

The challenges and future perspective for the management of systemic lupus erythematosus in China: A concise annual report of 2020

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Introduction

Systemic lupus erythematosus (SLE) is a systemic chronic autoimmune disease characterized by various autoantibodies in blood and multiple organ involvement. A majority of SLE patients are young females of child-bearing age. The disease usually presents as waxing and waning. SLE has become a common chronic but major disease that threatens the public health of the Chinese population. A preliminary epidemiological study has shown that the prevalence of SLE is 30–70/100,000. Based on this rate, it is estimated that there are about 1 million SLE patients in China currently. As the clinical presentations of SLE are very complicated and heterogeneous, the diagnosis and treatment of SLE are very challenging. However, rheumatology is the youngest specialty of internal medicine in China and has existed for only 40 years; thus, there is a severe shortage of rheumatologists across the country. In addition, some physicians who take care of SLE patients did not receive the training for the management of SLE. The awareness of the diagnosis and treatment of the disease in primary health care professionals is far from adequate. These factors lead to the under standardization

of the management of SLE in certain areas of the country. Furthermore, the public do not have enough understanding of the disease but only have a feeling of “fear” about the disease. Some patients have a wishful thinking that the disease could be cured by some “magic pills or herbs,” and so poor compliance to treatment is very common. Therefore, some patients have had uncontrolled active disease for a long time. This has become a major cause of irreversible organ damage and the accrual of internal organ damage, which finally leads to high mortality. Not only can SLE cause psychosomatic suffering but also its care imposes a heavy economic burden on families and society.

Considering the current status of the management of SLE in China, the National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID) in partnership with the Chinese Rheumatism Data Center (CRDC) has organized and compiled this annual report of 2020. The goals are to understand the epidemiological and clinical characteristics of the disease of the country, identify the gap in the management of the disease between China and developed countries, ensure the direction of future development of the disease management in the country and facilitate the rapid progress of Chinese rheumatology. This is the first national report on SLE in the history of Chinese rheumatology. In this report, the most current epidemiological data, clinical features, diagnosis level, resources, and future development are comprehensively reviewed. This report has not only revealed the challenges and opportunities in the management of SLE but also explored the future directions for the development of Chinese rheumatology. This report provides real-world data to the Chinese health care authorities for future resource

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allocation for SLE management and provides a reference to health care professionals who are taking care of SLE patients. This report can also be a guide for members of the public and SLE patients who wish to understand the disease and its prevention in depth.

The Epidemiological Characteristics of Chinese SLE Patients

The prominent epidemiological characteristics of Chinese SLE patients are “large patient population with severe disease and heavy disease burden” and “high complication rate and adverse impact on fertility.”

Large Patient Population

The only epidemiological study on the prevalence of SLE in China was published in 2008. This study showed that the prevalence of SLE in China was 30–70/100,000,^[1] ranking the second-highest in the world. Based on this data, it is estimated that there are at least 1 million SLE patients in the country. SLE has become a common chronic autoimmune disease in China.^[2] In 2009, the Chinese SLE Treatment and Research Group (CSTAR) was established under the leadership of the Department of Rheumatology of Peking Union Medical College Hospital (PUMCH). CSTAR has set up a nationwide registration system and conducted an epidemiological study in the country. From the data of CSTAR, the average age of patients at disease onset was 30.7 years with a female-to-male ratio of 12:1.^[3, 4] The average age at diagnosis was 31.6 years, 4.58% were younger than 18 years, and 79.56% were between 18 years and 40 years old. These data indicated that the majority of SLE patients in China were young people. For geographic distribution, the prevalence rate (25.03%) in northern China was higher than that in the southern part. The disease was more severe in patients with low levels of education and local health care, with longer sun exposure, and who are living in the southern part of the country.^[5] Furthermore, ultraviolet light exposure and smoke were the precipitating factors for disease onset and flare. The disease was more severe in smokers who were prone to have kidney involvement.^[6] All these observations have provided clues for taking preventive measures to fight the disease. In addition, according to the data from CSTAR, 4.2% of Chinese SLE patients had a family history of autoimmune diseases.^[7]

More Severe Disease

Based on the data from CSTAR, the clinical presentations of Chinese SLE patients were different from those reported in Western countries.^[8] Approximately 45.0% of Chinese SLE patients had renal damage, whereas it is only 27.9% in the European SLE patients. Approximately 37.2% of Chinese SLE patients had hematological changes, whereas only

18.2% of the European SLE patients have them. The proportions of patients with pulmonary artery hypertension and interstitial lung disease were 3.8% and 4.2%, respectively, which are much higher than those for the European SLE patients. All these data indicated that the disease was much more severe in Chinese SLE patients than in the European patients.

More Severe Disease in Male Patients

The CSTAR data showed that the disease was more severe in male patients than female patients in China. The disease activity score was higher in male patients than that in females. Kidney involvement, vasculitis presentation, neuropsychiatric lupus, and complications were more prevalent in male patients than in females. The survival rate of male patients was lower than that of females. These data suggested a worse prognosis in male patients than that in females.^[9]

Distinct Disease Presentation in Pediatric Patients

The CSTAR cohort analysis showed that clinical presentations of pediatric patients were distinct from those of adults. Fever, cutaneous and mucosal involvement, and renal damage were the most common initial presentations in pediatric patients. Although the prevalence of joint involvement was lower in pediatric patients than adults, there was no significant difference in disease activity score between pediatric and adult patients. Also, there was no significant difference in the 5-year survival rate between pediatric and adult patients.^[10]

Very Heavy Economic Burden

Under the supervision of CSTAR, a survey was conducted in 34 provinces, autonomous regions, and cities in 2019. In this survey, 1096 valid questionnaires were collected. The survey showed that 28.19% of patients met the expenses caused by the disease through medical insurance for urban employees, 19.89% through new rural cooperative medical insurance, 15.33% through social insurance for urban residents, and 32.85% through their own funds. The expenses ranged between 1000 Yuan and 5000 Yuan (154–770 USD) per month, in which drug cost accounted for 59.49% of the total expenses, ranking the highest, while the cost for laboratory tests and imaging studies made up 19.07%, ranking the second highest. According to the data from CSTAR, 49.45% of patients were unemployed. A monthly income per family ranged between 3001 Yuan and 6000 Yuan (462–924 USD) in 38.69% of patients and 3000 Yuan (462 USD) or less in 25.64%. From all these data, we could see that the disease imposed a heavy economic burden on patients and their families. In the survey, 91.15% of patients thought that the disease brought a heavy burden to them and 13.23% were

of the opinion that they could hardly afford the medical costs of the disease.

Adverse Impacts on Working Capability, and Daily and Social Life

The disease had adversely affected the daily life of patients. Among patients, 42.88% thought that their abilities to carry out intensive physical activity were severely compromised, while only 7.66% thought that their ability to perform intensive physical activity was not restricted by the disease. Among patients, 75.82% believed that their social life was impaired due to their health condition, 52.46% thought that they lost confidence because of the disease, and 27.01% thought that they were discriminated because of their disease. In the survey conducted in 2019, it was recorded that many patients lost a chance to get a job and even lost opportunities to get married or have a baby as a result of the impact of the disease.

In a cross-sectional study of 105 SLE patients conducted in the Hong Kong region,^[11] patients had impaired working capability in the first 2 years after the disease, and the accrual rate of work disability increased to 36% at 5 years after the disease. Even for patients who had their disease in remission for 10 years, 37% of such patients lost their work ability directly or indirectly due to the disease. Another study showed that 65.61% of patients had decreased work efficiency due to the disease. As they had to go to hospitals for follow-up visits and to refill medications, and even required to be hospitalized due to the disease flares, they could not continue their previous jobs. Some patients were dismissed by their employers, and some patients had difficulty in getting new jobs because of the disease.

High Complication Rate

In addition to the heavy economic burden, the complications associated with SLE also brought a heavy disease burden to patients. Among patients, 0.84% developed stroke during the course of the disease, 0.8% experienced fragile fractures, 1.17% had complications such as bone infarctions and femoral head osteonecrosis, and 0.85% had coronary heart disease, according to the CSTAR. Of those with coronary heart disease, 38.33% had myocardial infarctions, 61.67% had angina pectoris, and 0.69% had cancer/carcinoma according to the CSTAR registry data.

Adverse Impact on Fertility

Data from the CSTAR showed that the overall adverse pregnancy outcome was as high as 10.89% in Chinese SLE patients, much higher than 6.6% in the general population at the same period of time. It was further observed that 22.32% of Chinese SLE patients have a premature delivery, while only 5.3% had it in the general population.^[12,13] Among patients,

5.56% had induced labor due to disease deterioration or obstetrical complications. Spontaneous abortion, premature rupture of the membrane, oligohydramnios, and low fetal body weight occurred in 2.02%, 1.52%, 4.04%, and 2.02% of patients, respectively. These data indicated that the fetal loss rate of SLE patients was significantly higher in Chinese SLE patients than that in the general population.

The Current Status of SLE Management in China

The Low Awareness of the Disease among Patients

Several studies on patients' awareness of their disease showed that most patients had very limited knowledge about the disease. In addition, they had very limited access to knowledge about the disease and the medications involved in its treatment. In a study of 100 SLE patients,^[14] 87% of patients obtained knowledge about the disease from their physicians, 20% learned about the disease from books, 14% from media, 14% from other people, and 2% from other sources such as the internet. In this study, only 42% of patients could give correct answers to the disease knowledge, and only 17% could correctly answer how to manage the disease in their daily life.

Another prominent phenomenon in the perception of the disease by patients was that they could not appreciate the severity of their disease correctly. Among patients, 14.5% could not judge the severity of their disease. Only 30% of patients considered their disease in good control even though their disease was in remission and in very stable stage.

The Initial Visit Department is Incorrect

As the clinical manifestations of SLE are protean and heterogeneous, initial symptoms of the disease are non-specific. As a result, many patients could not choose the right department to seek medical care initially. Furthermore, some physicians do not have the needed knowledge to recognize patients with SLE at an early stage, and thus the disease diagnosis and treatment are delayed to some extent. In a multicenter survey in 2008, it was revealed that only 35.3% of patients initially went to a rheumatology department to seek medical care. The delay from symptom onset to diagnosis confirmation of SLE was 5 months on average, and even as long as 1 year in 23.7% of patients.

Serious Lack of Disease Knowledge in Primary Care Health Professionals

Although the diagnosis and treatment knowledge and skills for SLE in China have improved remarkably, as reflected by the comparable long-term survival of both the Chinese and global SLE patients, the diagnosis and treatment levels for SLE provided by the community health care workers and

primary health care workers in China are far from satisfactory. In a survey, 225 community general internists were asked to answer questions about knowledge of the disease and its management.^[15] The correct answer rate was 47.0% for disease knowledge, only 28.3% for the diagnosis, and 58.4% and 49.0%, respectively, for medical treatment and nonpharmacological management.

Low Rate of Utilizing Standardized Treatment

The median dosage of prednisone intake was 25 mg/d in a study of 42 Chinese patients with diffuse proliferative lupus nephritis, and the cumulative dosage of prednisone was 4.23 g at 6 months. In contrast, in a study of 82 American patients with proliferative lupus nephritis, the median dosage of prednisone intake was 12.8 mg/d and the cumulative dosage of prednisone was 2.153 g at 6 months.^[16] From the cross-sectional data of the CSTAR, 84.13% of patients were on oral prednisone, while only 46.20% of SLE patients were on prednisone at any point of the disease course as per the global reports. Based on the CSTAR data, 0.27% of patients took prednisone 15 mg/d or an equivalent dosage of glucocorticoids over 6 months. All these data indicated that more Chinese patients took glucocorticoids with higher dosages and higher cumulative dosages than those reported in the literature. In contrast, 73.21% of Chinese patients were on the background treatment drug, hydroxychloroquine.

High Relapse Rate and Low Remission Rate

According to the CSTAR data, the relapse rate of Chinese SLE patients could be as high as 18.19%, but this might be underestimated. Only 0.76% of patients from the registry could reach definitions of remission in systemic lupus erythematosus (DORIS) “remission off treatment.” The international reported rate of “remission off treatment” has been increased from 2.5% in 1982 to 10.9% in 2019. In a report from the Hong Kong region, the “remission off treatment” was 10.9% in a 5-year follow-up cohort in 2017. The CSTAR data also showed that only 2.47% of Chinese SLE patients were in “clinical remission on therapy,” while this rate increased from 2.1% in 2014 to 22.9% in 2019 according to the international report. The “clinical remission on therapy” rate was 7% in the Hong Kong cohort report in 2017. Over the last 5 years, 21.1–70.0% of patients could remain in persistent remission during 5 years of follow-up according to the global report. But this rate was 32.95% in the cross-sectional data from the CSTAR, and only 7.85% of patients could reach DORIS “low disease activity.” From all these data, we can see that the gap of disease remission rate between China and the global report is approximately 5 years.

Treatment outcome has markedly improved in China in the past 20 years, as reflected by the increase of survival rate

from 50% in the 1950s to 89% in 2020,^[14] and 5-year survival rate could be as high as 94%, similar to the global report^[15]; however, the survival rate has reached the plateau since the 1990s. The survival rate of 20–30 years is as low as 30%. This low rate is closely related to irreversible internal organ damage accrual, cerebral–cardiovascular complications, and malignant carcinomas. Based on this estimate and the average age of 30 years at disease onset in China, approximately 50% of SLE patients could die at the age of 55–60 years. The estimated cross-sectional death rate of Chinese SLE patients was 3.07%.

The Challenges in SLE Management in China

Severe Shortage of Rheumatologists in China

Rheumatology is the youngest specialty of internal medicine in China. Many hospitals, primary hospitals in particular, do not have a rheumatology specialty. Widespread knowledge of rheumatic disease is not prevalent in China. As a result, with regard to rheumatic diseases, many health care providers, especially primary health care professionals, have very limited knowledge on the clinical presentations, diagnosis, medications, assessment of disease activity and treatment efficacy, and disease management and prevention. Additionally, laboratory tests for disease diagnosis and disease management are not widely available. Consequently, these have led to frequent misdiagnosis of SLE, a low rate of early diagnosis, and missing the best window of opportunity for treatment in many cases.

Lack of Efficient Chronic Disease Management System

Over the years, partly due to the health care system, Chinese SLE patients have not been used to a long-term regular follow-up with physicians yet, resulting in a low compliance rate to treatment. The National Nursing Cooperative Group for Chronic Rheumatic Disease Management developed the consensus for chronic rheumatic disease management in 2014, but there have been little evidence-based standards and guidelines for the management of chronic rheumatic diseases; for SLE particularly, there has been no specific model for chronic disease management available in China. Rheumatologists or other physicians have no guidelines or policies to follow, and the habit of monitoring rheumatic patients regularly is largely not inculcated in them.

The Achievements in the Research and Management of SLE in China

Establishment of the CSTAR

In order to do in-depth studies of SLE in China, the Department of Rheumatology at PUMCH pioneered and organized a nationwide study group on SLE, which initially

aimed to complete the “Comprehensive study on the clinical diagnosis and treatment of systemic lupus erythematosus” project granted by “the 11th Five Year Development Plan for Science and Technology Support Program” in 2009. This study group was given the name “Chinese SLE Treatment and Research Group (CSTAR).” The establishment of the CSTAR has opened a new avenue for a deeper study of SLE in China. Under the leadership of the CSTAR, a national registration platform was developed for physicians to register SLE patients and real-world clinical studies, and design/performance programmatic clinical trials. As of December 31, 2019, 25,147 SLE patients with complete core data were registered. CSTAR has become the largest study group for SLE in the world and the only multicenter nationwide collaborative study on SLE in China. The goals of the CSTAR are “to build up the infrastructures for SLE study, to conduct the clinical, translational, and basic research on SLE across the country, and to develop a model for SLE study that can self-persist in China.” Based on the CSTAR network, several prospective, interventional, and observational studies were conducted. These studies explored the clinical characteristics of Chinese SLE patients and have contributed to the treatment regimens that are tailored to suit Chinese SLE patients. Since the establishment of the CSTAR, a series of original articles on SLE were published under the name of the CSTAR and more than 100 papers were published in the SCI journals. Twenty-seven national awards have been granted. The epidemiological and clinical characteristics and prognosis of SLE in China were identified. The CSTAR and CRDC have become an important “big-data” platform for rheumatic disease research in China. The CSTAR and CRDC have played increasingly important roles in the clinical, translational, and basic research and education on SLE, as well as rheumatic disease in general.

“One City, One Department, and One Center” Program and the Formation of Chinese Rheumatology Center Alliance (CRCA)

In order to improve the quality and quantity of Chinese rheumatologists to meet the needs of Chinese SLE patients, under the leadership of the Chinese Rheumatology Association (CRA), along with the Rheumatology and Immunology Physicians Committee of Chinese Medical Doctors Association, a program called “One city, one department, and one center” was established in 2015. The goal was to set up 1 medical center for rheumatic disease or 1 Department of Rheumatology in 1 city. In this program, rheumatic disease centers have been developed at the regional level. These centers are designed to exert their impact on their affiliated regions to facilitate the development of rheumatic disease departments or centers at different geographical levels. This program will speed up the formation of more free-standing rheumatic disease departments across the country. This may partially alleviate the

national shortage of rheumatologists. This program will help spread standardization on SLE diagnosis and management. CRCA was developed in Beijing in November 2017 under the joint leadership of the Department of Rheumatology of PUMCH and CRDC. One of the goals of this organization is to facilitate the standardization of SLE patient health care. As of December 2019, 76 more rheumatology departments were set up with an increase of 6.40% in 2019 when compared with 2018, though this number was still lower than the average increase of 7.5% for other specialties in internal medicine.

Achievements in Research

Over the past 20 years, Chinese rheumatologists and researchers have conducted a number of studies. They have identified certain cells and intestinal flora that may play important roles in the pathogenesis of the disease. They have also discovered new biomarkers and imaging modalities to predict disease activity. Potential new therapeutic targets and technologies have been explored. These achievements have greatly advanced research on SLE in China.

Opportunities for the Management of SLE in China

From the epidemiological data and current status of SLE management, we can see that there are tremendous challenges in the management of SLE in China. SLE remains a major chronic disease that threatens the public health of the country. In order to improve the treatment and prevention of SLE in China, it would be critical to build up a research model that connects the basic science research with clinical studies, and changes the disease management pattern from treatment to chronic disease management. Therefore, future development would be to focus on strengthening the study of the disease pathogenesis, integrating randomized controlled clinical trials with real-world clinical studies, and emphasizing studies of pharmacoeconomics.

Being the birthplace of the Chinese rheumatology where pioneers spearheaded the clinical study of rheumatic disease in China, the Department of Rheumatology of PUMCH was named the “National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID)” in May 2019, the only national clinical research center for rheumatic disease. This center was jointly granted by the Ministry of Science and Technology of the People’s Republic of China, National Health Commissions of the People’s Republic of China, Logistics Support Department of Ministry of National Defense of the People’s Republic of China, and National Medical Products Administration. Under the leadership of the CSTAR and with the support of the CRDC study network, a nationwide research network has been formed recently, a digital data repository and a biobank for rheumatic disease

have been set up, and a platform for practice standardization, education, and multidisciplinary collaboration has been established across the country. Based on these infrastructures, several guidelines have been proposed and released for Chinese patients with rheumatic disease and numerous research achievements have been made.

Rheumatology is the youngest subspecialty in internal medicine in China, receiving less attention than needed from health authorities and the public. This is reflected by the unbalanced development of rheumatology in the country and the serious shortage of rheumatologists. On October 31, 2019, the National Health Commission of the People's Republic of China issued "Guideline for the development and administrative management of rheumatology departments in general hospitals in China" and "The basic requirement for Department of Rheumatology in general hospitals in China." These guidelines and requirements are aimed at strengthening the development and administrative management of rheumatology departments in China and improving the diagnosis and treatment of rheumatic disease in China. These 2 documents have proclaimed rheumatology as a specialty to speed up its progress in China.

Prospect for the Future Development of Chinese Rheumatology

Undoubtedly, we can predict that this pair of documents will become guidelines and will play an important role in the development of rheumatology specialty and personnel training. For effective control and prevention of the disease in China, it is imperative to set up a comprehensive chronic disease management system for SLE in the "tertiary diagnosis and treatment network for rheumatic disease" and CRCA across the country. It is necessary to build up a patient management model that will be suitable for Chinese SLE patients. Additionally, there will be a need to explore the best practice for different areas of China. This will be critical for the successful management of chronic diseases like SLE. NCRC-DID will serve as a platform for basic, translational, and clinical research. It will support the development of the "ecological environment" for collaborative research into SLE and provide the translational platform for research and pharmaceutical product development. Hopefully, NCRC-DID will inspire the entire society to speed up new drug research and development for SLE.

We would predict that the naming and establishment of the NCRC would become the engine and motive force for the rapid development of Chinese rheumatology.

Conflict of Interest

Xinping Tian is the Executive Editor-in-Chief of the journal; Mengtao Li is an Associate Editor-in-Chief; Qian Wang and Jiuliang Zhao are Editorial Board Members; and Xiaofeng Zeng is the Editor-in-Chief. The article was subject to the journal's standard procedures, with peer review handled independently of these members.

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