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ORIGINAL RESEARCH

Integration of Chinese Herbal Medicine into Routine Care Was Related to Lower Risk of Chronic Kidney Disease in Patients with Rheumatoid Arthritis: A Population-Based Nested Case–Control Study in Taiwan

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Objective: Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used as the first-line agents for the symptomatic relief of rheumatoid arthritis (RA), but it may insidiously provoke the onset of renal diseases, especially chronic kidney disease (CKD). While Chinese herbal medicine (CHM) has become an increasingly popular adjunctive therapy among RA groups, there are currently no available data on the effect of CHM use towards risk of CKD. This study aimed to explore on a population-level whether CHM use decreases sequent CKD risk among them.

Methods: In this nested case–control study retrieved from the nationwide insurance database of Taiwan from 2000 to 2012, we looked at the association between CHM use and the likelihood of developing CKD, with a focus on usage intensity. Cases with CKD claims were defined and matched to one randomly selected control case. Conditional logistic regression was then applied to estimate odds ratio (OR) of CKD from CHM treatment measured before the index date. For each OR, we calculated a 95% confidence interval for CHM use relative to the matched control.

Results: This nested case–control study included 5464 patients with RA, where after matching comprised 2712 cases and 2712 controls. Among them, there were 706 and 1199 cases that ever received CHM treatment, respectively. After the adjustment, CHM use in RA individuals was related to a lower likelihood of CKD, with an adjusted OR of 0.49 (95% CI: 0.44–0.56). Additionally, a dose-dependent, reverse association was found between the cumulative duration of CHM use and risk of CKD.

Conclusion: Integrating CHM into conventional therapy may reduce the likelihood of developing CKD, which could be a reference in instituting novel preventive strategies to improve treatment outcomes and reduce related fatalities for RA subjects.

Keywords: rheumatoid arthritis, chronic kidney disease, Chinese herbal medicine, nested case–control study

Introduction

Rheumatoid arthritis (RA) is a chronic disabling illness characterized by pain and joint inflammation. Recent studies have shown that RA patients also have a high incidence of chronic kidney disease (CKD), which may be attributed to the systemic chronic inflammation, and renal toxicity due to uses of non-steroidal anti-inflammatory drugs (NSAIDs).[1]

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NSAIDs are often recommended as first-line therapy for the symptomatic management of RA to block the production of prostaglandins through the inhibition of two cyclooxygenase enzymes, like COX-1 and COX-2,[2] yet the inhibition of cyclooxygenase enzymes with subsequent reduction in prostaglandin synthesis may lead to reversible kidney ischemia, such as a decline in glomerular hydraulic pressure and acute kidney injury.[3]

In this case, subjects taking higher dose of NSAIDs were found to have a higher risk of CKD than their counterparts. Möller et al investigated the effects of NSAID use on long-term decline of renal function in a cohort of RA subjects, and found that high cumulative NSAID usage substantially induced the rapid CKD progression.[4] Notably, once RA patients developed end-stage renal disease, they may be at higher risk of severe disease and death.[5] Considering the high level of morbidity caused by these conditions, implementing a novel treatment notion may be of importance during early stages of RA than during late disease stages in which irreversible physiological manifestations may have already taken place.

Today, use of Chinese Herbal Medicine (CHM) products has become one of the fastest growing forms of health care proven beneficial in treating a variety of muscle and joint disorders.[6] Similarly, ample evidence suggests that the herbal products can be used to prevent CKD progression and ameliorate the impacts of CKD.[7,8] Using a rodent model, Zhang et al mentioned a major compound purified from Rheum officinale, could provide renal protective properties by reversing Klotho repression via promoter demethylation.[9] Additionally, one recent meta-analysis of 27 studies indicated that the administration of Rheum *officinale* Baill. was beneficial in lowering serum creatinine and blood urine nitrogen,[10] both of these products were commonly used for the RA treatment so far.[11] In this context, there is an urgent need to explore whether adding CHM to conventional RA treatment may be beneficial in preventing or delaying CKD onset.

After a detailed literature review, we discovered that few studies, if any, have been conducted to explore the long-term effect of use of CHM treatment in diminishing the subsequent risk of CKD among RA groups. To take a close look at this question, we conducted a nested case–control study to address this issue on the basis of a random sample from a nationwide claims database.

Methods

Data Source

We performed a nested case–control study using 2000–2012 data from the Longitudinal Health Insurance Database (LHID) held by the Bureau of National Health Insurance (NHI) in Taiwan.[12] At present, more than 95% of Taiwan's healthcare providers have contracted with the NHI and nearly 99% of Taiwan's residents have enrolled in the National Health Insurance Administration Ministry of the Health and Welfare's program. The implementation of the national insurance program has enabled residents to receive universal participation and equal-opportunity medical care.[12] LHID comprises a data subset of the NHI program and incorporates the claims of 1 million beneficiaries, randomly selected from all beneficiaries under the NHI program. This database contains all NHI enrollment files, inpatient and outpatient claims data, primary and secondary diagnoses, procedures, prescription drugs and medical costs that provide comprehensive information on all insured subjects.

Underlying Cohort Establishment

Using the LHID, we identified subjects 20–80 years of age who had more than 2 outpatient, or a single inpatient, visits due to RA diagnosis from January 2000 to December 2010 (The International Classification of Diseases, 9th Revision, Clinical Modification, ICD-9-CM 714.0). Afterwards, all enrolled cases were linked to the catastrophic illness registry to ensure diagnostic validity. Under the NHI program, the beneficiaries with major diseases, such as autoimmune disorders, are exempt from the required cost sharing policy. This approach allowed us to strictly define RA cases and reduce any potential misclassification bias. We then utilized the date of approval for catastrophic illness registration as the starting point for the time at risk with RA. Meanwhile, we are bound to obey the rule that subjects would be excluded if they had any history of CKD prior to RA onset. All enrollees were followed up until the earliest CKD incident (defined in the case ascertainment), death, withdrawal, or the end of this study (December 31, 2012), whichever came first. This research project was approved by the Ethics Committee of the Buddhist Dalin Tzu Chi Hospital (No. B10004021-3) and was

conducted with consideration of the Helsinki Declaration in all phases of the study. Additionally, the institutional review board waived the need for informed consent for this study since an encrypted database was fully used.

Case and Control Ascertainment

The study outcome measure was first-time diagnosis of CKD, which occurred between 2001 and 2012. The documentation of the CKD code was regarded as valid if the enrollee has incurred at least twice in the records of outpatient clinics within 1 year, or at least once during hospitalization (ICD-9-CM code of 585).[8] The date of the first diagnosis of CKD onset was deemed the index date. Of the study cohort, each CKD case was matched, according to age (within 2 years) and sex, using a risk set sampling of 1:1, with a control subject who was not diagnosed with CKD (Figure 1). After matching, the outcome date for each case group was assigned as the index date to the control group, for case and control groups with the same probability to occur of CKD outcome during the follow-up period.

Exposure Assessment of CHM Use

To define CHM exposure of subjects, we examined the individual CHM treatment records occurring from the cohort entry date to the index date. In this study, CHM users were defined as those who ever received the relevant CHM treatment for more than 30 days due to diagnosis of RA or its associated symptoms. In contrast, those who were treated by Western medical physicians were classified as non-CHM users.[13] Following this step, we reviewed the study period for claims of CHM treatments and summed up the total days of CHM sessions. For CHM users, their prescription days were further categorized into low, medium, or high sub-periods, based on the tertile distribution of the length (in days) of

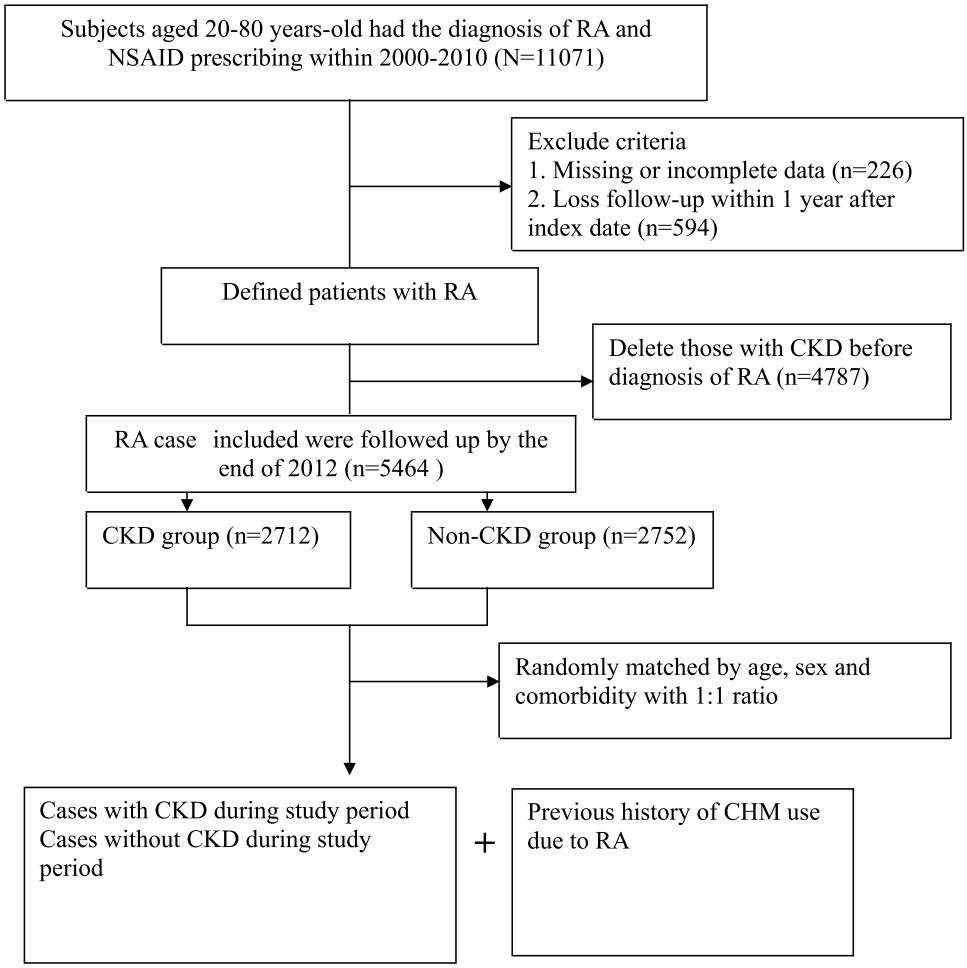

Figure 1 Flowchart of patient screening.

time of receiving CHM treatments due to RA. This procedure allowed us to clearly shed light on the impact of CHM on prevention of CKD among them.

Measurement of Covariates

Of the covariates considered for the study, it comprised gender, age, income for estimating insurance payment, urbanization of the subject's residential area and former comorbidities. Regarding income, we used the premium category as a proxy and it was transformed to ordinal variables, namely New Taiwan Dollars [NTD] ≦17,880, 17,881–40,000, and ≥400,001. Furthermore, we adopted the urbanization system of insured zones, studied by former scholars, and these ranged from level 1 (highly urban) to level 7 (highly rural), as the standard to assess personal urbanization.[14] Baseline comorbidities considered in our analysis included several chronic illnesses, such as cancer (ICD-9-CM 140–208), hypertension (ICD-9-CM 401–405), depression (ICD-9-CM 296.2, 296.3, 300.4 and 311), diabetes (ICD-9-CM 250) and heart disease (ICD-9-CM 410–429).

Statistical Modeling

For baseline characteristics, we reported continuous variables using means (and standard deviation, SD) and categorical variables with frequencies (and percentages). Comparisons between groups were made using Student's *t*-test and Chi-square test. Univariate conditional logistic regression analysis was employed to estimate the crude OR of CKD events among CHM users. We then utilized the multivariate conditional logistic regression to adjust all covariates that were measured in one year preceding the index date, which included age, gender, urbanization level, income and comorbidities. All analyses were done using SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC, USA), and all statistical tests were performed at the two-tails significance level of 0.05.

Results

We identified 11,071 RA subjects who met the selection criteria within the study period. Among those, 2,712 matched pairs of RA patients with and without CKD were recruited. Baseline characteristics are shown in Table 1. The mean age was 50.5 years (SD = 13.1), and the majority were female (68.0%). Also, the majority of patients had a monthly income of NTD 17,881–43,900 (51.6%) and lived in urbanized areas (57.9%). The most common comorbidities in both groups were hypertension (23.0%), followed by heart disease (12.2%) and diabetes (10.1%). Collectively, there were no differences in initial demographic data and comorbidities between two groups.

Of the whole study cohort, nearly 26.0% (706/2712) and 44.2% (1199/2712) cases ever received CHM therapy in the CKD group and non-CKD group, respectively. After using multivariable logistic regression models to identify any association between previous CHM use and CKD risk (Table 2), we observed that those who ever used CHM had a lower risk of CKD than those who did not use CHM (adjusted OR, 0.49; 95% CI = 0.44–0.56). Notably, the high-intensity CHM use was remarkably associated with a nearly 60% lower risk of developing CKD, which suggests a dose-dependent inverse relation between CHM use and risk of developing CKD (adjusted OR, 0.42; 95% CI = 0.36–0.49). Of the commonly prescribed CHM formulas for RA (Table 3), we found that eight prescriptions were associated with a lower risk of CKD, and these included Yan-Hu-Suo, Tian-Hua-Fen, Ge-Gen, Da-Huang, Shao-Yao-Gan-Cao-Tang (SYGCT), Jia-Wei-Xiao-Yao-San (JWXYS), Chuan-Xiong-Cha-Tiao-San (CXCTS), and Gan-Lu-Yin (GLY) (Figure 2).

Discussion

Few studies, if any, have been conducted to explore the long-term effects of CHM on the reduction of CKD risk in RA patients. A total of 5464 patients with RA were included in this nested case–control study. After one-to-one frequency matching, the study found that the incidence of CKD was substantially lower in CHM users, with an adjusted OR of 0.49 (95% CI = 0.44–0.56). In addition, the longer use of CHM treatments, the more positive prevention against incident CKD. We observed that RA patients with a high-intensity CHM use experienced a nearly 60% reduced risk of CKD, which coincided with the earlier reports.[7,15] A variety of natural products from traditional Chinese medicine have been shown to safely regulate proinflammatory pathways and control inflammation-associated diseases.[16] In addition, some of

Table 1 Demographic Data and Selected Comorbidities Between Two Groups

Variables	Total Group	CKD Case	Non-CKD Case	*p*
		N =2712 (%)	N =2712 (%)	
Age (years)				0.07
≤50	2410(44.4)	1172(43.2)	1238(45.6)	
>50	3014(55.6)	1540(56.8)	1474(54.4)	
Mean (SD)	50.5±13.1	50.5±13.1	50.6±11.9	0.89
Sex				0.95
Female	3688(68.0)	1843(68.0)	1845(68.0)	
Male	1736(32.0)	869(32.0)	867(32.0)	
Monthly income				0.71
Low	2347(43.3)	1164(42.9)	1183(43.6)	
Median	2797(51.6)	1402(51.7)	1395(51.4)	
High	280(51.)	146(5.4)	134(4.9)	
Residential area				0.40
Urban	3141(57.9)	1546(57.0)	1595(58.8)	
Suburban	870(16.0)	442(16.3)	428(15.8)	
Rural	1413(26.1)	724(26.7)	689(25.4)	
Comorbidity				
Hypertension	1248(23.0)	619(22.8)	629(23.2)	0.75
Diabetes	550(10.1)	282(10.4)	268(9.9)	0.53
Heart disease	663(12.2)	334(12.3)	329(12.1)	0.84
Depression	160(2.9)	74(2.7)	86(3.2)	0.34
Cancer	69(1.3)	40(1.5)	44(1.6)	0.66

Table 2 The Association Between CKD Onset and Use of CHM Treatment

CHM Exposure	Subjects [n (%)]				Crude OR (95% CI)	Adjusted OR* (95% CI)
	Patients n = 2712		Controls n = 2712			
Non-CHM users	2006	74.0	1513	55.8	1	1
CHM users	706	26.0	1199	44.2	0.44(0.39–0.49)	0.49(0.44–0.56)
Low intensity	209	7.71	255	9.4	0.62(0.51–0.75)	0.68(0.56–0.83)
Medium intensity	180	6.64	297	11.0	0.46(0.38–0.56)	0.51(0.41–0.62)
High intensity	317	11.69	647	24.0	0.37(0.32–0.43)	0.42(0.36–0.49)

Note: *Model adjusted for age, residential area, monthly income, and comorbidity.

the ingredients extracted from medicinal herbs have demonstrated effective anti-inflammatory along with antiarthritic activities,[17,18] which may explain the beneficial effect of CHM found in our work.

Of the commonly used single-herb products to treat RA, we found that Yan-Hu-Suo would reduce the risk of CKD by nearly 40%. This result was similar to that of from another retrospective population-based cohort study among hepatitis patients.[19] Its components are believed to reduce the blood pressure and exert anti-oxidative, anti-fibrotic, and anti-thrombotic effects. Tetrahydropalmatine, one of the active components isolated from Yan-Hu-Suo, was found to possess antihypertensive activity by decreasing hypothalamic serotonin and noradrenaline release in the rodent model.[20,21] Anti-platelet aggregative and anti-oxidative effects have also been detected from Tetrahydro berberine, a major compound purified from this formula,[22–24] all of which may support its therapeutic benefit.

The current study pointed to a lower incidence of CKD among RA patients who received Da-Huang. A human clinical study addressed that Da-Huang supplementation could improve the renal function in the CKD patients with stage 3 or 4.[25] Clinically, though Da-Huang has been traditionally used as laxative, several recent studies noted that Da-Huang possessed various renal protective effects including diuretic, purgative, anti-inflammatory, anti-oxidative and anti-fibrosis

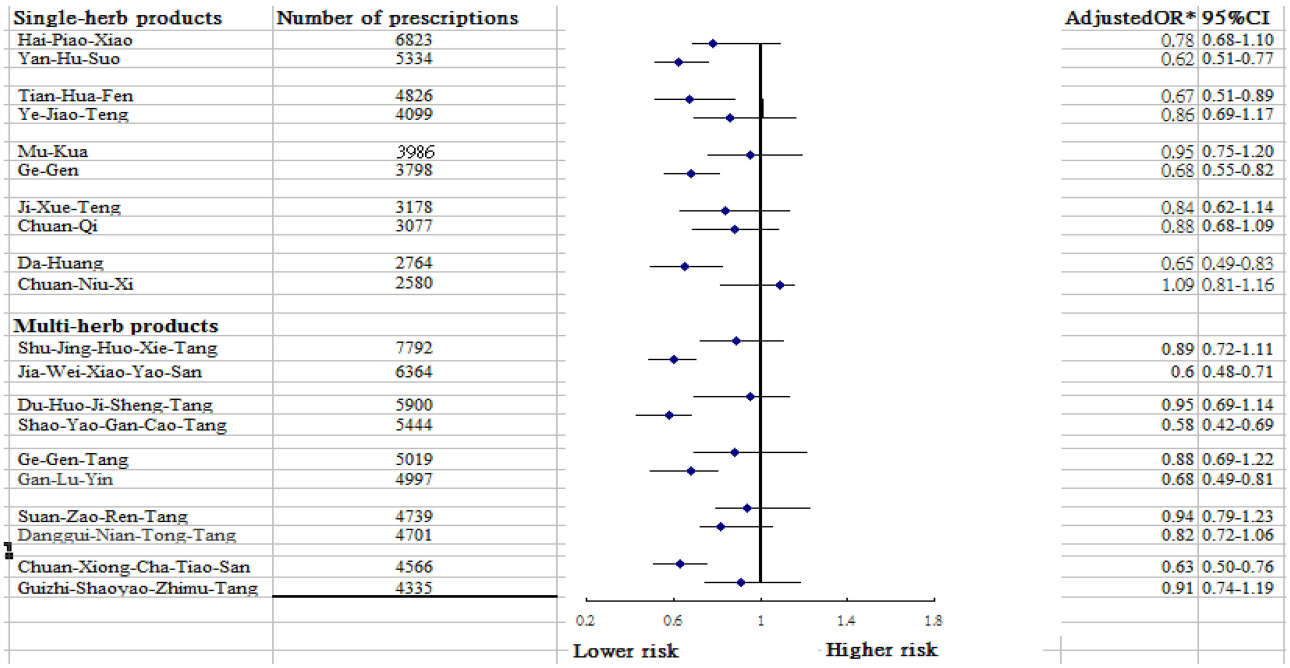

Figure 2 Risk of CKD in relation to the 10 most-used single-herb and multi-herb CHM products for RA patients.

activities.[26,27] In addition, Chrysophanol, purified from Da-Huang, has been indicated to alleviate renal interstitial fibrosis by inhibiting Smad3 phosphorylation and suppressing the progression of diabetic nephropathy via the TGF-β signaling pathway inactivation.[28,29]

Our findings depicted the protective effect of Tian-Hua-Fen and Ge-Gen in preventing the onset of CKD as well. This reaction may have several scientific explanations behind it. For example, the dry root tuber of Tian-Hua-Fen has been shown to possess antioxidant and anti-inflammatory properties both in vitro and in vivo.[30,31] Furthermore, a recent experiment based on the murine model indicated that this herbal formula might significantly enhance serum creatinine, blood urea nitrogen, and 24-h urinary albumin through the inhibition of cell apoptosis.[32] All of these may improve renal tissue function to lower the vulnerability of CKD. Regarding Ge Gen, this herbal product also appears to lower the risk of CKD among RA patients. Several priori studies have found that Ge-Gen produces possessed the antioxidative, antifibrotic and anti-inflammatory effects in reducing kidney damage,[33,34] which may point to the possible mechanism of this herbal medicine.

Of the commonly prescribed multi-herb products, use of SYGCT may reduce the risk of CKD. Several previous animal experiments described that the compounds in SYGCT may produce anti-inflammatory, anti-oxidant and anti-thrombotic effects in the kidney.[35–37] Furthermore, the antihypertensive activity of *Radix Paeoniae Alba*, a major component of this formula, had been proved to improve vascular health and reduce endothelial dysfunction in a rat model.[38,39] Those with endothelial dysfunction were more likely to progress to renal failure to suffer cardiovascular malfunctioning.

Compatible with recent scientific findings, use of JWXYS could improve both short-term and long-term renal outcomes.[7,40] One experiment based on the animal model disclosed that the herb JWXYS attenuated kidney fibrosis via inhibition of the Hedgehog pathway.[41] Additionally, other frequently used CHM therapies targeting RA, such as GLY and CXCTS, were remarkably associated with the predisposition of CKD. Both human and animal studies postulated that these remedies could decrease the levels of IL-6 and TNF-α via the suppression of nuclear factor kappa beta (NF-κB) activation.[42–44] As a whole, we inferred that the anti-inflammatory effects derived from these polyherbal formulations may account for its beneficial impact in reducing incident CKD.

Despite its promising findings, several important limitations may restrict the generalizability of our study's findings. First, several sources of data regarding family history, lifestyle, body weight, exercise regimen, and laboratory parameters were not recorded in the database. Thus, residual confounding might occur in the observed association of CHM use to the CKD risk.

Table 3 The Ingredient Herbs Contained in the Most-Used Single-Herb and Multi-Herb Products Among Participants

CHM Name	Ingredients or Generic Name	Functional Classification
Single-herb products		
Hai-Piao-Xiao	Sepiella maindroni de Rochebrune	Anti- stomach acid and relief of epigastric pain
Ye-Jiao-Teng	Polygonum multiflorum Thunb.	Nourishes the heart and calms the mind
Yan-Hu-Suo	Corydalis yanhusuo (Y.H.Chou & Chun C.Hsu)W.T.Wang ex Z.Y.Su & C.Y.Wu	Release pain Anti-oxidative, anti-fibrotic, and anti-thrombotic effects.
Mu-Gua	Papaya aurantiaca (Regel) Kuntze	Soothes the muscles
Tian-Hua-Fen	Trichosanthes kirilowii Maxim.	Clearing stomach heat and quenching thirst Antioxidant and anti-inflammatory properties
Chuan-Qi	Anredera cordifolia (Ten.) Steenis	Stopping bleeding, activating blood circulation to stop bleeding pain
Ge-Gen	Pueraria lobata (Willd.) Ohwi	Releases the neck and upper back muscles Discharges measles Antioxidative, antifibrotic and anti-inflammatory effects
Ji-Xue-Teng	Millettia aboensis (Hook.f.) Baker	Tonifying the blood, invigorating the blood, relaxing the muscles and activating the joints
Chuan-Niu-Xi	Cyathula officinalis K.C.Kuan	Strengthens muscles and bones
Da-Huang	Rheum palmatum L.	Laxative for bowel movement Clearing heat Renoprotection
Multi-herb products		
Shu-Jing-Huo-Xue-Tang	Bai-Shao (Radix Paeoniae Alba; Paeonia lactiflora Pall.), Dang-Gui (Radix Angelicae Sinensis; Angelica sinensis (Oliv.) Diels), Chuan-Xiong (Rhizoma Chuanxiong; Ligusticum striatum DC.), Di-Huang (Radix Rehmanniae; Rehmannia glutinosa (Gaertn.) DC.), Tao-Ren (Semen Persicae; Prunus persica (L.) Batsch), Cang-Zhu (Rhizoma Atractylodis; Atractylodes lancea (Thunb.) DC.), Fu-Ling (Poria; Wolfiporia cocos (Schw.) Ryv. and Cilbn.), Niu-Xi (Radix Cyathulae; Cyathula officinalis K.C. Kuan), Wei-Ling-Xian (Radix Clematidis; Clematis chinensis Osbeck), Han-Fang-Ji (Radix Stephaniae Tetrandrae; Stephania tetrandra S.Moore), Qiang Huo (Rhizoma et Radix Notopterygii; Notopterygium incisum K.C.Ting ex H.T.Chang), Fang-Feng (Radix Saposhnikoviae; Saposhnikovia divaricata (Turez.) Schischk.), Long-Dan-Cao (Radix Gentianae; Gentiana scabra Bunge), Bai-Zhi (Radix Angelicae Dahuricae; Angelica dahurica (Hoffm.) Benth. and Hook.f. ex Franch. and Sav.), Chen-Pi (Pericarpium Citri Reticulatae; Citrus reticulata Blanco), Gan-Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.), Sheng-Jiang (Rhizoma Zingiberis Recens; Zingiber officinale Roscoe)	Muscle relaxation, activating blood circulation and relieving swelling and pain
Du-Huo-Ji-Sheng-Tang	Du-Huo (Radix Angelica Pubescentis; Angelica pubescens Maxim.), Xi–Xin (Herba cum Radix Asari; Asarum sieboldii Miq.), Fang-Feng (Radix Saposhnikoviae; Saposhnikovia divaricata (Turcz.) Schischk.), Qin-Jiao (Radix Gentianae Macrophyllae; Gentiana macrophylla Pall.), Sang-Ji-Sheng (Herba Taxilli; Taxillus chinensis (DC.) Danser), Du-Zhong (Cortex Eucommiae; Eucommia ulmoides Oliv.), Niu-Xi (Radix Cyathulae; Cyathula officinalis K.C. Kuan), Rou-Gui (Cortex Cinnamomi; Cinnamomum cassia (L.) J.Presl), Dang-Gui (Radix Angelicae Sinensis; Angelica sinensis (Oliv.) Diels), Chuan-Xiong (Rhizoma Chuanxiong; Ligusticum striatum DC.), Di-Huang (Radix Rehmanniae; Rehmannia glutinosa (Gaertn.) DC.), Bai-Shao (Radix Paeoniae Alba; Paeonia lactiflora Pall.), Ren-Shen (Radix Ginseng; Panax ginseng C.A. Mey.), Fu-Ling (Poria; Wolfiporia cocos (Schw.) Ryv. and Cilbn.), Gan-Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.)	Dispelling wind-dampness and relieving paralysis and pain
Shao-Yao-Gan-Cao-Tang	Bai-Shao (Radix Paeoniae Alba; Paeonia lactiflora Pall.), Gan-Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.)	Muscle relaxation Anti-inflammatory, anti-oxidant and anti-thrombotic effects

(*Continued*)

Table 3 (Continued).

CHM Name	Ingredients or Generic Name	Functional Classification
Jia-Wei-Xiao-Yao-San	Dang-Gui (Radix Angelicae Sinensis; Angelica sinensis (Oliv.) Diels), Bai-Shao (Radix Paeoniae Alba; Paeonia lactiflora Pall.), Fu-Ling (Poria; Wolfiporia cocos (Schw.) Ryv. and Cilbn.), Bai-Zhu (Rhizoma Atractylodis Macrocephalae; Atractylodes macrocephala Koidz.), Chai-Hu (Radix Bupleuri; Bupleurum chinense DC.), Mu-Dan-Pi (Cortex Moutan; Paeonia × suffruticosa Andrews), Zhi-Zi (Fructus Gardeniae; Gardenia jasminoides J.Ellis), Gan-Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.), Bo-He (Herba Menthae Haplocalycis; Mentha alaica Boriss.), Sheng-Jiang (Rhizoma Zingiberis Recens; Zingiber officinale Roscoe)	Treat for anxiety and release stress Attenuated kidney fibrosis
Dang-Gui-Nian-Tong-Tang	Qiang-Huo (Rhizoma et Radix Notopterygii; Notopterygium incisum K.C.Ting ex H.T. Chang), Fang-Feng (Radix Saposhnikoviae; Saposhnikovia divaricata (Turcz.) Schischk.), Sheng-Ma (Rhizoma Cimicifugae; Cimicifuga foetida L.), GeGen (Radix Puerariae; Pueraria lobata (Willd.) Ohwi), Bai-Zhu (Rhizoma Atractylodis Macrocephalae; Atractylodes macrocephala Koidz.), Dang-Gui (Radix Angelicae Sinensis; Angelica sinensis (Oliv.) Diels), Cang-Zhu (Rhizoma Atractylodis; Atractylodes lancea (Thunb.) DC.), Gan-Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.), Ku-Shen (Radix Sophorae Flavescentis; Sophora flavescens Aiton), Huang-Qin (Radix Scutellariae; Scutellaria baicalensis Georgi), Zhi-Mu (Rhizoma Anemarrhenae; Anemarrhena asphodeloides Bunge), Yin-Chen-Hao (Herba Artemisiae Scopariae; Artemisia capillaris Thunb.), Zhu-Ling (Polyporus; Polyporus umbellatus (Pers) Fries), Ze-Xie (Rhizoma Alismatis; Alisma orientale (Sam.) Juz.)	Removing wind and dampness, clearing heat and relieving pain
Chuan-Xiong-Cha-Diao-San	Chuan-Xiong Bai-Zhi (Radix Angelicae Dahuricae; Angelica dahurica (Hoffm.) Benth. and Hook.f. ex Franch. and Sav.) Gan Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.) Qiang-Huo (Rhizoma et Radix Notopterygii; Notopterygium incisum K.C.Ting ex H.T. Chang) Jing-Jie (Schizonepeta annua (Pall.) Schischk.) Xi–Xin (Herba cum Radix Asari; Asarum sieboldii Miq.) Fang-Feng (Radix Saposhnikoviae; Saposhnikovia divaricata (Turcz.) Schischk.) Bo-He (Herba Menthae Haplocalycis; Mentha alaica Boriss.)	Dispersal of wind disorders
Ge-Gen-Tang	Ge-Gen (Radix Puerariae; Pueraria lobata (Willd.) Ohwi), Ma-Huang (Herba Ephedrae; Ephedra sinica Stapf), Gui-Zhi (Ramulus Cinnamomi; Cinnamomum cassia (L.) J.Presl), Bai-Shao (Radix Paeoniae Alba; Paeonia lactiflora Pall.), ShengJiang (Rhizoma Zingiberis Recens; Zingiber officinale Roscoe), Da-Zao (Fructus Jujubae; Ziziphus jujuba Mill.), Gan Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.)	Sweating Relieving external influences Releases the neck and upper back muscles
Gui-Zhi-Shao-Yao-ZhiMu-Tang	Gui-Zhi (Ramulus Cinnamomi; Cinnamomum cassia (L.) J.Presl), Ma-Huang (Herba Ephedrae; Ephedra sinica Stapf), FuZi (Radix Aconiti Lateralis; Aconitum carmichaeli var. carmichaeli), Zhi-Mu (Rhizoma Anemarrhenae; Anemarrhena asphodeloides Bunge), Bai-Shao (Radix Paeoniae Alba; Paeonia lactiflora Pall.), Bai-Zhu (Rhizoma Atractylodis Macrocephalae; Atractylodes macrocephala Koidz.), Fang-Feng (Radix Saposhnikoviae; Saposhnikovia divaricata (Turcz.) Schischk.), Sheng-Jiang (Rhizoma Zingiberis Recens; Zingiber officinale Roscoe), Gan-Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.)	Dispelling wind and dampness, warming the meridians and dispersing cold
Suan-Zao-Ren-Tang	Suan-Zao-Ren (Semen Zizyphi Spinosae; Ziziphus jujuba var. spinosa (Bunge) Hu ex H.F. Chow), Fu-Ling (Poria; Wolfiporia cocos (Schw.) Ryv. and Cilbn.), Zhi-Mu (Rhizoma Anemarrhenae; Anemarrhena asphodeloides Bunge), ChuanXiong (Rhizoma Chuanxiong; Ligusticum striatum DC.), Gan-Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.)	Calms the mind and eliminates irritability
Gan-Lu-Ying	Di-Huang (Radix Rehmanniae; Rehmannia glutinosa (Gaertn.) DC.), Shi-Hu (Herba Dendrobii; Dendrobium loddigesii Rolfe), Tian-Men-Dong (Radix Asparagi; Asparagus cochinchinensis (Lour.) Merr.), Mai-Men-Dong (Radix Ophiopogonis; Ophiopogon japonicus (Thunb.) Ker Gawl.), Huang-Qin (Radix Scutellariae; Scutellaria baicalensis Georgi), Yin-Chen-Hao (Herba Artemisiae Scopariae; Artemisia capillaris Thunb.), Zhi-Ke (Fructus Aurantii; Citrus × aurantium L.), Pi-Pa-Ye (Folium Eriobotryae; Eriobotrya japonica (Thunb.) Lindl.), Gan-Cao (Radix Glycyrrhizae; Glycyrrhiza uralensis Fisch.)	Nourishing yin and clearing heat Anti-inflammatory effects

A randomized controlled trial to validate these findings is warranted. Second, this work was merely based on a retrospective cohort design that used ICD-9-CM diagnostic codes. Bias due to miscoding and misclassification may arise. To deal with this concern, we capitalized on procedural claims data to confirm ambulatory diagnostic codes, as well as use of inpatient claims data to minimize the possibility of misclassification. It should also be acknowledged that the NHI of Taiwan makes an effort to prevent false diagnoses by performing quarterly expert reviews of submitted diagnoses and imposes severe penalties for false diagnosis. On this note, the probability of individuals being misclassified is equal across groups in this investigation, so any misclassification was prone to be random, likely providing more conservative estimates. Third, data regarding RA severity are unavailable in the database, so we utilized the prescription of biological agents to be another proxy indicator to confirm RA severity, which contained adalimumab, etanercept, infliximab, rituximab and tocilizumab. Firstly, we separated all enrollees based on whether they received biological agents for more, or less, than 6 months after RA onset. Biological agents were used by 38.2% of the CHM users (1036/2712) and 40.1% (1088/2712) of the non-CHM users. After adjusting for this surrogate variable in the multivariate analysis, RA patients who used CHM still had a lower risk for CKD (adjusted OR, 0.50; 95% CI = 0.42–0.59), implying that the severity of RA may not affect the reported results herein. Despite our careful efforts to control for confounding factors in this study, we consent that the evidence from any observational cohort study is generally less robust than that from randomized trials due to the potential biases that may arise from unmeasured or unknown confounders. This study, however, offers several strengths that should be mentioned. First, we performed this investigation using a large population database. Over 90% of the Taiwanese population and their healthcare providers are covered under the NHI program, which includes a representative RA sample and leaves little room for non-response or loss to follow-up. Second, over 10-year follow-up period utilized allowed for ample opportunity to document the primary outcome. Last, the nested case–control approach used is a rival alternative to cohort analysis when studying time-dependent exposure, like the use of CHM treatments. Hence, our study could reflect real-world data that would be found in a clinical situation, as opposed to a randomized controlled trial.

In conclusion, findings of this study revealed that RA patients receiving CHM, in addition to conventional treatment, experienced a lower risk of developing CKD by 51%. As a consequence, more attention should be paid to preventing and managing symptoms of RA, especially the prevention of CKD. Future prospective randomized trials are, therefore, warranted to provide more robust evidence to support and guide the use of CHM in clinical practice targeting those diagnosed with rheumatic diseases.

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Author Contributions

All authors made a significant contribution to the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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