83; 95% CI 1.35 to 2.52, respectively). A similar result was found in the full adjusted model (OR 1.52; 95% CI 1.08 to 2.13; p=0.017). Furthermore, increased risk of death remained significant using the categorical CRP plus ALB variables (p for trend <0.05). Likewise, increased CRP plus ALB score was associated with higher infection-related 90-day mortality in the fully adjusted model (OR 1.55; 95% CI 1.07 to 2.25; p=0.020) (online supplemental table 1). Finally, the subgroup analysis by LN yielded a non-significant result, and also there was no significant heterogeneity in the interaction effects (p=0.536).

DISCUSSION

In this prospective cohort study of patients with SLE with serious infections, the 90-day mortality rate was 38%. As CRP elevated and ALB decreased, a gradual increase in mortality was observed. A change in CRP plus ALB score from 2 to 6 accompanied an elevation in the mortality rate from 14.71% to 58.33%. After multivariate adjustment for age, gender, qSOFA, bloodstream infection, BUN and maximum prednisone, CRP plus ALB score remained independently correlated with 90-day mortality, regardless of whether LN was present.

CRP and ALB have been widely acknowledged as systemic inflammatory markers. CRP produced by the liver and adipocytes is stimulated by a rise in interleukin-6, which is overexpressed in various autoimmune diseases like SLE. Thus, the range of CRP levels in patients with SLE with infections sometimes overlaps with those in an SLE flare episode. However, recent evidence indicates that the degree of CRP elevation was higher with infections. CRP levels are usually below 20 mg/L in an SLE flare,[25] whereas levels above 150 mg/L make infections very likely. In our study, patients with SLE with serious infections had markedly higher CRP levels than those in other studies.[26] The primary reason for this difference is the characteristics of the patients, especially regarding infection severity. Moreover, CRP levels in patients with systemic infections were found to be higher than in those with localised infections.[27] CRP has shown promise as a predictor of mortality in sepsis[28 29]; however, in the studies by Lu *et al* and Wang *et al*,[30 31] CRP showed no predictive accuracy in SLE with infections. We speculate that small sample size and infection site heterogeneity may play a role.

A strength of our study was the use of ALB combined with CRP to improve predictive ability. This combination allowed us to distinguish the varying risk of death for patients with SLE with serious infections because even at similar CRP levels (50 mg/L <CRP ≤ 150 mg/L), the mortality data revealed a clear divergence between ALB <25 g/L and ALB ≥30 g/L (69.23% vs 30.77%). Several data revealed a significantly higher incidence of hypoproteinaemia in SLE with infections compared with the non-infection group of patients.[17 32 33] There may be multiple mechanisms, such as decreased synthesis of ALB in the liver, protein loss through the gut mucosa and significant proteinuria,[34] which contributed to the development of hypoproteinaemia.

The predictive value of combined CRP and ALB in sepsis has been broadly validated. To our knowledge, this study is the first to apply the combined indices in SLE with infections. In addition, based on the existing

Table 3 The all-cause 90-day mortality rate of patients in different score groups

	CRP ≤50 mg/L score=1 (n=81)	50 mg/L <CRP ≤ 150 mg/L score=2 (n=51)	CRP >150 mg/L score=3 (n=18)	Total
ALB ≥30 g/L score=1 (n=52)	5/34 (14.71%)	4/13 (30.77%)	1/3 (33.33%)	10/50 (20.00%)
25 g/L <ALB < 30 g/L score=2 (n=37)	7/20 (35.00%)	3/12 (25.00%)	1/5 (20.00%)	11/37 (29.72%)
ALB ≤25 g/L score=3 (n=61)	11/25 (44.00%)	18/26 (69.23%)	7/12 (58.33%)	36/63 (57.14%)
Total	23/79 (29.11%)	25/51 (49.02%)	9/20 (45.00%)	

ALB, albumin; CRP, C reactive protein.

Table 4 Univariate and multivariate analyses of risk factors associated with all-cause 90-day mortality

	Univariate analysis		Multivariate analysis	
Parameters	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Gender (female)	0.70 (0.21 to 2.40)	0.576		
Age on admission	1.01 (0.99 to 1.04)	0.214		
Diabetes mellitus	1.50 (0.64 to 3.53)	0.348		
qSOFA score	3.12 (1.75 to 5.58)	<0.001	3.06 (1.45 to 6.45)	0.003
SLEDAI score	1.06 (1.00 to 1.12)	0.061		
Lupus nephritis	1.66 (0.84 to 3.28)	0.143		
Neuropsychiatric lupus	2.40 (1.05 to 5.47)	0.037		
Pulmonary hypertension	0.95 (0.40 to 2.25)	0.909		
Bloodstream infection	3.17 (1.36 to 7.39)	0.008	3.68 (1.23 to 11.05)	0.020
SCR (μmol/L)	1.00 (1.00 to 1.01)	0.039		
BUN (mmol/L)	1.07 (1.03 to 1.11)	<0.001	1.06 (1.02 to 1.10)	0.006
Leucocyte count ($\times10^9$/L)	1.13 (1.04 to 1.22)	0.003	1.14 (1.02 to 1.26)	0.020
Lymphocyte count ($\times10^9$/L)	0.40 (0.19 to 0.85)	0.017		
LAC (mmol/L)	1.43 (1.06 to 1.93)	0.020		
CRP plus ALB score	1.77 (1.32 to 2.38)	0.000	1.54 (1.08 to 2.18)	0.016
Maximum prednisone-equivalent dose ≥60 mg/day*	3.52 (1.58 to 7.84)	0.002	3.40 (1.25 to 9.23)	0.016
Hydroxychloroquine use*	0.47 (0.24 to 0.92)	0.028		
Mycophenolate mofetil use*	2.60 (1.19 to 5.67)	0.016		
Immunosuppressant use†	1.72 (0.87 to 3.41)	0.121		

*The usage of these drugs was assessed from the time of inclusion in the study to the past 6 months.
†Immunosuppressant use was identified as treatment with any of methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, ciclosporin and rituximab.
ALB, albumin; BUN, blood urea nitrogen; CRP, C reactive protein; qSOFA, quick Sequential Organ Failure Assessment; SCR, serum creatinine; SLEDAI, SLE Disease Active Index.

literature[35] and the popular used standard, CRP and ALB levels in this work were divided into three categories that maximise their clinical applicability.

This study identified that pulmonary infection was the most prevalent site, and the most common fungi were *Candida* spp (27 episodes), followed by A*spergillus* (15

Table 5 Associations of CRP plus ALB score with all-cause 90-day mortality

	Model 1*		Model 2†		Model 3‡	
Variables	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Continuous	1.77 (1.32 to 2.38)	0.0001	1.85 (1.35 to 2.52)	0.010	1.52 (1.08 to 2.13)	0.017
Category						
Score=2	1.00		1.00		1.00	
Score=3	2.90 (0.88 to 9.57)	0.008	2.83 (0.85 to 9.36)	0.089	3.55 (0.83 to 15.20)	0.088
Score=4	3.48 (1.11 to 10.93)	0.033	3.50 (1.11 to 11.04)	0.033	4.70 (1.20 to 18.50)	0.027
Score=5 or 6	8.87 (2.87 to 27.43)	0.000	9.89 (3.09 to 31.64)	0.000	5.77 (1.49 to 22.31)	0.011
P value for trend 0.5						**0.015**
Subgroup analysis						
Lupus nephritis	1.65 (1.12 to 2.44)	0.012	1.66 (1.10 to 2.52)	0.017	1.34 (0.83 to 2.19)	0.233
Non-lupus nephritis	1.86 (1.17 to 2.96)	0.008	1.92 (1.18 to 3.13)	0.009	1.62 (0.94 to 2.78)	0.081
P value for interaction						**0.536**

*Model 1: no adjustment.
†Model 2: adjusted for age, gender.
‡Model 3: adjusted for model 2+qSOFA, bloodstream infection, BUN and maximum prednisone.
BUN, blood urea nitrogen; qSOFA, quick Sequential Organ Failure Assessment.

episodes) and *C. neoformans* (4 episodes). These findings are consistent with a retrospective national cohort study of 3815 patients with SLE by Chen *et al*.[17] As for the isolated bacteria, relative to prior reports from Asian and European studies,[3 36 37] Gram-negative bacteria predominated by *Escherichia coli* was replaced with *K. pneumoniae*, and Gram-positive bacteria continued to predominate with *S. aureus*. Not surprisingly, *K. pneumoniae* has been highly prevalent in Southeast Asia recently.[38] Our study also found that mixed infections accounted for 21.3% of the cohort, and for 42.1% in deceased patients (data not shown) was consistent with the results of study by Fei *et al*[39] comprising a large sample size of 3831 patients in China. Based on our results, it is critical for clinicians to actively seek out all of the possible pathogens.

This study also confirms that HCQ was protective against mortality from serious infections.[10] More than 50% of our patients received HCQ as part of their treatment regimens. Unfortunately, HCQ as a protective factor in 90-day mortality was only demonstrated in the univariate analysis but not in the multivariate model. A possible explanation for our results is that HCQ use was relatively low compared with other studies.[40]

Our results were somewhat inconsistent with a nationwide longitudinal study of Medicaid patients with SLE, which showed that mortality did not differ among users of immunosuppressive medications[7 41] and corticosteroids. An implication of this observation is the possibility that corticosteroids had a dose-dependent effect on death risk. Defining maximum prednisone-equivalent dose ≥60 mg as a predictor was another methodological advantage of our work. Similarly, this value is also likely to be of clinical significance for patients using glucocorticoids under the aforementioned dose and for the shortest possible time period. In summary, these results provide important information regarding the characteristics of patients with SLE with serious infections and the relevant potential prognostic factors.

Our study has some limitations. We did not evaluate the impact of pharmacological therapies on CRP and ALB levels. However, this effect was very mild when compared with the response resulting from infections. In addition, owing to the relatively small sample and corresponding low number of events, adjusting confounding factors were restricted to a limited number. Nevertheless, the key confounding factors were screened by optimised statistical methods. Moreover, the dynamic measurement of CRP and ALB may be a much stronger predictive tool for outcomes compared with single measurements, and further investigation is needed. Finally, our study only included serious infection patients, so the conclusions may be limited in terms of extrapolation to other populations.

CONCLUSION

In conclusion, we demonstrated that a combination CRP and ALB score was associated with poor prognosis in patients with SLE with serious infections. This score can provide clinicians with critical information for identifying patients at risk of death. Additional studies testing these correlations in larger sample populations with more stringent follow-up are needed.

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REFERENCES

1 Chang Y-S, Liu C-J, Wu T-H, *et al*. Survival analysis in systemic lupus erythematosus patients on maintenance dialysis: a nationwide population-based study in Taiwan. *Rheumatology* 2013;52:166–72.
2 Tselios K, Gladman DD, Sheane BJ, *et al*. All-cause, cause-specific and age-specific standardised mortality ratios of patients with systemic lupus erythematosus in Ontario, Canada over 43 years (1971-2013). *Ann Rheum Dis* 2019;78:802–6.
3 Goldblatt F, Chambers S, Rahman A, *et al*. Serious infections in British patients with systemic lupus erythematosus: hospitalisations and mortality. *Lupus* 2009;18:682–9.
4 Jordán-González P, Shum LM, González-Sepúlveda L, *et al*. Clinical correlates and outcomes in a group of Puerto Ricans with systemic lupus erythematosus hospitalized due to severe infections. *SAGE Open Med* 2018;6:205031211877838.
5 Feldman CH, Hiraki LT, Winkelmayer WC, *et al*. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. *Arthritis Rheumatol* 2015;67:1577–85.
6 Rúa-Figueroa I, López-Longo FJ, Del Campo V, *et al*. Bacteremia in systemic lupus erythematosus in patients from a Spanish registry: risk factors, clinical and microbiological characteristics, and outcomes. *J Rheumatol* 2020;47:234–40.
7 Lim CC, Liu PY, Tan HZ, *et al*. Severe infections in patients with lupus nephritis treated with immunosuppressants: a retrospective cohort study. *Nephrology* 2017;22:478–84.
8 Ahn SS, Park ES, Shim JS, *et al*. Decreased ex vivo production of interferon-gamma is associated with severity and poor prognosis in patients with lupus. *Arthritis Res Ther* 2017;19:193.

9 Noël V, Lortholary O, Casassus P, *et al*. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. *Ann Rheum Dis* 2001;60:1141–4.
10 Teh CL, Wan SA, Ling GR. Severe infections in systemic lupus erythematosus: disease pattern and predictors of infection-related mortality. *Clin Rheumatol* 2018;37:2081–6.
11 Kim H-A, Jeon J-Y, An J-M, *et al*. C-reactive protein is a more sensitive and specific marker for diagnosing bacterial infections in systemic lupus erythematosus compared to S100A8/A9 and procalcitonin. *J Rheumatol* 2012;39:728–34.
12 Wang J, Wu X, Tian Y, *et al*. Dynamic changes and diagnostic and prognostic significance of serum PCT, hs-CRP and S-100 protein in central nervous system infection. *Exp Ther Med* 2018;16:5156–60.
13 Cui N, Zhang H, Chen Z, *et al*. Prognostic significance of PCT and CRP evaluation for adult ICU patients with sepsis and septic shock: retrospective analysis of 59 cases. *J Int Med Res* 2019;47:1573–9.
14 Fukaya S, Yasuda S, Hashimoto T, *et al*. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: analysis of 30 cases. *Rheumatology* 2008;47:1686–91.
15 Chelazzi C, Villa G, Mancinelli P, *et al*. Glycocalyx and sepsis-induced alterations in vascular permeability. *Crit Care* 2015;19:26.
16 Gatta A, Verardo A, Bolognesi M. Hypoalbuminemia. *Intern Emerg Med* 2012;7:193–9.
17 Chen D, Xie J, Chen H, *et al*. Infection in southern Chinese patients with systemic lupus erythematosus: spectrum, drug resistance, outcomes, and risk factors. *J Rheumatol* 2016;43:1650–6.
18 Takegawa R, Kabata D, Shimizu K, *et al*. Serum albumin as a risk factor for death in patients with prolonged sepsis: an observational study. *J Crit Care* 2019;51:139–44.
19 Murashima M, Nishimoto M, Kokubu M, *et al*. Inflammation as a predictor of acute kidney injury and mediator of higher mortality after acute kidney injury in non-cardiac surgery. *Sci Rep* 2019;9:20260.
20 Kayapinar O, Ozde C, Kaya A. Relationship between the reciprocal change in inflammation-related biomarkers (Fibrinogen-to-Albumin and hsCRP-to-Albumin ratios) and the presence and severity of coronary slow flow. *Clin Appl Thromb Hemost* 2019;25:107602961983538.
21 Oh TK, Song I-A, Lee JH. Clinical usefulness of C-reactive protein to albumin ratio in predicting 30-day mortality in critically ill patients: a retrospective analysis. *Sci Rep* 2018;8:14977.
22 Ranzani OT, Zampieri FG, Forte DN, *et al*. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. *PLoS One* 2013;8:e59321.
23 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
24 Schneeweiss S, Robicsek A, Scranton R, *et al*. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. *J Clin Epidemiol* 2007;60:397–409.
25 Littlejohn E, Marder W, Lewis E, *et al*. The ratio of erythrocyte sedimentation rate to C-reactive protein is useful in distinguishing infection from flare in systemic lupus erythematosus patients presenting with fever. *Lupus* 2018;27:1123–9.
26 Soyfoo MS, Roth J, Vogl T, *et al*. Phagocyte-specific S100A8/A9 protein levels during disease exacerbations and infections in systemic lupus erythematosus. *J Rheumatol* 2009;36:2190–4.
27 El-Serougy E, Zayed HS, Ibrahim NM, *et al*. Procalcitonin and C-reactive protein as markers of infection in systemic lupus erythematosus: the controversy continues. *Lupus* 2019;28:1329–36.
28 Godínez-Vidal AR, Alcántara-Gordillo R, Aguirre-Rojano VI, *et al*. Evaluation of C-reactive protein, procalcitonin and the PCR/PCT index as indicators of mortality in abdominal sepsis. *Cir Cir* 2020;88:150–3.
29 Devran O, Karakurt Z, Adıgüzel N, *et al*. C-reactive protein as a predictor of mortality in patients affected with severe sepsis in intensive care unit. *Multidiscip Respir Med* 2012;7:47.
30 Lu Z, Li J, Ji J, *et al*. Mortality prediction in systemic lupus erythematosus patients with pulmonary infection. *Int J Rheum Dis* 2019;22:1077–83.
31 Wang M, Zhang H, Yang X, *et al*. Laboratory-confirmed bloodstream infection in systemic lupus erythematosus: risk profiling and short-term mortality. *Lupus* 2020;29:1520–7.
32 Schurder J, Goulenok T, Jouenne R, *et al*. Pneumococcal infection in patients with systemic lupus erythematosus. *Joint Bone Spine* 2018;85:333–6.
33 Zhan Z, Lao M, Su F, *et al*. Hospital-acquired infection in patients with systemic lupus erythematosus: a case-control study in a southern Chinese population. *Clin Rheumatol* 2018;37:709–17.
34 Bessone F, Poles N, Roma MG. Challenge of liver disease in systemic lupus erythematosus: clues for diagnosis and hints for pathogenesis. *World J Hepatol* 2014;6:394–409.
35 Firooz N, Albert DA, Wallace DJ, *et al*. High-sensitivity C-reactive protein and erythrocyte sedimentation rate in systemic lupus erythematosus. *Lupus* 2011;20:588–97.
36 Al-Rayes H, Al-Swailem R, Arfin M, *et al*. Systemic lupus erythematosus and infections: a retrospective study in Saudis. *Lupus* 2007;16:755–63.
37 Teh CL, Ling GR. Causes and predictors of mortality in hospitalized lupus patient in Sarawak General Hospital, Malaysia. *Lupus* 2013;22:106–11.
38 Wyres KL, Nguyen TNT, Lam MMC, *et al*. Genomic surveillance for hypervirulence and multi-drug resistance in invasive Klebsiella pneumoniae from South and Southeast Asia. *Genome Med* 2020;12:11.
39 Fei Y, Shi X, Gan F, *et al*. Death causes and pathogens analysis of systemic lupus erythematosus during the past 26 years. *Clin Rheumatol* 2014;33:57–63.
40 Herrinton LJ, Liu L, Goldfien R, *et al*. Risk of serious infection for patients with systemic lupus erythematosus starting glucocorticoids with or without antimalarials. *J Rheumatol* 2016;43:1503–9.
41 Feldman CH, Marty FM, Winkelmayer WC, *et al*. Comparative rates of serious infections among patients with systemic lupus erythematosus receiving immunosuppressive medications. *Arthritis Rheumatol* 2017;69:387–97.