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ORIGINAL RESEARCH

Major Infections of Newly Diagnosed Childhood-Onset Systemic Lupus Erythematosus

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Objective: To evaluate the risk of major infections in children with newly diagnosed childhood-onset systemic lupus erythematosus (cSLE).

Methods: Predictors of major infections were identified by the multivariable logistic regression. Major infection free was defined as no major infection events within 6 months after the diagnosis of cSLE. The Kaplan–Meier survival plot was performed. A prediction model for major infection events was established and examined by receiver operating characteristic (ROC) curve analysis.

Results: A total of 98 eligible patients were recorded in the medical charts. Sixty-three documented events of major infections were found in 60 (61.2%) cSLE patients. Furthermore, 90.5% (57/63) of infection events occurred within the first 6 months after the diagnosis of cSLE. The high SLEDAI (SLEDAI >10), lupus nephritis and lymphocyte count <0.8×109/L were predictors for major infections. The CALL score (Children with high disease activity [SLEDAI >10], lymphopenia, and LN) was defined by the number of predictors. Patients were then categorized into two groups: low-risk (score 0–1) and high-risk (score 2–3). Patients in the high-risk group had higher rates of the major infection occurrence than those in the low-risk group during the 6 months after the diagnosis of the cSLE (P<0.001) (HR:14.10, 95% CI 8.43 to 23.59). The ROC curve analysis indicated that the CALL score was effective both in the whole cSLE cohort [area under the curve (AUC) = 0.89, 95% CI: 0.81–0.97] and in the subgroup of lung infections (n = 35) (AUC = 0.79, 95% CI: 0.57–0.99).

Conclusion: High disease activity, LN and lymphopenia were predictors for major infections in newly diagnosed cSLE patients. Specific predictors help identify the cSLE patients with the high risk of major infections. The CALL score could be a useful tool to stratify cSLE patients in practice.

Keywords: lupus, infection, pediatrics

Introduction

Systemic lupus erythematosus (SLE) is a multi-systemic disease with heterogenous manifestations causing great morbidity and mortality. Previous studies found that death pattern of SLE was bimodal, and the infection was contributed to its early deaths.[1,2] Infections were largely considered a complication of immunosuppressive therapy; however, over 25.0% major infectious events were reported at the time of diagnosis without any immunosuppressive medication.[3] A recent study also showed that the prevalence of major infections in newly diagnosed SLE population was 82% and the infection-related mortality rate was 61%.[4] Therefore, infection may be not only induced by the immunosuppressive therapy, but also by the immune disturbances of the disease itself.[1]

Over ninety percent of major infectious events were reported to occur in the first 4 months after diagnosis and were correlated with mortality.[1] In a retrospective research of patients with SLE admitted to the intensive care unit (ICU), inadequate antimicrobial therapy was the most significant predictor for death.[5] Therefore, figuring out risk factors for the major infection was significant. Wang et al found that SLE Disease Activity Index (SLEDAI) >10, poor kidney function

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(serum creatinine >104μmol/L) and lymphopenia were risk factors for major infection events in adult-onset SLE patients.[1] However, compared with the adult-onset SLE, a more aggressive disease course with higher flare rate was reported in childhood-onset SLE (cSLE) patients. Therefore, whether these risk factors for the major infection could be extrapolated to cSLE remains uncertain. To our knowledge, no studies have investigated major infection events in the newly diagnosed cSLE before. This study aimed to analyze the risk factors for the major infection in cSLE patients and to establish a clinical prediction model for the 6-month major infection events in newly diagnosed cSLE patients.

Methods

Study Population

We conducted a retrospective study of 98 cSLE patients (9 males and 89 females) who were diagnosed in the Department of Rheumatology & Immunology at Shanghai Children's Medical Center from Jan 2016 to Oct 2022. The mean age at diagnosis was [11.10±2.13 years (range: 3~18 years)] with the mean follow-up of 2.8±2.0 years. All patients fulfilled the ACR criteria.

Patient's demographic information and lab tests were collected from the medical charts. The disease activity was evaluated by SLE Disease Activity Index 2000 (SLEDAI).

Newly diagnosed cSLE was defined as patients in the first 3 months post-diagnosis.

The trial was approved by the ethics committee of Shanghai Children's Medical Center and was carried out in accordance with the Declaration of Helsinki.

Definition of Major Infection

A definitive diagnosis was considered when the organism was isolated in patients with correspondent clinical characteristics.[1,6] On the other hand, when clinical manifestations, laboratory results and imaging findings were correspondent with an invasive infection, a clinical diagnosis was made even lack of the colonisation evidence.[1,6] None of patients had primary immunodeficiencies or HIV.

Major infection was referred to as the diagnosis with either microbiological or clinical evidences and the treatment with intravenous antibiotics.[1,7] Common Terminology Criteria for Adverse Events (CTCAE) was applied to grade the infection event.[1] The grade of the CTCAE in our cases with major infection events was 3 or higher.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) and median (range). Categorical variables were presented as an absolute number (frequency). Independent-sample Student's *t*-test was used to analyse the normally distributed continuous variables. Mann–Whitney *U*-test for skewed distribution and $\chi 2$ test were conducted when appropriate. Multivariate logistic stepwise regression was performed to find the predictors of major infection. Candidate predictors were selected based on feasibility, previous studies and clinical significance and were weighted by odds ratio (OR).

The predictors were then combined to establish a prediction model for the major infection. Major infection free was defined as no major infection events within 6 months after the diagnosis of the cSLE. The major infection-free survival was studied by the Kaplan–Meier survival plot. The ROC curve analysis was performed to evaluate the performance of the new prediction model.

All statistical analyses were performed using the Statistical Package for Social Sciences version 26.0 (SPSS, Inc., NY, USA). $P < 0.05$ was considered statistically significant.

Result

Basic Data

Sixty-three major infectious events were recorded in 60 (61.2%) patients (Figure 1A). Among them, 10 patients had admitted to the intensive care unit (ICU) related to the infection event (Figure 1B). Furthermore, 90.5% (57/63) of major infection events happened in the first 6 months following the initial diagnosis of the cSLE.

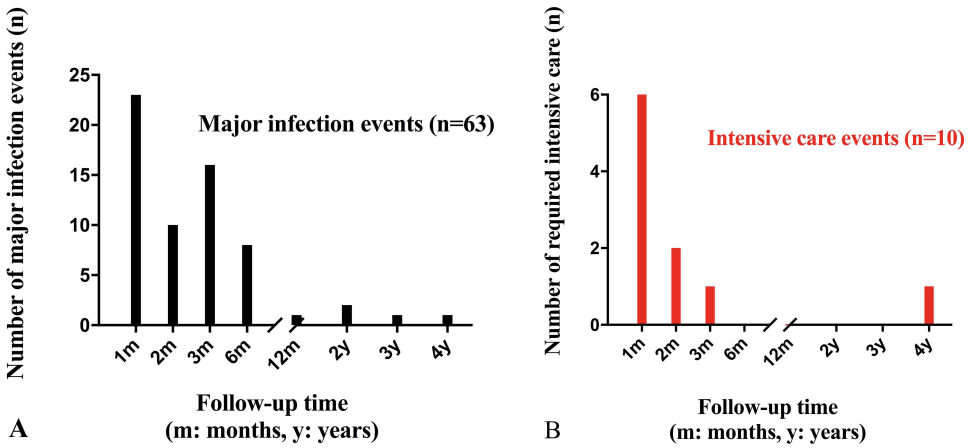

Figure 1 (**A**) Sixty-three major infection events were recorded. Over ninety present (n=57, 90.5%) of the infection events happened within the first 6 months after the initial diagnosis of cSLE. (**B**) Ten patients had admitted to the intensive care unit (ICU) related to the infection event.

Demographics for the major infection group (newly diagnosed patients with major infection events in the first 6 months) and the control group (newly diagnosed patients without major infection events) are presented in Table 1. There were no significant differences in age and gender between the groups ($P < 0.05$).

Pneumonia (n=35, 55.6%) was the most common infection event, followed by bacteremia (n=18, 28.6%), and serous cavity infections (n=6, 9.5%). Central nervous system infections (n=2, 3.2%) and urinary tract infections (n=2, 3.2%) were less common (Table 2).

Table 1 Demographics and Characteristics of Patients with or without Major Infections Within the First 6 Months After the Diagnosis of the cSLE

	Patients with Major Infection Within 6 Months n=57	**Patients without Major Infection (Controls) n=41**	***P***
Age at diagnosis, (years)	11.23±1.99	10.93±1.90	0.454
Female, n(%)	51 (89.5%)	38 (92.7%)	0.587
SLEDAI scores	13.82±4.28	9.49±3.80	<0.001
Lupus Nephritis, n(%)	26 (45.6%)	7 (17.1%)	0.003
Neuropsychiatric Lupus, n(%)	15 (26.3%)	7 (17.1%)	0.279
Serositis, n(%)	15 (26.3%)	4 (9.8%)	0.041
Gastrointestinal involvement, n(%)	6 (10.5%)	3 (7.3%)	0.587
TMA and TTP, n(%)	5 (8.8%)	1 (2.4%)	0.197
Leucocyte count <3×109/L, n(%)	38 (66.7%)	22 (53.7%)	0.192
Lymphocyte count <0.8×109/L, n(%)	28 (49.1%)	2 (4.9%)	<0.001
Platelet count <100×109/L, n(%)	23 (40.4%)	18 (43.9%)	0.725
IgG <7g/L, n(%)	10 (17.5%)	6 (14.6%)	0.701
Treatment involved within 1 months before major infection events or enrolment			
Use of hydroxychloroquine, n(%)	44 (77.2%)	38 (92.7%)	0.041
Methylprednisolone pulse therapy, n(%)	29 (50.9%)	13 (31.7%)	0.059
Maximum prednisone (mg/day)	414.47±401.18	277.81±367.76	0.088
Use of cyclophosphamide, n(%)	10 (17.5%)	3 (7.3%)	0.141
Use of mycophenolate mofetil, n(%)	8 (14.0%)	3 (7.3%)	0.299
Use of cyclosporine A, n(%)	4 (7.0%)	1 (2.4%)	0.310
Use of methotrexate, n(%)	0 (0.0%)	1 (2.4%)	0.236
Use of Rituximab, n(%)	1 (1.8%)	0 (0.0%)	0.394

Abbreviations: TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Table 2 Characteristics of Major Infection Events

Site	Number	Microbiology (n)
Definitive diagnosis		
Pneumonia	2	*Pneumocystis jirovecii* (2)
Bacteremia* identified by blood cultures or next-generation sequencing	18	*Staphylococcus* (9), *Streptococcus* (3), *Klebsiella pneumoniae* (2), *Enterococcus* (2), *Pseudomonas aeruginosa*(2)
Serous cavity infections	6	*Streptococcus* (3), *Mycoplasma*(2), *Klebsiella pneumoniae* (1)
Central nervous system infections	2	*Cryptococcus neoformans* (2)
Urinary tract infections	2	*Staphylococcus* (2)
Clinical diagnosis		
Pneumonia	33	/

Note: *Among the above 18 bacteremia events, 2 cases were mixed infected with *Epstein-Barr virus* at the same time.

In addition, 60.2% (59/98) patients were prescribed with the oral trimethoprim/sulfamethoxazole (TMP/SMX) as the prevention of pneumocystis jirovecii pneumonia. No breakthrough infection and no TMP/SMX toxicities were observed in patients with the prophylaxis treatment. Two patients were diagnosed with pneumocystis jirovecii pneumonia, who were not on prophylaxis with the TMP/SMX.

Tuberculosis (TB) was screened in all patients with newly diagnosed cSLE before the immunosuppressive medication. Three cSLE patients were diagnosed as the latent TB infection and were treated with the isoniazid preventive therapy. Active pulmonary TB was not found in our cohort.

Predictors for Major Infection Within 6 Months

Patients with major infection events had higher SLEDAI scores, higher incidences of lupus nephritis (LN) and serositis than controls. There were significant differences in the use of hydroxychloroquine within 1 month of enrollment between groups (Table 1).

The following 6 candidate predictors were included in the multivariable logistic regression model: SLEDAI >10, LN, serositis, lymphocyte count $<0.8\times10^9$/L, the methylprednisolone pulse therapy and the use of hydroxychloroquine before the enrollment (Table 3). SLEDAI >10, LN and lymphocyte count <0.8×109/L were identified as predictors for major infections within the first 6-month after the diagnosis of the cSLE.

Establishment of Risk Scores for the Major Infection: The CALL Score

The CALL score (Children with high disease activity [SLEDAI >10], lymphopenia, and LN) was established by combining the three predictors (Figure 2). The risk score was determined by the number of predictors.[1] The high-risk group was defined as cSLE patients with the risk score ≥2, and the low-risk group was those with risk score ≤1.[1] The frequency of major infections in cSLE patients with the risk scores of 0, 1, 2 and 3 was 0.0% (0/19), 22.2% (4/18), 82.1% (32/39) and 95.5% (21/22), respectively (Figure 2A).

Table 3 Multivariate Analysis of the Factors Associated with the Major Infection Events Within the First 6-Month After the Diagnosis of cSLE

	Unadjusted			Adjusted for Age and Gender		
	OR	95% CI	*P*	OR	95% CI	*P*
SLEDAI >10	3.78	1.19 to 11.97	0.024	3.69	1.13 to 12.04	0.030
Nephritis	4.18	1.22 to 14.26	0.023	4.18	1.07 to 16.37	0.040
Serositis	1.70	0.37 to 7.87	0.500	1.78	0.38 to 8.47	0.468
Lymphocyte count <0.8×109/L	21.95	4.15 to 116.14	<0.001	21.90	4.08 to 117.33	<0.001
Methylprednisolone pulse therapy	1.98	0.63 to 6.18	0.240	1.91	0.60 to 6.02	0.272
Hydroxychloroquine	0.47	0.08 to 2.74	0.398	0.441	0.07 to 2.74	0.380

A

Risk score	Risk level	n=98
0		0/19
1		4/18
≤1	Low	4/37
2		32/39
3		21/22
≥2	High	53/61

B

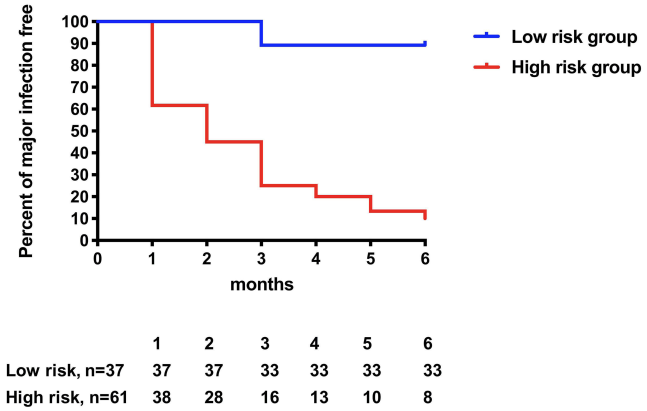

Figure 2 (**A**) The number and frequency of major infection events in the cSLE patients with different risk scores was presented. (**B**) Patients in the high risk group [score (number of predictors) ≥2] had higher rates of the major infection occurrence than those in the low risk group (score ≤ 1) during the 6 months after the diagnosis of the cSLE. (HR:14.10, 95% CI 8.43 to 23.59, P<0.001).

Evaluation of the CALL Scoring System

Major infection-free survival curves within 6 months between the groups were determined by Kaplan–Meier analysis. Patients in the high-risk group had higher rates of the major infection occurrence than those in the low-risk group during the 6 months after the diagnosis of the cSLE (Figure 2B) (P<0.001) (HR:14.10, 95% CI 8.43 to 23.59).

The ROC curve analysis indicated that a CALL score was effective both in the whole cSLE cohort [area under the curve (AUC) = 0.89, 95% CI: 0.81–0.97] and in the subgroup of lung infections (n = 35) (AUC = 0.79, 95% CI: 0.57–0.99) (Table 4).

Discussion

Assessment of the major infection is important for the management of cSLE patients. Through the investigation of the cSLE patients, we explored the characteristics of the major infection. A high frequency of major infections was found within the first 6 months after the diagnosis of the cSLE. To be noticed, the major infection was related to the ICU admission and the largest risk factor for death of cSLE patients was reported to be the inadequate treatment with antibiotics.[5] In order to identify and cure infected cSLE patients as soon as possible, we found that the high SLEDAI score, lymphopenia and LN were three risk factors for the major infection. The CALL score (Children with high disease activity [SLEDAI >10], lymphopenia, and LN) was established by the number of predictors and could be a useful tool to identify the cSLE patients with the high-risk of major infection.

Table 4 Performance of the CALL Score Evaluated by Receiver Operating Characteristic (ROC) Curve Analysis

Model	AUC (95% CI)	Sensitivity	Specificity
Whole cohort (n=98)	0.89(0.81–0.97)	93.1%	84.6%
Subgroup of pneumonia (n=35)	0.79(0.57–0.99)	85.7%	71.4%

Abbreviation: AUC, area under receiver operating characteristic curve.

We found that the lung was the most common infectious site of the cSLE. The bacterium was the most common pathogen. The results were correspondent with the previous study of SLE.[1,8,9] In our study, 90.5% (57/63) of major infection events happened in the first 6 months following the initial diagnosis of the cSLE. The reason for a high incidence of infections in the first six months may be due to the uncontrolled immunological abnormalities of the disease, such as lymphopenia, impaired T cell–mediated cytolytic activity, suppressed cytotoxicity of NK cells, abnormal function of B cell subsets, low production of interleukin-2 (IL-2) and etc.[10]

Although opportunistic infections were not common in cSLE patients,[11] guidelines for the antifungal prophylaxis were widely performed in the immunocompromised patients, especially those with the transplantation or the hematological tumor.[12] In our study, 60.2% (59/98) patients were prescribed with the oral TMP/SMX as the prevention of pneumocystis jirovecii pneumonia. No breakthrough infection and no TMP/SMX toxicities were observed in patients with the prophylaxis treatment. On the other hand, three patients were identified with the latent tuberculosis infection and were treated with the isoniazid preventive therapy, which was already proved to lower the risk of active TB in the rheumatic population.[13]

The LN and the high SLEDAI score (SLEDAI score >10) were risk factors for major infection in our study, correspondent with the result of Hiraki et al.[14] The LN was also reported to be associated with significantly lower survival rate in those with LN than those without LN.[15] These results suggested that the autoimmune status of the SLE disease itself contributed to the susceptibility to major infections. Therefore, major infection should be noticed in the newly diagnosed patients with active LN.

The glucocorticoid did not serve as a significant factor to predict the major infections of the cSLE patients in our study. The result was in contrast with the prior studies of the adult-onset SLE patients that the risk of the infection could be increased by the glucocorticoid with the dose effect.[16,17] This discrepancy may be explained by the Wu et al's finding[18] that the phagocytic ability of polymorphonuclear cells (PMNs) was not influenced by the cumulative steroid dose or the immunosuppressive medication in the cSLE patients, even the phagocytic ability was impaired compared with the normal controls. It seems that the immune disturbance of the SLE itself rather than the glucocorticoid is the essence of the reason why the newly diagnosed cSLE is prone to have higher risks of major infections.

Although there was significant difference in the use of hydroxychloroquine between the major infection group and the control groups by $\chi 2$ test, the high SLEDAI score, low lymphocyte count and LN outweighed the absence of hydroxychloroquine treatment as predictors for major infection events in the multivariable logistic regression. Whether the hydroxychloroquine treatment could prevent the infection remains controversial.[1,17,19] Our result was correspondent with Wang et al's study.[1] Further research on the measurement of hydroxychloroquine concentration may provide more reliable information instead of the investigation of the medication adherence of hydroxychloroquine.[20]

Through multivariate logistic stepwise regression, our study showed that SLEDAI >10, lymphocyte count $<0.8\times10^9$/L and LN were risk factors for major infection events. Patients in the high-risk group had higher rates of the major infection occurrence than those in the low-risk group during the 6 months after the diagnosis of the cSLE (HR:14.10, 95% CI 8.43 to 23.59). In previous study, the SLE infection predictive index (LIPI) was reported to predict the infection in the next year.[21] Meanwhile, the LUPHAS score was provided by Wu et al in the adult-onset SLE patients to predict the mortality within the following 3 months.[8] However, it is not rigorous to extrapolate the conclusions of the adult population and the different ethnicity to the juvenile. To our knowledge, no studies have investigated major infection events in the newly diagnosed cSLE before. Here, a simple score system, established by the number of predictors, was provided as the CALL score (Children with the high disease activity [SLEDAI >10], lymphopenia, and LN). With the ROC curve analysis, the CALL score was proved to be capable of predicting the major infection within 6 months in the newly diagnosed cSLE patients. We also examined the accuracy of the CALL score in the cSLE patients with the pneumonia because the pneumonia was the most common infection event. Further prospective studies are necessary to figure out whether the CALL score system could improve the prognosis for the cSLE patients with major infections.

Our study had several limitations. The major limitation of the current study is its retrospective design with limited cases. A prospective study with a larger sample size needs to be carried out. Second, infections were identified from diagnosis codes due to the retrospective design. Not all infectious events could be confirmed with the microbiological evidence. Third, the vaccination status and the antibiotic prophylaxis will be further evaluated.[22]

Conclusion

High disease activity, LN and lymphopenia were predictors for major infections in the newly diagnosed cSLE patients. Specific predictors help identify the cSLE patients with the high risk of major infection. The CALL score could be a useful tool to stratify cSLE patients in practice. Further interventions, including screening latent infections, appropriate use of antibiotics, improving vaccination coverage, testing levels of immunoglobulins and T cell subsets before and after the immunosuppressive treatments, and etc., seem necessary to prevent infections in cSLE patients, especially those with high risk of infection.

Data Sharing Statement

Data are available on reasonable request. Researchers need to send requests with protocols to the corresponding authors to gain access.

Ethical Approval and Consent

This was a study based on a retrospective chart review. The trial protocol was approved by the ethics committee of Shanghai Children's Medical Center (SCMCIRB-K2022068-1) and the study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from the parents/guardians.

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Disclosure

The authors report no conflicts of interest in this work.

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