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Causes and Factors Associated with Frequent Hospitalization in Chinese Patients with Systemic Lupus Erythematosus: An Ambispective Cohort Study

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Background: Hospitalizations in patients with systemic lupus erythematosus (SLE) have been reported from different regions in the world. This study aimed to evaluate the annual hospitalization rate, causes of hospitalization, and potential factors associated with frequency of hospitalization in Chinese patients.

Material/Methods: We performed an ambispective cohort study for hospitalized patients with SLE in a Chinese single center. Data on demographics, organ involvements, laboratory abnormities, clinical treatments, causes of hospitalization, and survival outcomes were recorded at the time of SLE diagnosis and during a follow-up period. Poisson regression models were created to identify the potential factors associated with frequency of hospitalization.

Results: Of 526 patients with SLE, 242 patients (46%) had 1 or more admissions amounting to a total of 449 times during a median follow-up period of 4.73 years. The annual hospitalization rate was 18% and death occurred in 2.5% of total admissions. SLE flare, infection and pregnancy-related morbidity were the most common causes of hospitalization. Besides, the multivariate Poisson regression analysis revealed that decreased albumin, decreased renal function, and high disease damage were the risk factors for more frequency of hospitalization, whereas positive anti-SSA antibody and use of hydroxychloroquine were protective factors.

Conclusions: Nearly half of patients (46%) with SLE experience 1 or more hospitalizations, mainly due to SLE flare, infection, and pregnancy-related morbidity. Lupus patients with decreased albumin, decreased renal function, and high disease damage are more susceptible to have frequent hospitalization.

MeSH Keywords: China • Hospitalization • Lupus Erythematosus, Systemic • Risk Factors

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Background

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by protean clinical manifestations and follows a relapsing and remitting course [1]. The mortality of SLE has decreased significantly over the past few decades, possibly due to earlier diagnosis, more conservative use of glucocorticoids, and modified immunosuppressive regimens [2]. However, SLE is still associated with excess mortality requiring more hospital admissions for patients compared to the general population [3,4]. Moreover, hospitalizations are a source of high healthcare costs and a major financial burden for patients with SLE [5,6].

Several previous cohorts have focused on the hospitalizations of patients with SLE. The hospitalization rates ranged from 8.6% to 18.9% per year in California and Pennsylvania patients, from 22% to 28% per year in Canadian patients, and up to 50% per year in Danish patients [7–9]. The most common causes of hospitalization in lupus patients were SLE flare and infection. Additional reported causes included pregnancy-related morbidity, cardiovascular disease, thromboembolic event, adverse drug reaction, and incidental causes [8–15]. An inception cohort of Korean patients with SLE has showed that arthritis, pericarditis, and positive anti-Sjögren's syndrome A antibody were risk factors for frequent hospitalization [12]. Another cohort study in Canada has discovered that the presence of disease damage was associated with increased hospitalizations, while use of antimalarial might be a protective factor [14]. Nevertheless, after extensively reviewing published reports, we found that there was no similar study focusing on these aspects in China.

Therefore, we performed an ambispective cohort study for hospitalized patients with SLE in a Chinese single center. The aims of this study were to evaluate the annual hospitalization rate, causes of hospitalization, and potential factors associated with frequency of hospitalization in Chinese SLE patients.

Material and Methods

Study population

This was an ambispective cohort study. We used the International Classification of Diseases, 10th ed. code for SLE (M32.9) to identify medical records of patients hospitalized in Anhui Provincial Hospital from January 2010 to December 2017. The recruitment for the study population was shown in Figure 1. Inclusion criteria were patients who met the 1997 revised American College of Rheumatology (ACR) classification criteria or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [16–18]. Exclusion

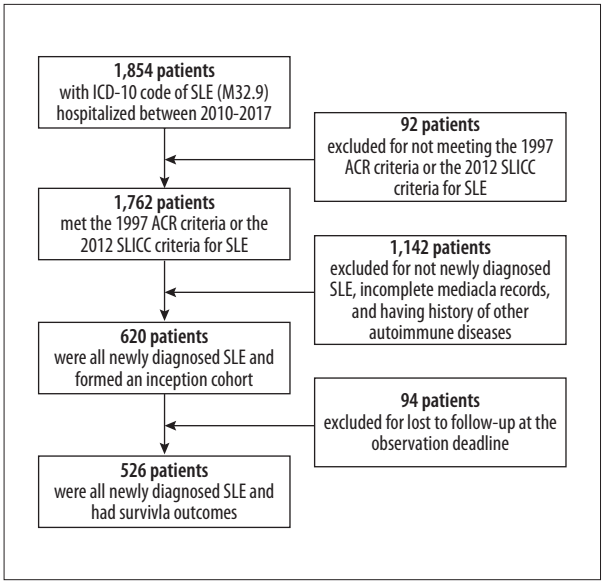

Figure 1. Diagram of recruitment for the study population.

criteria were 1) patients having diagnosed SLE before recruitment; 2) patients with incomplete or loss of medical records; 3) patients have history of other autoimmune diseases. All newly diagnosed SLE patients were recruited and formed an inception cohort in our study. Survival conditions of these patients were checked in January 2019 and those lost to follow-up were excluded from final analysis. This study was conducted with the provisions of the World Medical Association Declaration of Helsinki and approved by the ethics committee of Anhui Medical University.

Data collection

Using the hospital electronic database, the following data at the time of SLE diagnosis were recorded: age, gender, organ involvements, laboratory abnormities, and clinical treatments. Eight organ involvements in patients with SLE were assessed according to the British Isles Lupus Assessment Group (BILAG) 2004 index [19]. Patients were classified as having a specific organ involvement if they had one of the manifestations. Laboratory abnormalities were defined as follows: anemia, hemoglobin <110 g/L in females or <120 g/L in males; leukopenia, leukocyte $<4\times10^9$/L; thrombocytopenia, platelet $<100\times10^9$/L; decreased albumin, albumin <35 g/L. The estimated glomerular filtration rate (eGFR) was calculated using the abbreviated modification of diet in renal disease equation modified by Chinese researchers [20], and decreased eGFR was defined as eGFR less than 90 mL/min/1.73 m^2. The presences of autoantibodies included anti-Smith (anti-Sm) antibody, anti-nuclear RNA protein (anti-RNP) antibody, anti-Sjögren's syndrome A (anti-SSA) antibody, anti-Sjögren's syndrome B (anti-SSB) antibody, and anti-double stranded DNA (anti-dsDNA) antibody. For clinical treatments, data on use of glucocorticoids, hydroxychloroquine,

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and immunosuppressants were also obtained from the medical records. The SLE disease activity index 2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index were evaluated by an experienced rheumatologist [21,22].

In the present study, the annual hospitalization rate was calculated as the total number of hospitalizations divided by the duration of SLE (in years) [12]. The causes of hospitalization were classified according to discharge diagnoses. Multiple categories were recorded by an experienced rheumatologist when there was more than one reason for hospitalization. SLE flare denoted the clinical manifestations or organ involvements typically seen in SLE. Infection denoted the signs and symptoms of a microorganism invasion confirmed by microbial testing, imaging analysis, and laboratory examination [12]. Pregnancy-related morbidity denoted a pregnant woman with SLE that was admitted to hospital for healthcare. Adverse vascular event comprised cardiovascular event, cardiovascular event, and deep venous thrombosis. Renal insufficiency denoted SLE patients with progressive rise in serum creatinine or establishing and maintaining dialysis. Adverse drug reaction was defined as a side effect of drug that correlated with the treatment of SLE.

Statistical analysis

Continuous variables were presented as medians (ranges), and categorical variables as numbers (percentages). Poisson regression models were created to identify the potential factors associated with frequency of hospitalization after examining the distribution of outcome variable. Akaike information criterion was used as model-fitting statistics for Poisson. Because longer disease duration may provide a greater opportunity for hospital admission, SLE duration was also included in the univariate and multivariate regression models. Results were presented as risk ratios (RRs) along with their 95% confidence intervals (CIs). All statistical analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA). *P* values less than 0.05 were considered to be statistically significant.

Results

A total of 526 newly diagnosed patients with SLE that met our inclusion and exclusion criteria were retrospectively reviewed in our study. Table 1 provides the baseline characteristics of the full cohort. The majority of SLE patients were female (male versus female=1: 11). The median age at diagnosis was 31 years (ranged 10 to 84 years). At the time of SLE diagnosis, the most common manifestations were hematologic (88.4%), mucocutaneous (71.7%), musculoskeletal (62.2%), and renal (52.7%) involvements. More than one quarter of patients (28.5%) presented with cardiopulmonary manifestations,

Table 1. Baseline characteristics of 526 patients with SLE in our ambispective cohort.

Characteristics	Number (N)	Percentage (%)
Female	482	91.6
Age at diagnosis, years, median (range)	31	10–84
Organ involvements		
Neuropsychiatric	36	6.8
Mucocutaneous	377	71.7
Musculoskeletal	327	62.2
Cardiopulmonary	150	28.5
Gastrointestinal	56	10.6
Renal	277	52.7
Hematologic	465	88.4
Ophthalmologic	13	2.5
Laboratory abnormities		
Anemia	370	70.3
Leukopenia	327	62.2
Thrombocytopenia	154	29.3
Decreased albumin	296	56.3
Decreased eGFR	70	13.3
Positive autoantibodies		
Anti-Sm	188	35.7
Anti-RNP	278	52.9
Anti-SSA	300	57.0
Anti-SSB	122	23.2
Anti-dsDNA	331	62.9
Clinical treatments		
Glucocorticoids	522	99.2
Hydroxychloroquine	493	93.7
Immunosuppressants	168	31.9
SLEDAI-2K score, median (range)	14	3–42
SLICC/ACR damage index, median (range)	1	0–5

SLE – systemic lupus erythematosus; eGFR – estimated glomerular filtration rate; SLEDAI-2K – Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR – Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology.

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Table 2. Causes of hospitalization for patients with SLE during the follow-up period.

Causes of hospitalization	Number (N)	Percentage (%)
SLE flare	**227**	**50.6**
Hematologic disorder	65	14.5
Renal disorder	48	10.7
Mucocutaneous disorder	34	7.6
Musculoskeletal disorder	29	6.5
Cardiopulmonary disorder	18	4.0
Neuropsychiatric disorder	15	3.3
Gastrointestinal disorder	13	2.9
Miscellaneous	5	1.1
Infection	**162**	**36.1**
Respiratory tract infection	89	19.8
Urinary tract infection	32	7.1
Varicella zoster	20	4.5
Intestinal infection	12	2.7
Miscellaneous	9	2.0
Pregnancy-related morbidity	**31**	**6.9**
Caesarean section	14	3.1
Normal delivery	11	2.5
Therapeutic abortion	4	0.9
Premature delivery	1	0.2
Gestational diabetes	1	0.2
Adverse vascular event	**17**	**3.8**
Cardiovascular event	9	2.0
Cerebrovascular event	5	1.1
Deep venous thrombosis	3	0.7
Renal insufficiency	14	3.1
Malignancy	9	2.0
Adverse drug reaction	5	1.1
Others	32	7.1

SLE – systemic lupus erythematosus.

while few patients had gastrointestinal (10.6%), neuropsychiatric (6.8%), and ophthalmologic (2.5%) involvements.

In addition, most patients had SLE combined with anemia (70.3%), leukopenia (62.2%), or decreased albumin (56.3%), yet 29.3% of patients experienced thrombocytopenia and 13.3% of patients had decreased eGFR. The profiles of autoantibodies included the presence of anti-Sm antibody in 188 cases (35.7%), anti-RNP antibody in 278 cases (52.9%), anti-SSA antibody in 300 cases (57.0%), anti-SSB antibody in 122 cases (23.2%), and anti-dsDNA antibody in 331 cases (62.9%). For the clinical treatments in our cohort, 99.2% of patients took glucocorticoids, 93.7% of patients took hydroxychloroquine, and 31.9% of patients received immunosuppressants. Meanwhile, the median SLEDAI-2K score was 14 (range 3 to 42) and the median SLICC/ACR damage index was 1 (range 0 to 5).

During a median follow-up period of 4.73 years (range 0.03 to 9.17 years), 242 patients (46%) with SLE had one or more admissions amounting to a total of 449 times. Simultaneously, the crude hospitalization rate was 18% per year according to the defined calculation formula. Eleven (2.5%) of hospitalization events resulted in death, and the reasons for these deaths were infection in 8 cases, lupus encephalopathy in 2 cases, and renal failure in 1 case. The causes of hospitalization in our cohort are described in Table 2. The most common cause for hospitalization was SLE flare (50.6%), followed by infection (36.1%), and pregnancy-related morbidity (6.9%). Among the other causes of hospitalization, 17 cases (3.8%) occurred due to adverse vascular events, 14 cases (3.1%) due to renal insufficiency, 9 cases (2.0%) due to malignancy, and 5 cases (1.1%) due to adverse drug reaction.

With regard to SLE flare, the specific causes of hospitalization were hematologic disorder in 65 cases (14.5%), renal disorder in 48 cases (10.7%), mucocutaneous disorder in 34 cases (7.6%), musculoskeletal disorder in 29 cases (6.5%), cardiopulmonary disorder in 18 cases (4.0%), neuropsychiatric disorder in 15 cases (3.3%), and gastrointestinal disorder in 13 cases (2.9%). In cases of infection, the specific causes of hospitalization included respiratory tract infection in 89 cases (19.8%), urinary tract infection in 32 cases (7.1%), varicella zoster in 20 cases (4.5%), and intestinal infection in 12 cases (2.7%). Among pregnant women with SLE, 14 patients (3.1%) had caesarean sections, 11 patients (2.5%) had normal deliveries, 4 patients (0.9%) had therapeutic abortions, 1 patient (0.2%) had premature delivery due to preeclampsia, and 1 (patient 0.2%) had gestational diabetes.

Poisson regression models were applied to assess the potential factors associated with frequency of hospitalization. As shown in Table 3, SLE duration, cardiopulmonary involvement, gastrointestinal involvement, ophthalmologic involvement, anemia, decreased albumin, decreased eGFR, positive anti-SSA antibody, use of hydroxychloroquine, and SLICC/ACR damage index were associated with frequency of hospitalization in the univariate

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Table 3. Univariate poisson regression on factors associated with frequency of hospitalization.

Variables	RR	95% CI	*P* value
SLE duration	1.011	1.008–1.014	<0.001
Female	1.080	0.765–1.524	0.663
Age at diagnosis	1.004	0.998–1.010	0.182
Organ involvements			
Neuropsychiatric	1.186	0.844–1.669	0.325
Mucocutaneous	0.855	0.700–1.043	0.121
Musculoskeletal	0.837	0.694–1.010	0.063
Cardiopulmonary	1.257	1.034–1.530	0.022
Gastrointestinal	1.319	1.007–1.728	0.044
Renal	1.120	0.927–1.349	0.236
Hematologic	1.096	0.812–1.478	0.549
Ophthalmologic	1.649	1.028–2.641	0.038
Laboratory abnormities			
Anemia	1.284	1.036–1.590	0.022
Leukopenia	1.165	0.960–1.416	0.123
Thrombocytopenia	1.027	0.839–1.257	0.792
Decreased albumin	1.431	1.179–1.737	<0.001
Decreased eGFR	1.795	1.433–2.250	<0.001
Positive autoantibodies			
Anti-Sm	1.085	0.897–1.314	0.402
Anti-RNP	0.896	0.745–1.078	0.245
Anti-SSA	0.784	0.652–0.945	0.010
Anti-SSB	1.062	0.856–1.318	0.587
Anti-dsDNA	1.140	0.938–1.385	0.189
Clinical treatments			
Glucocorticoids	0.680	0.282–1.642	0.392
Hydroxychloroquine	0.460	0.349–0.608	<0.001
Immunosuppressants	1.179	0.972–1.430	0.093
SLEDAI-2K score	1.008	0.094–1.022	0.281
SLICC/ACR damage index	1.215	1.119–1.319	<0.001

SLE – systemic lupus erythematosus; eGFR – estimated glomerular filtration rate; SLEDAI-2K – Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR – Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology; RR – risk ratio; CI – confidence interval.

analysis. Additionally, after adjusting for SLE duration, the multivariate regression analysis revealed that decreased albumin (RR=1.234, 95% CI: 1.001–1.519), decreased eGFR (RR=1.520, 95% CI: 1.178–1.964), and high SLICC/ACR damage index (RR=1.143, 95% CI: 1.034–1.265) were the risk factors for more frequency of hospitalization, while positive anti-SSA antibody (RR=0.785, 95% CI: 0.649–0.951) and use of hydroxychloroquine (RR=0.634, 95% CI: 0.473–0.849) were protective factors (Table 4).

Discussion

We conducted an ambispective cohort to evaluate the annual hospitalization rate, causes of hospitalization, and potential factors associated with frequency of hospitalization in Chinese patients. The baseline characteristics of our cohort were similar to another study on hospitalized patients in China [23]. Of 526 patients with SLE, nearly half (46%) had 1

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Table 4. Multivariate poisson regression on factors associated with frequency of hospitalization.

Variables	RR	95% CI	*P* value
SLE duration	1.012	1.009–1.015	<0.001
Cardiopulmonary involvement	1.069	0.856–1.335	0.553
Gastrointestinal involvement	1.100	0.819–1.476	0.529
Ophthalmologic involvement	1.114	0.679–1.829	0.668
Anemia	1.164	0.931–1.455	0.183
Decreased albumin	1.234	1.001–1.519	0.049
Decreased eGFR	1.520	1.178–1.964	0.001
Anti-SSA	0.785	0.649–0.951	0.013
Hydroxychloroquine	0.634	0.473–0.849	0.002
SLICC/ACR damage index	1.143	1.034–1.265	0.009

SLE – systemic lupus erythematosus; eGFR – estimated glomerular filtration rate; SLICC/ACR – Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology; RR – risk ratio; CI – confidence interval.

or more admissions during a median follow-up period of 4.73 years. The annual hospitalization rate was 18%, which is in accordance with that reported in several previous studies with ranging from 8.6% to 28%, but lower than 50% in the population-based Danish cohort [7–9]. The hospitalization rate varies among these cohorts, probably owing to the differences in accessibility to healthcare services, medical insurance policies, and local economic conditions. In this study, death occurred in 2.5% of the hospitalizations, which was in line with previous studies that deadly outcome amounted to 1% to 5.8% of admissions [8–15].

The most common causes of hospitalization in our study were SLE flare (50.6%) and infection (36.1%). The overall percentages of hospitalizations for these causes were comparable to other Asian populations, with SLE flare comprising 58% to 80.8% of admissions and infection representing 17.1% to 37% of admissions [10–12]. However, the proportions appeared to be lower in North American patients, which found to be 11.7% to 35% for SLE flare and 10.9% to 16.2% for infection [4,8,13]. Similar proportions were reported in Tunisian patients that SLE flare and infection accounted for 43% and 9.4% of total admissions, respectively [15]. We believe that the discrepancies in these proportions may attribute to ethnic variations, socio-economic differences, different criteria for hospitalizations and different clinical practices.

In this survey, pregnancy-related morbidity was the third cause of hospitalization and accounted for 6.9% of total admissions, which is lower than that of 9% to 12% in previous cohorts [4,8,12]. Pregnant patients with SLE may experience a higher risk for cesarean sections, preterm labor, and preeclampsia, as well as other medical conditions, including diabetes, hypertension, and thrombophilia [24]. During the study period, 1 case of gestational diabetes and 1 case of preterm delivery due to preeclampsia were the only pregnancy complications in our cohort. Therefore, this finding may suggest a more general trend of improved pregnancy outcomes in lupus patients [25]. In addition, clinicians should always provide more prenatal care for pregnant women with SLE during the course of the disease.

The frequency of hospitalization reflects not only the severity of disease, but also the economic burden for patients with SLE. In our cohort, decreased albumin, decreased eGFR, and high SLICC/ACR damage index at the time of SLE diagnosis were risk factors for more frequency of hospitalization. Serum albumin can be regard as a surrogate marker for disease activity in lupus patients [26]. Lower serum albumin is associated with higher SLEDAI, which may lead to disease flares and more hospital admissions. The decline in eGFR at the time of SLE diagnosis is an independent risk factor for mortality [27]. Similarly, early damage as measured by the SLICC/ACR damage index is a predictor of mortality [28]. Besides, the presence of disease damage is also associated with increased hospitalizations in patients with SLE [14]. Overall, a novel finding of our study is that patients with decreased albumin, decreased renal function, and high disease damage at the time of SLE diagnosis were more susceptible to have frequent hospitalization. Accordingly, patients with SLE who clinically fulfill these associations should warrant more careful attentions, especially when establishing treatment plans in the future.

Interestingly, our data displayed that the presence of anti-SSA antibody was associated with fewer frequency of hospitalization, which is opposite to a former research in Korean patients [12]. Previous studies have found that anti-SSA antibody may play a protective role in lupus nephritis [29,30]. However, the opposite

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result was observed in a cohort of 201 Puerto Ricans patients with SLE [31]. Consequently, further studies are needed to illuminate the association between anti-SSA antibody and frequency of hospitalization in SLE patients. Use of hydroxychloroquine was associated with fewer frequency of hospitalization in our study. The Canadian cohort also has demonstrated that antimalarial use was correlated with about 18% decreased frequency of hospitalization in lupus patients [14]. Moreover, antimalarial drugs have potential effects on reducing disease activity, preventing lupus flares, and improving patient's survival [32–34]. Therefore, these findings would further support the importance of antimalarial drugs in the treatments of SLE.

To our knowledge, this was the first study to illustrate the profiles of hospitalizations among Chinese patients with SLE. Nevertheless, our study also has several limitations to consider when interpreting the relevant results. First of all, socio-economic status, a known predictor of hospitalization in SLE, was not evaluated in our regression analysis. Secondly, we were unable to collect whole clinical data for patients who were admitted to other hospitals during the follow-up period, possibly resulting in an underestimated hospitalization rate annually. Finally, only hospitalized patients with SLE were included in this cohort, which represented a SLE subgroup with relatively high disease activity. Thus, a comprehensive study is expected to reveal more details of hospitalizations and corroborate these findings further.

Conclusions

In summary, nearly half of patients (46%) with SLE experience 1 or more hospitalizations during a median of 4.73 years follow-up period. The annual hospitalization rate is 18% and death occurs in 2.5% of total admissions. SLE flare, infection, and pregnancy-related morbidity are the most common causes of hospitalization. Patients with decreased albumin, decreased renal function, and high disease damage at the time of SLE diagnosis are more susceptible to have frequent hospitalization. Moreover, these findings further underline that clinicians should be concerned with the characteristics of hospitalizations when establishing appropriate treatment plans and understand prognosis of the disease.

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Conflict of interest

None.

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