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 (73.3%) 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.

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 SLE2 and account for 13%–37% of hospitalisations.3,4 The well-known prognostic factors for predicting poor outcomes include diabetes,4 lupus nephritis (LN),5 high-dose prednisolone6 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 studies also displayed poor performance in predicting patients’ prognosis. 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 as well as a good clinical prognostic value for patients with central nervous system infections and sepsis. Frequently, acute inflammation can result in a decrease in serum ALB, regardless of the nutritional status of patients. In SLE or sepsis infections, hypoproteinaemia has a high incidence and is known to be associated with poor prognosis and mortality.

Recently, CRP combined with ALB has been identified as a promising marker of inflammation. More specifically, the notable performance of CRP plus ALB has been observed in septic and critically ill patients. 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 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 gastrointestinalopathy, 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.

#### Laboratory parameters

Blood samples were obtained at the emergency department. The concentrations of ALB in serum were analysed by using a standardised collection form. Baseline data after enrolment, 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.

#### 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.

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#### Definitions

Serious infections were defined as a deep infection for bacterial infection (cellulitis, endocarditis, pneumonia,
pyelonephritis, septic arthritis, osteomyelitis and bacte-
reriaemia), mycobacterial infections (tuberculosis and
non-tuberculous mycobacteria), fungal infections (crypt-
tococcosis, aspergillosis, histoplasmosis and pneumocyo-
tosis) and viral infections (cytomegalovirus, influenza,
herpes zoster, varicella-zoster, Epstein-Barr meningitis
and encephalitis). When it was difficult to differenti-
ate between infection and lupus activity in patients with
negative culture tests, treatment response to antimicro-
bial therapy was considered by the assigned physician
to confirm the infection diagnosis. Interpretation of micro-
biological 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
mean±SD for data with normal distributions and median
(IQR) for non-normally distributed data. One-way anal-
yses of variance, Kruskal-Wallis H tests and $\chi^2$
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 covari-
ates 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 multivar-
iate analysis, we included variables that were significant in
the univariate analysis at the $p<0.01$ significance level to
determine 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.empow-
erstats.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 demo-
graphic, clinical and laboratory characteristics of the
patients at baseline and at the end of the study period are
presented in table 1.

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 patho-
gens 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 neo-
formans (n=3), Mycobacterium tuberculosis bacillus (n=3)
and four of unknown causes. Among the bacterial infections,
the most frequently identified species was Staphylo-
coccus 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.
| 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 (×10^9/L)                            | 6.71 (3.85–9.18)  | 6.11 (3.69–7.96) | 8.28 (5.19–11.50)| 0.003   |
| Lymphocyte count (×10^9/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
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 1.10) was significantly associated with 90-day mortality.

Table 1

| 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 disease; 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.

Table 2

| 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.
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 2.38 and OR 1.83; 95% CI 1.45 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, 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. 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. CRP has shown promise as a predictor of mortality in sepsis; however, in the studies by Lu et al and Wang et al, 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 ≥25 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. There may be multiple mechanisms, such as decreased synthesis of ALB in the liver, protein loss through the gut mucosa and significant proteinuria, 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 | 50 mg/L < CRP ≤ 150 mg/L | Score = 2 | CRP > 150 mg/L | Score = 3 | Total |
| ALB ≥30 g/L | (n=51) | (n=37) | (n=61) | (n=52) | (n=18) | (n=18) | (n=71) |
| 25 g/L < ALB < 30 g/L | 5/34 (14.71%) | 4/13 (30.77%) | 1/3 (33.33%) | 10/50 (20.00%) |
| ALB ≤25 g/L | 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%) | 10/50 (20.00%) |

ALB, albumin; CRP, C reactive protein.
Immunology and inflammation

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

| Parameters                        | Univariate analysis | Multivariate analysis |
|-----------------------------------|---------------------|-----------------------|
|                                   | 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 (×10⁹/L)          | 1.13 (1.04 to 1.22) | 0.003                 | 1.14 (1.02 to 1.26) | 0.020                 |
| Lymphocyte count (×10⁹/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.

This study identified that pulmonary infection was the most prevalent site, and the most common fungi were Candida spp (27 episodes), followed by Aspergillus (15 episodes) and the popular used standard, CRP and ALB levels in this work were divided into three categories that maximise their clinical applicability.

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

| Variables            | Model 1* | Model 2† | Model 3‡ |
|----------------------|----------|----------|----------|
|                      | 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.
ALB, 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.* As for the isolated bacteria, relative to prior reports from Asian and European studies, *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. 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.* 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. 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.

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 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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