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Traditional Chinese medicine therapy improves the survival of systemic lupus erythematosus patients

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ABSTRACT

Objective: No previous studies have evaluated the effect of traditional Chinese medicine (TCM) treatment on the survival of patients with systemic lupus erythematosus (SLE). Hence, in this study, we determined whether TCM treatment affects the survival of SLE patients.
Methods: This nationwide population-based retrospective cohort study assessed 23,084 patients newly diagnosed with SLE between 1999 and 2009, using the database of the Taiwan National Health Insurance program.
Results: Among these patients, 9267 (40.15%) used TCM for SLE treatment and exhibited a significantly decreased risk of death [hazard ratio (HR) = 0.73; 95% confidence interval (CI): 0.68–0.78], with multivariate adjustment, compared with those without TCM use. A similar significant protective effect of TCM use was found across various subgroups of comorbidities. TCM use 1 year before diagnosis also reduced the risk of death. Our study findings indicated that Zhi Bo Di Huang Wan (HR = 0.54; 95% CI: 0.32–0.91), Jia Wei Xiao Yao San (HR = 0.35; 95% CI: 0.16–0.73), Liu Wei Di Huang Wan (HR = 0.51; 95% CI: 0.28–0.93), Gan Lu Yin (HR = 0.40; 95% CI: 0.17–0.96), and Yin Qiao San (HR = 0.22; 95% CI: 0.05–0.86) were the most effective TCM agents that improved survival.
Conclusions: This nationwide retrospective cohort study provided information that combined therapy with TCM may improve the survival in SLE patients. This study also suggests that TCM may be used as an integral element of effective therapy for SLE.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that affects multiple organ systems. The clinical manifestations vary widely and exhibit fluctuations in the phases of remission and flares [1]. The prevalence of SLE is estimated to vary from 4.3 to 150 per 100,000 people worldwide, with a higher prevalence in women [2,3].

SLE has several comorbidities, including cardiovascular disease, diabetes mellitus, dyslipidemia, osteoporosis, avascular bone necrosis, infection, and malignancy. Cardiovascular diseases, infections, renal diseases, and disease activity are the major causes of death in SLE [3–5]. The mortality rate of SLE patients is 2–5 fold higher than that of the general population [6,7]. SLE not only increases mortality but also affects quality of life and increases the economic burden [8,9]. The conventional treatments of SLE are nonsteroid anti-inflammatory drugs (NSAIDs), glucocorticoids, antimalarial medications, and immunosuppressive agents [1,10–12]. These drugs may prevent the active exacerbation of SLE but

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may also lead to severe side effects and may increase the risk of severe infections [13–16]. Thus, many SLE patients seek help from complementary and alternative therapies (CATs).

The popularity of CATs for the treatment of SLE has increased worldwide. More than 40% of SLE patients in Western countries are pursuing CATs [17]. As one of the main components of CATs, traditional Chinese medicine (TCM) plays a crucial role in medical practice in Asian countries. In Taiwan, TCM is covered by the National Health Insurance (NHI) program and plays a crucial role in the modern health care system. Randomized controlled trials have provided evidence for the treatment effects of TCM on SLE [18–20]. However, no previous study has evaluated the effects of TCM treatment on the survival of SLE patients. Thus, in this study, we determined whether TCM use affects the survival of SLE patients in Taiwan.

Methods

The National Health Insurance (NHI) program, a national government-run single-payer compulsory insurance plan, was instituted in 1995 and currently covers almost the entire population (99.62%) of Taiwan. The National Health Insurance Administration conducts an expert review of random samples for every 50–100 outpatient and inpatient claims in each hospital and clinic every 3 months, and false reports of diagnoses are severely penalized [21]. Datasets of the National Health Insurance Research Database (NHIRD) for the 1999–2011 period were used, consisting of a registry of beneficiaries, registry for catastrophic illness, and outpatient and inpatient care claims released by the Taiwan National Health Research Institutes. The registry of catastrophic illnesses contains data of beneficiaries suffering from major diseases who have been approved by the National Health Insurance Administration. The incentives for beneficiaries suffering from major diseases to apply for a catastrophic illness certificate are that they are exempted from making copayments. Patients with SLE who were registered in the catastrophic illness database have to attach pathological report of biopsy-proven lupus nephritis or hematological reports, including antinuclear antibodies, anti-double-stranded DNA, anti-Smith, anti-phospholipid antibodies, complements C3, C4, and C50, rheumatoid factor, C-creative protein, or erythrocyte sedimentation rate to ensure diagnosis accuracy. And, these SLE patients have to be diagnosed by rheumatologic physicians who file the application for the patient. The process of reviewing the qualification of a patient for a catastrophic illness enhances the true positives of SLE cases by excluding those patients with the ICD code for SLE (710.0) but actual not meeting American College of Rheumatology criteria. The date of the first diagnosis of SLE was defined as the entry date. For a patient meeting the criteria of registration in the catastrophic illness database, the attending physicians or medical institutions provide assistance in the patient's application. The NHIRD contains the demographic data; dates of outpatient visits; diagnostic codes according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM); and details of prescriptions. Data of detailed diagnoses and treatments provided by TCM physicians are also included. The proportion of enrollees who have withdrawn from the NHI program is considerably low; thus, potential bias caused by loss to follow-up is negligible.

Study population

This nationwide population-based retrospective cohort study assessed patients newly diagnosed with SLE. SLE patients aged $\geq$ 18 years who were diagnosed with the ICD-9-CM code 710.0 from 1999 to 2009 were identified from the catastrophic illness database with the date of first diagnosis as the index date and were then followed-up until December 31, 2011, withdrawal from the NHI program, or death. Their TCM use status was ascertained from outpatient visits within 3 years of the first diagnosis. To ensure patient privacy, data regarding their identities and health care institutions are cryptographically scrambled in the NHIRD. The current study was approved by the Institutional Review Board of the Public Health, Social and Behavioral Science Committee Research Ethics Committee, and China Medical University (CMU-REC-101-012).

Sociodemographic factors, urbanization levels, and comorbidities

Sociodemographic factors included age, sex, amount of insurance premium, residential area, and insured unit. Age was classified into following four age groups: 18–30, 31–45, 46–60, and $\geq$ 61 years. The amount of insurance premium, determined by the patient's salary, was classified into four categories, NT$ < 20,000, NT$20,000–39,999, NT$40,000–59,999, and $\geq$ NT $60,000. The classification of residential areas of the study population was based on the district branches of the National Health Insurance Administration, consisting of Northern Taiwan, Taipei, Central Taiwan, Southern Taiwan, Eastern Taiwan, and Kao-Ping. The insured unit included five categories: government school employees, private enterprise employees, members of the occupational sector, farmers, and fishermen, and low-income household veterans and other region.

The urbanization level of towns or city districts was classified into following seven levels: non-developed or seclusion area (the lowest urbanization), rural area, aging society area, general area, newly developed area, medium-density urban area, and high-density urban area (the highest urbanization). The variables analyzed to determine the clusters of the urbanization level included the ratio of people with a college education or higher, population density (number of people/km^2), ratio of people over 65 years of age, number of physicians per 100,000 residents, and ratio of farmers [22].

Comorbidities were identified using the ICD-9-CM codes in outpatient, inpatient, and catastrophic illness registry files. Data of these coexisting conditions were extracted for a 12-month period before the entry date. Histories of diabetes mellitus (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), cerebral vascular disease (ICD-9-CM codes 430–438), coronary artery disease (ICD-9-CM codes 410–414), disease of kidney (ICD-9-CM codes 580–589), chronic obstructive pulmonary disease (ICD-9-CM codes 490–496), disease of musculoskeletal system (ICD-9-CM codes 710–739), disease of urinary system (ICD-9-CM codes 590–599), disease of nervous system (ICD-9-CM codes 320–359), and cancer (ICD-9-CM codes 140–149, 150–159, 160–165, 170–175, 179–189, 190–200, 202, 203, 210–213, 215–229, 654.1, and 654.10–654.14) were identified as comorbidities before the index date. Patients were classified having comorbidities if they had a diagnosis of above comorbidities for at least three ambulatory claims, or for at least one inpatient claim during that specific year.

Primary outcome

The primary outcome was all-cause mortality during the 11-year follow-up period. The date of death of patients was extracted from the registry for catastrophic illness of the NHIRD. All eligible patients were followed up from the index date to the date of death of the patient, withdrawal from NHI, or until December 31, 2011, whichever occurred first.