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ORIGINAL RESEARCH

Association of Chinese Herbal Medicines Use with Development of Chronic Obstructive Pulmonary Disease Among Patients with Rheumatoid Arthritis: A Population-Based Cohort Study

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Purpose: Rheumatoid arthritis (RA) patients appear to report a higher risk of chronic obstructive pulmonary disease (COPD). While Chinese herbal medicine (CHMs) is proven to lower COPD risk, the scientific evidence regarding its effect in relation to COPD onset among them is limited. This longitudinal cohort study aimed to determine the relationship between CHMs use and the COPD risk in RA patients.

Methods: Using the nationwide claim data, 8349 patients newly diagnosed with RA and simultaneously free of COPD between 1998 and 2010 were eligible for enrollment. From this sample, we enrolled 3360 CHMs users and 3360 non-CHMs users, randomly selected using propensity scores matching from the remaining cases. They were followed until the end of 2012 to record COPD incidence. The hazard ratio (HR) of COPD with regard to CHMs use was estimated by the Cox proportional hazards regression model.

Results: In the follow-up period, 136 CHMs users and 202 non-CHMs users developed COPD, representing incidence rates of 5.16 and 7.66, respectively, per 1000 person-years. CHMs use was associated with a 32% lower subsequent risk of COPD (adjusted HR: 0.68, 95% Confidence Interval: 0.54–0.84). Eight commonly prescribed CHMs were discovered to be associated with lower COPD risk: Yan Hu Suo, Sāng Zhī, Dang Shen, Huang Qin, Jia-Wei -Xiao-Yao-San, Shu-Jing-Huo-Xue-Tang, Du-Huo-Ji-Sheng-Tang and Ge-Gen-Tang.

Conclusion: A significant association of CHMs use with a lower risk of COPD onset in RA patients was found, suggesting that CHMs could be integrated into conventional therapy to reduce COPD risk.

Keywords: rheumatoid arthritis, Chinese herbal medicines, chronic obstructive pulmonary disease, cohort study

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder affecting about 1% of the population worldwide, with many patients ultimately developing progressive functional limitations and physical disabilities.[1] Notably, it usually occurs in middle-age adults, and more than one-third of affected individuals exhibit arthritis-attributable work limitations, thus posing a significant burden for patients, families, and social care systems.[2] In the United States, a recent investigation revealed that the healthcare cost of RA was approximately US$20,919 per affected person per year, approximately three times higher than for non-RA patients.[3] A review of the financial

burden of RA in the US reported that the total annual costs for RA was US$19.3 billion, and when adding the intangible costs, this amount exceeds US$39 billion.[4]

RA not only results in enormous economic losses but also presents a significant problem for public health. Due to the systemic inflammation inside the body, individuals with RA have a higher risk of pulmonary disease, especially chronic obstructive pulmonary disease (COPD). A recent British study following 24,625 patients with RA, for over 10 years, found that those with RA had a 47% higher risk of COPD than a non-RA patient group.[5] Another meta-analysis of four studies showed that RA patients indeed had a greater risk of COPD than did non-RA patients, with a pooled risk of 1.99 (95% Confidence Interval [CI]: 1.61–2.45).[6] Furthermore, a study revealed that patients with RA, suffering from concomitant COPD, had double the likelihood of mortality of those with RA only.[7] Accordingly, RA patients were found to have 6–7 years' lower life expectancy as compared with the general population.[8] These data, therefore, imply that it is of utmost urgency to prevent or treat COPD when managing RA subjects.

Recently, Chinese herbal medicines (CHMs) have been widely used in clinical practice to treat patients with chronic diseases. The estimated prevalence of CHMs usage varies across populations, ranging from 16% to 90%.[9–12] CHMs facilitate improved clinical outcomes and promote improved quality of life in individuals with chronic illnesses. A 10-year cohort study of 729 patients with advanced breast cancer showed that those receiving CHMs had a 45% reduced risk of all-cause mortality than those who did not receive CHMs.[13] A randomized controlled trial of 352 individuals with COPD compared the effectiveness of combining conventional Western medicine with herbal products for 1 year. The results suggested that the integration of CHMs and Western medicine significantly improved pulmonary function, quality of life and psychological health (mood and depression) in this population.[14]

Although CHMs have attracted attention for some time, to the best of our knowledge, no study has been done to verify its long-term effect among RA patients, let alone the prevention of COPD in this group. From a standpoint of disease management for RA, the identification of the association of CHMs with lower COPD risk may help improve clinical outcomes and extend the life expectancy of RA patients. We, therefore, analyzed a nationwide population-based database to assess COPD risk among RA patients who had either received or not received CHMs.

Methods

Data Source

For this study, we used a publicly released cohort dataset, the Longitudinal Health Insurance Database (LHID), comprised of approximately 1,000,000 randomly sampled people, and collected all records from 1996 to 2012. The database has been confirmed by the National Health Research Institute to be representative of the Taiwanese population and its data have been used in many published scientific papers.[15] The encrypted information protects patient privacy and allows linkage of all claims for the same patient within the database. This database contains all National Health Insurance (NHI) enrolment files, claims data and the registry for prescription drugs, to provide comprehensive utilization information on those individuals covered by the insurance program. This study was conducted in accordance with the Helsinki Declaration, and was evaluated and approved by the local Institutional Review Board and ethics committee of Buddhist Dalin Tzu Chi Hospital, Taiwan (No. B10004021-3).

Study Subjects

Diagnoses in the insurance claims data were coded using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). We identified the patients who were aged 20 years or older and who sought ambulatory health care services between 1998 and 2010 for RA (ICD-9-CM code 714.0). To reduce the potential for disease misclassification, only those with catastrophic illness certification due to RA were recruited. In Taiwan, insured persons with major diseases, such as schizophrenia, mood disorders, immune disease and cancer, can apply for a catastrophic illness certificate that grants exemption from co-payment. The date when each RA patient gained approval for catastrophic illness registration was considered as the index date. To confirm that all patients with RA were indeed incident cases, only new-onset RA cases were included (n=8725). Therefore, the 312 patients diagnosed with COPD before the date of the first RA diagnosis were excluded from the study. Patients were considered to have a history of COPD if they had at least three outpatient visits or at least one inpatient claim for COPD (ICD-9-CM codes 491, 492 and 496), dating from 1996, when the computerized claims data from the LHID became available, until the date of the cohort study. Also excluded were those with missing data and those who were not followed for at least

1 year after RA onset (n=64). Overall, we identified 8349 new-onset RA subjects (Figure 1).

Thereafter, we applied the frequency of visits to Chinese medicine physicians to confirm the CHMs exposure of each RA patient. Those who used CHMs for more than 30 days after RA onset were considered CHMs users; enrollees treated for 30 days or less were considered non-CHMs users.[16] Using this procedure, 3360 cases were designated as CHMs users. A comparison cohort was randomly selected from the remaining insured RA cases without CHMs use. For each RA patient receiving CHMs treatment, one control patient not receiving CHMs treatment was selected by 1:1 matching based on a propensity score. Propensity scores representing the likelihood of receiving CHMs were calculated using logistic regression analysis, conditional on the baseline covariates listed in Table 1. Person-years (PYs) of the non-CHMs users were determined by calculating the time from the index date to the earliest of one of the following: the diagnosis of COPD, the date of withdrawal from the insurance program or the date of December 31, 2012. The PYs of CHMs users was calculated from the initiation of CHMs in combination corrected by immortal time bias.

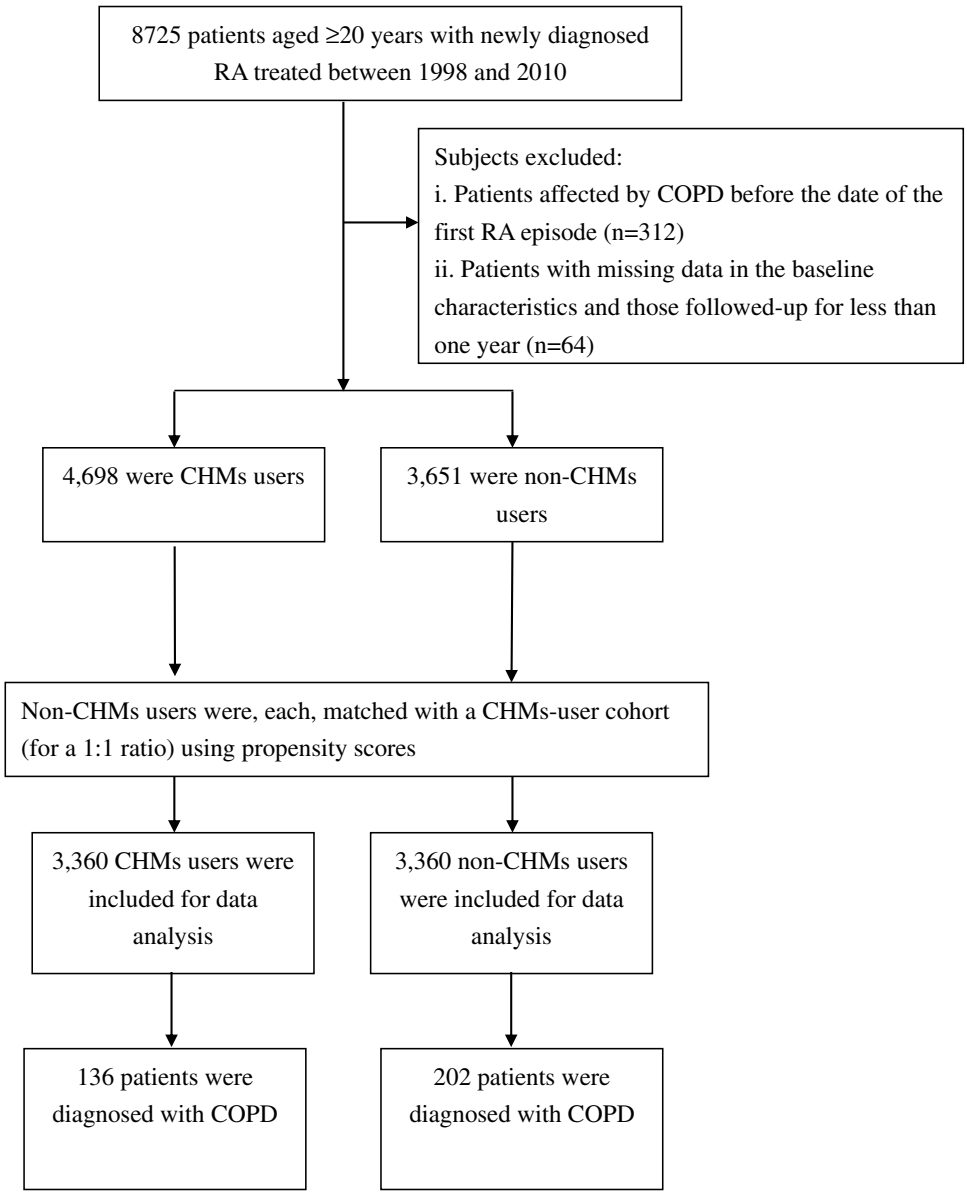

Figure 1 Flowchart showing the method of selecting and following study subjects.

Table 1 Characteristics of the Study Subjects

Variables	Total Group	Non-CHMs Users	CHMs Users	*P*
		N =3360 (%)	N =3360 (%)	
Age (years)				0.75
≤50	2743(40.8)	1378(41.0)	1365(40.6)	
>50	3977(59.2)	1982(59.0)	1995(59.4)	
Mean (SD)	53.8±14.0	53.80±14.3	53.72±13.5	0.81
Sex				0.53
Female	4945(73.6)	2461(73.2)	2484(73.9)	
Male	1775(26.4)	899(26.8)	876(26.1)	
Monthly income				0.44
Low	2972(44.2)	1504(44.8)	1468(43.7)	
Median	3485(51.9)	1733(51.6)	1752(52.1)	
High	263(3.9)	123(3.7)	140(4.2)	
Residential area				0.84
Urban	3842(57.2)	1933(57.5)	1909(56.8)	
Suburban	1043(15.5)	518(15.4)	525(15.6)	
Rural	1835(27.3)	909(27.1)	926(27.6)	
Medication use				0.50
Yes	5008(74.5)	2492(74.2)	2516(74.9)	
No	1712(25.5)	868(25.8)	844(25.1)	
Comorbidity				
Hypertension	1816(27.0)	902(26.8)	914(27.2)	0.74
Diabetes	850(12.6)	411(12.2)	439(13.1)	0.30
Heart disease	1038(15.4)	499(14.9)	539(16.0)	0.18
Chronic kidney disease	87(1.3)	49(1.5)	38(1.1)	0.24
Cancer	206(3.1)	102(3.0)	104(3.1)	0.89
Alcohol dependence syndrome	14(0.2)	7(0.2)	7(0.2)	0.99
Tobacco use	7(0.1)	5(0.1)	2(0.1)	0.26
Follow-up time (years) (mean, median)	7.84(7.57)	7.85(7.56)	7.84(7.59)	

Covariate Assessment

Sociodemographic factors considered in this study included age, sex, income for estimating insurance payment, and urbanization level of the subject's residential area. Monthly incomes were stratified into three levels: ≤ New Taiwan Dollar (NTD) $17,880, NTD$17,881–43,900 and ≥ NTD$ 43,901. Urbanization levels were divided into three strata: urban (levels 1–2), suburban (levels 3–4) and rural (levels 5–7) areas. Level 1 refers to the "most urbanized" and level 7 refers to the "least urbanized" communities.[17] Baseline comorbidities included hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), heart disease (ICD-9-CM codes 410–429), chronic kidney disease (ICD-9-CM code 585), cancer (ICD-9-CM codes 140–208), alcohol dependence syndrome (ICD-9-CM code 303) and tobacco use (ICD-9-CM code 305.1); all these data were based on individual medical records 1 year prior to initial entry into the cohort. In addition, medication usage was stratified into whether or not the patient received corticosteroids or disease-modifying antirheumatic drugs for more than 6 months after the index date.

Statistical Analysis

We performed χ^2 test and *t*-test to examine the differences in demographic characteristics and comorbidities between RA patients with and without CHMs treatment. Then, the incidence rate of COPD between the two groups was calculated as the number of cases per 1000 PYs. Cox proportional hazards regression analysis was then applied to compute the HR with 95% CI of COPD risk in association with CHMs use. To further test the robustness of the relationship between CHMs use and COPD risk, we divided the CHMs

users into three subgroups: those who used CHMs for 31–365 days, those who used CHMs for 366–730 days and those who used CHMs for more than 730 days. We also used the Kaplan–Meier method to estimate the cumulative risk of COPD between groups and tested the difference with the log-rank test. Furthermore, a stratified analysis by age and sex using Cox proportional hazards regression was conducted to assess the HR of COPD among the subjects who did and did not receive CHMs. Log(-log[survival]) versus log of survival time plot was inspected to verify the proportional hazards assumption. All analyses were conducted using SAS version 9.3 software (SAS Institute Inc, Cary, NC, USA). Differences of $P < 0.05$ were considered statistically significant.

Results

The CHMs user and non-CHMs user cohorts provided data for 3360 subjects each, with a mean duration of 7.85 and 7.84 years, respectively. After the matching procedure with propensity score, there was no significant difference between the two groups in age, sex, monthly income, residential area and comorbidities, indicating that the two groups were comparable in terms of these characteristics (Table 1).

Among all eligible RA subjects, 338 first episodes of COPD occurred, 202 in non-CHMs users and 136 in CHMs users, during follow-up periods of 26,380.64 and 26,352.11 PYs, respectively. The incidence rate of COPD was significantly lower in CHMs users than in non-CHMs users (5.16 vs 7.66, respectively, per 1000 PYs), with an adjusted HR of 0.68 (95% CI: 0.54–0.84) (Table 2). Of note, those who used CHMs for more than 730 days had reduced the risk of COPD by 72%. Results of the Kaplan-Meier survival curve and log-rank tests also supported a statistically significant difference in the survival rate free from COPD across the three groups of users during the follow-up period. Those receiving CHMs for more than 730 days had a significantly lower incidence rate of COPD than those not receiving CHMs ($P < 0.001$) (Figure 2).

Table 3 presents the results from the analysis stratified by age and sex. Collectively, a more significant beneficial effect of CHMs was observed among older subjects. Furthermore, multivariable stratified analysis verified that the benefit of CHMs therapy in reducing the incidence of COPD was more predominant in females, with an adjusted HR of 0.57 (95% CI: 0.42–0.77) (Table 3). The 10 most commonly prescribed herbal formulae for those with RA are summarized in Table 4. Among them, the prescriptions of Yan Hu Suo, Sāng Zhī, Dang Shen, Huang Qin, Jia-Wei-Xiao-Yao-San, Shu-Jing-Huo-Xue-Tang, Du-Huo-Ji-Sheng-Tang and Ge-Gen-Tang were associated with a decreased risk of COPD (Table 4).

Discussion

This is the first evidence-based cohort study addressing the association between CHMs use and COPD risk in patients with RA using a large nationwide claims-based data source. In this follow-up study of 15 years (1998–2012), we found that patients with RA who were receiving CHMs had a 32% lower likelihood of COPD than those not using CHMs. Furthermore, those receiving CHMs for more than 2 years were found to have a nearly 72% lower risk of having COPD. The dose–response relationship may elucidate the causal relationships between CHMs use and the decrease in the predisposition to develop COPD. No previous studies have been conducted to determine the long-tern impact of CHMs use on COPD risk among RA patients, thus rendering a comparison of results impossible. But the positive therapeutic effect of CHMs observed in this study is consistent with earlier reports and adds to the growing body of literature on this topic.[12,18]

Additionally, findings from our study indicated that older patients benefited the most, by receiving CHMs treatment, from lowering the risk of COPD, echoing the findings of an earlier report.[19] Previous research indicated that younger adults are more likely than older adults to gain prompt access to social resources and maintain close

Table 2 Risk of COPD for RA Patients with and Without CHMs Use

Patient Group	N	Events	PYs	Incidence	Crude HR (95% CI)	Adjusted HR* (95% CI)
Non-CHMs users	3360	202	26,380.64	7.66	1.00	1
CHMs users	3360	136	26,352.11	5.16	0.67 (0.54–0.83)	0.68 (0.54–0.84)
CHMs use for 31–365 days	2749	122	20,773.28	5.87	0.77 (0.60–0.94)	0.77 (0.60–0.93)
CHMs use for 366–730 days	346	9	2966.02	3.03	0.40 (0.20–0.77)	0.44 (0.23–0.80)
CHMs use for more than 730 days	265	5	2612.81	1.91	0.25 (0.11–0.63)	0.28 (0.11–0.67)

Notes: *Model adjusted for sex, age, urbanization level, monthly income, medication use and comorbidities.

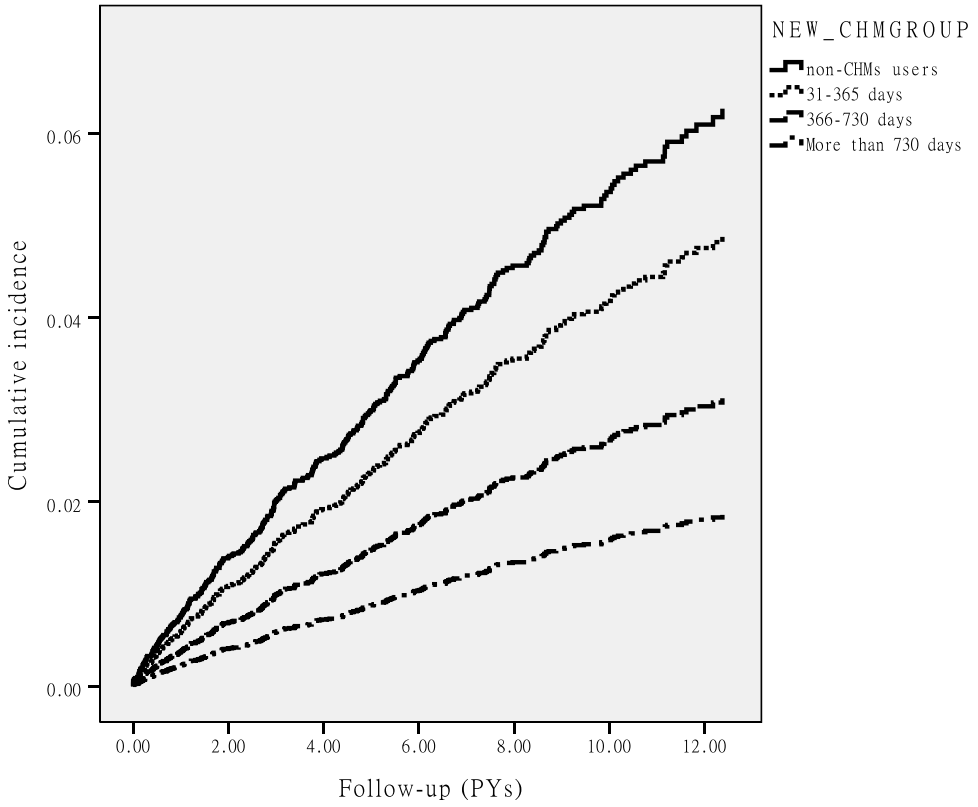

Figure 2 Cumulative incidence of COPD in RA patients with and without receiving CHMs treatment during the 15-year study period (log-rank test, *P*< 0.001).

proximity to their social network.[20] Younger RA patients, therefore, might more easily adapt to the effects of the progression of RA, thereby diluting the therapeutic effect of CHMs. Furthermore, the reduction in risk of COPD was found to be higher for females than for males (43% vs. 18%). We inferred that women might have superior health consciousness than men and immediately sought medical therapy at the slightest irregularity in well-being, and therefore, may be more likely to comply with the prescribed medical regimen to diminish the sequent risk of COPD.[21]

An notable contribution of this work is the list of herb products that are related to the reduced risk of COPD. First, we observed the positive therapeutic effects of Yan Hu Suo and Sāng Zhī in reducing the onset of COPD. These two herbal products are typically used to relieve the level of inflammation and neuropathic pain.[22,23] A murine model showed that the extract of Yan Hu Suo could suppress the production of interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) by modulating the activation of nuclear factor-kappa beta (NF-κB).[24] These mediators are well known to play an indispensable role in the pathogenesis of lung

Table 3 Incidence and COPD Risk for RA Patients with and Without CHMs Use, Stratified by Sex and Age

Variables	Non- CHMs Users			CHMs Users			Crude HR (95% CI)	Adjusted HR (95% CI)
	Case	PYs	Incidence	Case	PY	Incidence		
Sex								
Female	115	19,038.32	6.04	62	19,485.41	3.18	0.53 (0.38–0.71)	0.57[Y] (0.42–0.77)
Male	87	7342.32	11.85	74	6866.71	10.78	0.91 (0.66–1.21)	0.82[Y] (0.60–1.12)
Age (years)								
≤50	27	11,230.89	2.40	20	11,182.57	1.79	0.74 (0.42–1.33)	0.74* (0.41–1.32)
>50	175	15,149.74	11.55	116	15,169.54	7.65	0.66 (0.52–0.83)	0.63* (0.50–0.80)

Notes: [Y]Model adjusted for age, urbanization level, monthly income, medication use and comorbidities. *Model adjusted for sex, urbanization level, monthly income, medication use and comorbidities.

Table 4 Risk of COPD in Relation to the 10 Most Used Single-Herb and Multi-Herb CHMs Products for RA Patients

Chinese Herbal Product	Number of Prescriptions	Crude HR (95% CI)	Adjusted HR* (95% CI)
Single-herb products			
Yan Hu Suo	8699	0.45(0.34–0.62)	0.57(0.42–0.70)
Sāng Zhī	2119	0.41(0.24–0.70)	0.53(0.32–0.81)
Chuan-Niu-Xi	2186	0.67(0.43–1.04)	0.79(0.47–1.14)
Bei Mu	5221	0.61(0.54–0.96)	0.77(0.56–1.09)
Du-Zhong	5008	0.71(0.50–1.03)	0.72(0.51–1.08)
Dan-Shen	5775	0.52(0.36–0.75)	0.58(0.40–0.84)
Ji-Xue-Teng	4500	0.68(0.35–1.04)	0.69(0.37–1.04)
Huang Qin	5230	0.50(0.35–0.71)	0.59(0.45–0.90)
Hai Piao Xiao	3436	0.57(0.36–0.88)	0.77(0.47–1.15)
Da Huang	4585	0.53(0.35–0.81)	0.74(0.41–1.09)
Multi-herb products			
Shu-Jing-Huo-Xue-Tang	9390	0.58(0.44–0.74)	0.64(0.50–0.83)
Jia-Wei-Xiao-Yao-San	8898	0.41(0.29–0.58)	0.65(0.46–0.90)
Shao-Yao-Gan-Cao-Tang	5722	0.72(0.55–0.94)	0.83(0.63–1.10)
Ge-Gen-Tang	5819	0.51(0.37–0.70)	0.65(0.47–0.89)
Dang-Gui-Nian-Tong-Tang	5033	0.63(0.45–0.88)	0.77(0.55–1.07)
Xue-Fu-Zhu-Yu-Tang	4463	0.68(0.50–0.94)	0.76(0.57–1.06)
Du-Huo-Ji-Sheng-Tang	6623	0.56(0.41–0.77)	0.57(0.42–0.77)
Chuan-Xiong-Cha-Tiao-San	4827	0.68(0.47–0.95)	0.73(0.44–1.10)
Zhi-Gan-Cao-Tang	3677	0.71(0.48–1.07)	0.77(0.52–1.12)
Gan-Lu-Yin	4101	0.68(0.41–0.94)	0.75(0.45–1.06)

Notes: *Model adjusted for age, sex, urbanization level, monthly income, medication use and comorbidities.

diseases, especially COPD.[25] Additionally, a recent in vivo study revealed that Sāng Zhī inhibited the lipopolysaccharide-induced production of the pro-inflammatory cytokine in the Raw264.7 cell line by blocking the "BLT2 ligand-BLT2"-linked autocrine inflammatory axis,[23] which may explain its therapeutic effect of decreasing the risk of COPD onset.

Another herbal product proven effective in lessening COPD risk among RA patients is Dang Shen. This remedy belongs to the Campanulaceae family. The root extracts of the Codonopsis species have been shown to possess antioxidant, anti-tumor, anti-microbial and immune-boosting properties.[26] A meta-analysis of 48 randomized controlled trials highlighted that Dang Shen exerted a number of positive effects on pulmonary function, such as improvement of forced expiratory volume (FEV1) and 6-min walking distance, compared with conventional pharmacotherapy.[27] Most importantly, the integration of *Codonopsis* roots into routine therapy was found to significantly enhance patients' quality of life compared to placebo, as measured by St. George's Respiratory Questionnaire (standard mean difference: −7.19, 95% CI: −10.82 to −3.56).[27]

Huang Qin also appears to modulate the immune response, which may have important implications in chronic inflammatory diseases such as COPD.[18,26] Baicalin, a major component of this formula, was proven in both in vitro and in vivo studies to have anti-inflammatory, antioxidant and antibacterial actions, as it has been shown to inhibit cytokines and transcription factors. For example, using a rodent model, Kim and colleagues discovered that Huang Qin suppressed the activation of the MEK/ERK and IKKαβ/IκBα-dependent pathways via c-Raf-1 activation, thereby altering the synthesis of inflammatory mediators.[28]

Among the commonly used multi-herb products for RA patients, we noted that Jia-Wei-Xiao-Yao-San was significantly related to a lower risk of COPD. Recent scientific evidence indicates that this formula works by increasing synaptic plasticity, upregulating the expression of hippocampal brain-derived neurotrophic factor (BDNF),[29] and diminishing the level of inflammatory markers,[30] which in turn decreased the subsequent COPD risk in RA patients. Elevated concentrations of both BDNF and inflammatory cytokines in the sera are well documented before a definitive diagnosis of COPD,[31] implying that

these platelet mediators are likely involved in the pathogenesis of COPD.

The positive therapeutic effects of Shu-Jing-Huo-Xue-Tang and of Du-Huo-Ji-Sheng-Tang on the subsequent predisposition to COPD were also identified in this study. Both animal experiments and human studies have shown that the anti-inflammatory property could be extracted from their inherent compounds, such as ferulic acid and paeoniflorin from Shu-Jing-Huo-Xue-Tang, and gentianine from Du-Huo-Ji-Sheng-Tang. The relevant mechanisms by which these ingredients exhibit their powerful anti-inflammatory effects may be partially associated with inhibition of the NF-κB signaling pathway,[32–34] suggesting that these formulae have the potential to treat airway inflammation diseases in addition to rheumatologic disorders.

In our study, we also discovered that the prescription of Ge-Gen-Tang was associated with lower vulnerability to COPD, echoing a previous study finding.[35] It was inferred from this finding that this formula could ameliorate airway remodeling by modulating airway inflammation and oxidative stress in the lungs. Several recent studies have shown that puerarin, a major isoflavone glycoside purified from this formula, can not only help decrease the levels of IL-4 and TNF-α but also reduce oxidative stress in a rodent model of inflammatory disorders.[35,36] A study by Huang and colleagues further indicated that these plasma inflammatory cytokines were related to measures of the severity of airway diseases, such as the FEV1/forced vital capacity ratio, and may be potential markers for the evaluation of chronic inflammatory lung diseases.[37]

Findings from the current study have important clinical and research implications. However, several limitations should be noted when interpreting these results. First, coding errors are always a possibility in an administrative database. To minimize this bias, we enrolled only subjects with new-onset RA or COPD, and only after the patient had at least three outpatient visits reporting consistent diagnoses or at least one inpatient admission. To verify the accuracy of medical records, the Taiwan NHI randomly samples claims from hospitals, interviews patients and reviews medical charts.[15] Second, data on social network relationships, coping strategies and resources, religious beliefs or educational levels were not available from the claims files, and confounding by any of these factors may exist. Future research should include these uncontrolled variables to assess whether the present findings can be replicated across diverse groups of medical patients. Third, data regarding RA severity were not available in this database, and failure to adjust for this factor may bias the results. However, our multivariate analysis considered the impact of multiple comorbidities, including hypertension, stroke, diabetes, heart disease, chronic kidney disease, cancer, alcohol dependence syndrome and tobacco use. Furthermore, two sensitivity analyses were also performed to further examine the relationship between CHMs use and the subsequent risk of COPD. The first sensitivity analysis, limited to RA patients with no comorbidities, found CHMs to be still protective against the development of COPD (adjusted HR = 0.53, 95% CI, 0.38–0.73). Second, we used the prescription of biological agents as a surrogate for RA severity, dividing subjects by whether or not they received biological agents for≧ 6 months after the index date. The proportion of use of biological agents was 59.1% (1985/3360) in the CHMs user cohort and 55.2% (1858/3360) in the non-CHMs user cohort. The results of this re-analysis, that took into account the use of biological agents, were essentially the same as those reported in the original analysis (adjusted HR: 0.59, 95% CI: 0.37–0.80). Findings from these sensitivity analyses suggest that the severity of RA did not appreciably impact the relationship reported herein. Fourth, evidence from any observational cohort study is generally less robust than that obtained from randomized trials, because cohort study designs provide little safety against existing confounding bias. Despite our meticulous efforts to control for confounding factors, unpredictable biases may remain from unmeasured or unknown confounders. Fifth, although our study revealed a substantial benefit effect of CHMs use on the reduction of COPD onset among RA patients, it must be recognized that these patients were not randomly categorized into users and nonusers. Therefore, caution should be exerted when interpreting the findings. A randomized controlled trial is, therefore, recommended to clearly determine the efficacy of these CHMs, as well as the mechanisms that underlie their successful application. These limitations notwithstanding, this study also possessed several strengths. These include the immediate availability of data, the comprehensiveness of the database and the statistical power from the use of a large, nationally representative sample. In addition, this retrospective 15-year cohort study allowed us to robustly determine the relationship between CHMs use and COPD in RA patients. Furthermore, the present findings may serve as a useful reference for future studies on this topic among other populations of patients with severe and chronic illnesses.

Conclusion

This is the first large-scale nationwide cohort study to show the association of CHMs use with the subsequent risk of COPD among RA patients, thus suggesting a venue for further studies of the effect of CHMs on other medical conditions. We found that the integration of CHMs into the RA treatment regimen reduced the subsequent risk of COPD by 32%. Results of this study may serve as a reference to help healthcare providers when planning and implementing therapeutic interventions that seek to improve the health of patients with RA.

Abbreviations

RA, rheumatoid arthritis; COPD, chronic obstructive pulmonary disease; CHMs, Chinese herbal medicine; HR, hazard ratio; CI, Confidence Interval; LHID, Longitudinal Health Insurance Database; NHI, National Health Insurance; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; PYs, person-years; NTD, New Taiwan Dollar; IL, Interleukin; TNF-α, tumor necrosis factor-α; NF-κB, nuclear factor-kappa beta; FEV1, forced expiratory volume; BDNF, brain-derived neurotrophic factor.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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