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ORIGINAL RESEARCH

A Comparison of the Risk of Fracture in Rheumatoid Arthritis Patients with and without Receiving Chinese Herbal Medicine

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Objective: Patients with rheumatoid arthritis (RA) often suffer from bone complications due to persistent joint inflammation, especially incident fracture. Nowadays, Chinese herbal medicines (CHMs) have provided safe and effective therapy for treating skeletal conditions, but it is unclear whether CHMs can prevent fracture onset among RA individuals. This study aimed to determine the association between the use of CHMs and the risk of fracture among them.

Methods: This retrospective, population-based study retrieved administrative health data from the Taiwan National Health Insurance (NHI) database to identify patients with newly diagnosed RA between 2000 and 2009. Of the 6178 incident RA patients, 2495 matched pairs of CHMs users and non-CHMs users were identified by propensity score matching. Enrollees with hip fractures prior to RA onset were excluded. Included subjects were followed until the end of 2013. Incidence and adjusted hazard ratios (HR) of new-onset bone fracture in the multivariable Cox proportional hazard model were measured with 95% confidence interval (CI).

Results: Fracture incidence was lower in CHMs users than in the comparison cohort (26.91 vs 32.94 per 1000 person-years, respectively), with an adjusted HR of 0.82 (95% CI: 0.73–0.92). Subjects receiving CHMs for more than 2 years had a much lower risk of fracture onset by more than 50%. Some CHMs prescriptions (Yan Hu Suo, Bei Mu, Da Huang, Dang Shen, Fu-Zi, Shu-Jing-Huo-Xue-Tang, Dang-Gui-Nian-Tong-Tang, Jia-Wei-Xiao-Yao-San, Gan-Lu-Yin, and Gui-Zhi-Shao-Yao-Zhi-Mu-Tang) were associated with reduced fracture risk.

Conclusion: Adding CHMs to routine treatment was found to be related to lower fracture risk in RA patients.

Keywords: rheumatoid arthritis, fracture, Chinese herbal medicines, risk

Introduction

Rheumatoid arthritis (RA), a relatively common autoimmune disorder characterized by swelling, tenderness, and damage to synovial joints, affects 1% of adults globally.[1] Findings from recent studies showed that individuals diagnosed with RA may experience a higher risk of overall fracture, of which vertebral and hip fractures were the most common fracture sites.[2,3] Vertebral fractures may progressively exacerbate back pain and limit physical activity in RA patients.[3] Notably, prior research has shown a widening gap in mortality rates between RA individuals with the concurrent hip fracture and the general population.[4,5] The estimated excess

mortality rate after hip fracture ranged from 8.4% to 36% in the first year.[6] Additionally, Kwon et al reported that RA patients with concurrent osteoporotic fracture had a 30% greater risk of death from all causes than the general population.[7] Faced with the alarming clinical manifestations, it is imperative to prevent or treat osteoporotic fracture when managing RA patients.[2,8]

Over the past decade, Chinese herbal medicines (CHMs), as a time-honored medical science, have been regarded as a commonly used complementary therapy for patients with RA.[9–11] Previous studies have inferred that by abating the nuclear factor kappa beta (NF-κB) signaling, several Chinese herbs, including Bei-Mu and Da-Huang, may be beneficial in regulating pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[12] It is noteworthy that these inflammatory mediators have been shown to moderate the production of bone marrow, leading to hypo-development of the skeleton, as well as brittleness of bone, thereby increasing susceptibility to fracture after RA onset.[13,14] Given that there is growing evidence of abnormal inflammatory parameters in the link between RA and fracture, the application of CHMs might be considered in providing a care regimen for preventing or delaying the incidence of fracture among people with RA.

Despite the interest in CHMs, only a few studies have reported the characteristics of CHMs usage patterns in RA patients.[9,11] To the best of our knowledge, no previous studies have directly determined an association between CHMs use and osteo-protective influence among RA patients. This study, therefore, aimed to corroborate the association, over time, between CHMs use and incident osteoporotic fracture among RA patients, using a nationwide medical claims database representative of the Taiwanese population.

Methods
Sources of Data
The Longitudinal Health Insurance Database (LHID) was utilized as the data source in this retrospective cohort study. LHID is a sub-dataset of the National Health Insurance Research Database (NHIRD) of Taiwan, made up of one million randomly sampled people with over 10 years of follow-up. It has also been reported that these recruited individuals have similar age and sex distribution to the general population of Taiwan because the Bureau of National Health Insurance (NHI) performed a multistage stratified systematic sampling method.[15] This database

compiled (i) demographic information of enrollees; (ii) health insurance claims data; (iii) diagnostic codes; (iv) contracted pharmacies; and (v) medical examination information on persons under the NHI program. This study was conducted in accordance with the Helsinki Declaration, and was approved by the local institutional review board and ethics committee of Buddhist Dalin Tzu Chi Hospital (No. B10004021-1).

Definition of Subjects and Variables
In this exploration, the diagnostic codes were based on the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) in the diagnosis field. As shown in Figure 1, patients who sought ambulatory health care or inpatient services between 2000 and 2009 due to newly diagnosed RA (ICD-9-CM code: 714.0) were initially identified. These patients were further linked to the catastrophic illness registry to ensure the validity of their diagnoses. The catastrophic illness certificate is granted based on formal diagnoses issued by physicians, and includes schizophrenia, mood disorders, autoimmune disorders, and cancer. The index date was considered the date when RA patients gained approval for catastrophic illness registration. Only those 20–80 years of age were included. Patients with a diagnosis of fracture prior to the first RA diagnosis (n = 997), and those who were not followed for one year after RA (n = 113) were excluded. Patients were classified as having fracture if they had at least three ambulatory visits for treatment or if they had been hospitalized due to bone fracture, as defined by the use of ICD-9-CM codes 800-829. Finally, a total of 6178 patients with RA were included.

The frequency of visits to physicians who practice Traditional Chinese Medicine was used to determine whether the enrollees had ever used CHMs treatment. Among the eligible patients, those receiving CHMs to treat RA for more than 30 days were deemed CHMs users (n = 2617), whereas those treated for 30 days or less were considered non-CHMs users. To remove the confounding effects of sociodemographic variables and coexisting medical conditions on the relationship between CHMs treatment and fracture in RA patients, we used a matching procedure with propensity scores to select CHMs treatment and non-treatment controls. The multivariate logistic regression model was utilized to estimate propensity score value, namely a probability index, ranging between 0 and 1, derived from the influence of all observed characteristics (listed at Table 1). Patients were
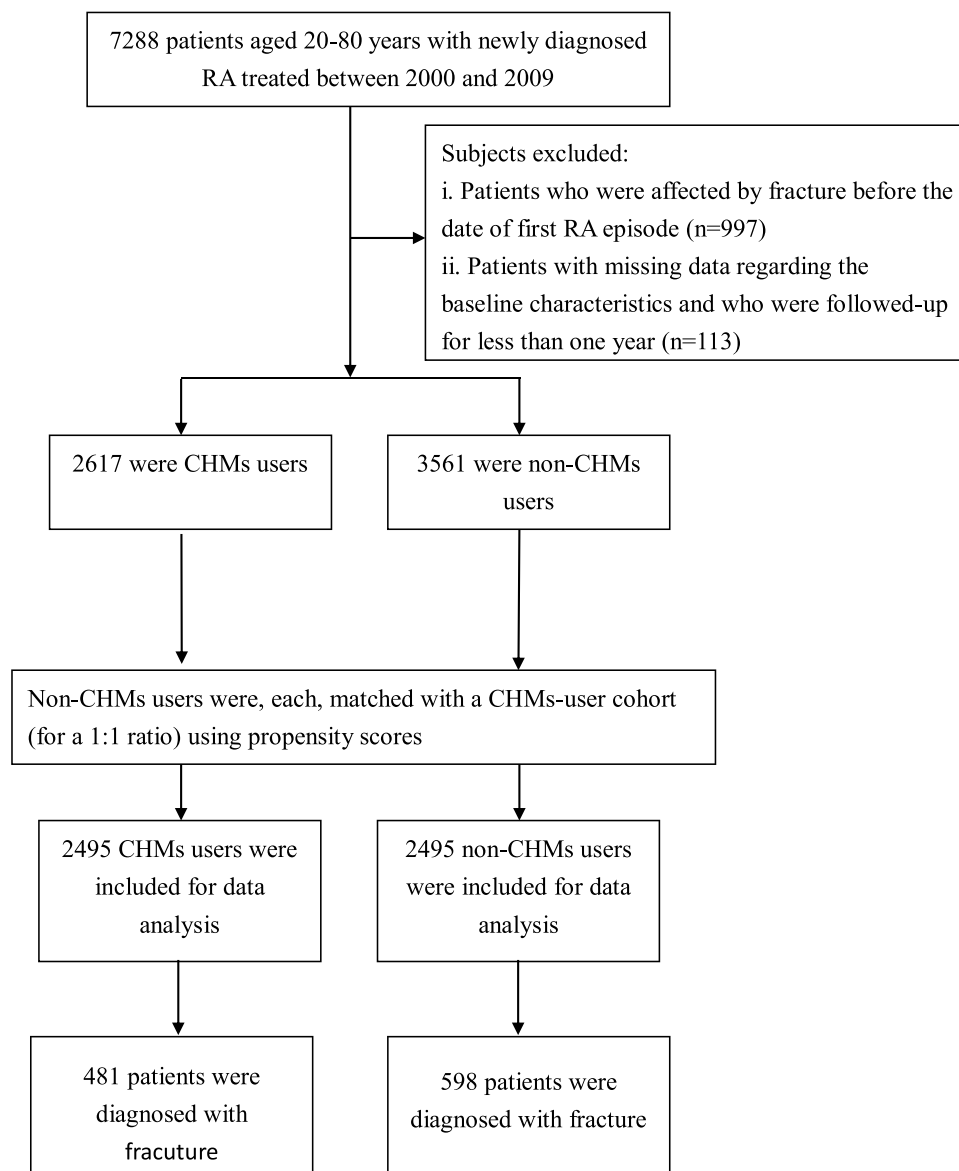
Figure 1 Flowchart showing the method of selecting and following study subjects.

matched by propensity score, using one-to-one nearest neighbor matching within 0.2 caliper distance, in which pairs of user and nonuser groups were formed, such that matched subjects had similar values of the propensity scores. Additionally, the index date for the follow-up period was the date of CHMs treatment initiation or, for non-CHMs users, the date of the initial RA onset, corrected by immortal time bias.[16] Each subject was followed from the index date to the end of 2013 or was censored. The follow-up time, in person-years (PYs), was calculated until the date of newly diagnosed fracture onset or until being censored due to death, withdrawal from the insurance system, or loss to follow-up.

Measurements of Covariates

Covariates assessed included baseline age, sex, monthly income, the urbanization level of enrollee's residential area, former comorbidities and medication usage. Regarding monthly income, we used the premium category as a proxy to divide participants into four groups: ≤ New Taiwan Dollar (NTD) 17,800, NTD 17,881–43,900, and ≥ NTD $43,901. As to the urbanization level, it was calculated according to a published scheme that classified 359 communities in Taiwan into seven stratums, with a higher level indicating a higher degree of urbanization. The classification scheme included the population density, proportion of persons with a college-level education or

Table 1 Demographic Data and Selected Comorbidities of Study Subjects

Variables	Total Group	Non-CHMs Users	CHMs Users	Standardized Difference
		N =2495(%)	N =2495(%)	
Age (yr)				0.041
≤50	2209(44.3)	1079(43.2)	1130(45.3)	
>50	2781(55.7)	1416(56.8)	1365(54.7)	
Mean (SD [b])	52.36(13.21)	52.54(13.45)	52.19(12.88)	0.024
Sex				0.007
Female	3698(74.1)	1845(73.9)	1853(74.3)	
Male	1292(25.9)	650(26.1)	642(25.7)	
Monthly income				0.008
Low	2144(43.0)	1072(43.0)	1072(43.0)	
Median	2640(52.9)	1322(53.0)	1318(52.8)	
High	206(4.1)	101(4.0)	105(4.2)	
Residential area				0.008
Urban	2869(57.5)	1435(57.5)	1434(57.5)	
Suburban	770(15.4)	388(15.6)	382(15.3)	
Rural	1351(27.1)	672(26.9)	679(27.2)	
Comorbidity				
Hypertension	1325(26.6)	675(27.1)	650(26.1)	0.021
Diabetes	620(12.4)	316(12.7)	304(12.2)	0.014
Heart disease	793(15.9)	405(16.2)	388(15.6)	0.016
Chronic kidney disease	49(1.0)	23(0.9)	26(1.0)	0.012
Cancer	131(2.6)	60(2.4)	71(2.8)	0.023
Alcohol dependence syndrome	9(0.2)	4(0.2)	5(0.2)	0.009
Tobacco use	4(0.1)	2(0.1)	2(0.1)	0.009
Follow-up time (mean, median)	7.22(7.24)	7.28(7.20)	7.16(7.26)	

higher, proportion of elderly residents, proportion of agricultural workers, and number of physicians per 100,000 population. In this work, the urbanization degree was grouped into three strata: urban (levels 1–2), suburban (levels 3–4), and rural (levels 5–7).[17] Meanwhile, the recorded clinical characteristics of baseline comorbidities, included hypertension (ICD-9-CM 401–405), diabetes mellitus (DM; ICD-9-CM 250), heart disease (ICD-9-CM 410–429), chronic kidney disease (CKD; ICD-9-CM 585), cancer (ICD-9-CM 140–208), tobacco use (ICD-9-CM 305.1) and alcohol dependence syndrome (ICD-9-CM 303); all comorbidities were based on the medical records of each included patient assessed at one year prior to the initial cohort entry.

Statistical Analysis

Data were analyzed using SAS version 9.3 software (SAS Institute Inc, Cary, NC, USA). The differences in distributions of sociodemographic data and comorbidities between the two groups were compared using standardized difference, which allowed to assess the balance of measured variables between CHMs and non-CHMs users in the matched sample, since assessment of balance in baseline variables between treated and untreated subjects must be performed by the methods that were not subject to the influence of sample size. A standardized difference of 0.1 or more was considered indicative of imbalance.[18] Thereafter, the adjusted hazard ratio (HR) was calculated using Cox proportional hazards regression analysis with 95% confidence interval of risk of fracture in association with CHMs use, after adjusting for confounders reported at baseline. To further test the robustness of the relationship of CHMs use with fracture risk, CHMs users were divided into three subgroups: the first group used CHMs for 31–365 days, the second group used CHMs for 366–730 days, and the third group used CHMs treatment

for more than 730 days. The Kaplan–Meier method was employed to estimate the cumulative risk of fracture in each group, and the differences across groups were assessed using the Log rank test. The proportional hazards assumption was examined by plotting the log (−log [survival function]) versus the log (survival time). A $P < 0.05$ was considered to be statistically significant.

Sensitivity analyses were performed to evaluate whether the association found was robust after considering the severity of RA. First, we only included RA patients who reported no comorbidities. Second, given the unavailability of RA severity index in this investigation, we substituted prescription of biological agents, used for six months or longer, as a surrogate variable for RA severity in the regression model. These agents included adalimumab, etanercept, infliximab, rituximab and tocilizumab.

Results
Distributions of demographic characteristics and comorbidities for the two groups are shown in Table 1. Of the total enrollees, 2495 were CHMs users and 2495 were the 1:1 propensity-score-matched controls. After the matching procedure, no significant differences were found between the two groups in age, sex, monthly income, residential area and comorbidities, indicating comparability of the two groups.

Among all eligible RA subjects, a total of 1079 first episodes of fracture occurred over an observation period of 36024.29 PYs in 4990 patients. CHMs users had a significantly lower incidence rate of fracture at 26.91 per 1000 PYs, compared with 32.94 per 1000 PYs for the non-CHMs users, with the adjusted HR of 0.82 (95% CI 0.73–0.92) (Table 2). Also, those receiving CHMs for more than 730 days experienced a 53% lower risk of fracture than those who did not receive CHMs. Figure 2 illustrates the Kaplan–Meier estimates of survival by days of CHMs use with a Log rank test of $P < 0.001$, which

supports a statistically significant difference in the fracture rate across three groups of CHMs users.

Table 3 shows the results stratified by age and sex. Collectively, a more beneficial effect of CHMs was detected among younger subjects. A multivariate stratified analysis further verified that the benefit of CHMs therapy in reducing the incidence of fracture was more predominant among females, with an adjusted HR of 0.80 (95% CI 0.71–0.92) (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, Bei Mu, Da Huang, Dang Shen, Fu-Zi, Shu-Jing-Huo-Xue-Tang, Dang-Gui-Nian-Tong-Tang, Jia-Wei-Xiao-Yao-San, Gan-Lu-Yin, and Gui-Zhi-Shao-Yao-Zhi-Mu-Tang were related to the significant reduction of fracture risk (Figure 3).

In the first sensitivity analysis, while we only recruited the RA patients who reported no comorbidities for data analysis, with 1509 in the CHMs use group and 1505 in the non-CHMs use group, respectively. In this context, the CHMs use was still associated with a lower incidence rate of fracture, with an adjusted HR of 0.74 (95% CI 0.63–0.88). In the second sensitivity analysis, 56.7% (1415/2495) of the CHMs users and 55.3% (1380/2495) of the non-CHMs users ever received biological agents for six months or longer. After adding this factor to the multivariate model, we found that CHMs use was still associated with a lower incidence rate of fracture, with an adjusted HR of 0.81 (95% CI 0.74–0.93).

Discussion
This is the first population-based cohort study to identify the relationship between CHMs use and the occurrence of incident osteoporotic fracture in RA patients based on a nationwide health research database. To objectively evaluate the association between CHMs and the risk of fracture in RA patients, we conducted 1:1 propensity score matching for age, sex, monthly income, residential area, comorbidities and follow-up time to ensure that the

Table 2 Risk of Fracture 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	2495	598	18156.35	32.94	1	1
CHMs users	2495	481	17867.94	26.91	0.82 (0.72–0.92)	0.82 (0.73–0.92)
CHMs use within 31–365 days	2053	421	14137.70	29.78	0.90 (0.80–1.02)	0.92 (0.81–1.03)
CHMs use for 366–730 days	255	35	2063.66	16.96	0.51 (0.37–0.72)	0.54 (0.39–0.76)
CHMs use for more than 730 days	187	25	1666.58	15.00	0.46 (0.31–0.68)	0.47 (0.32–0.70)

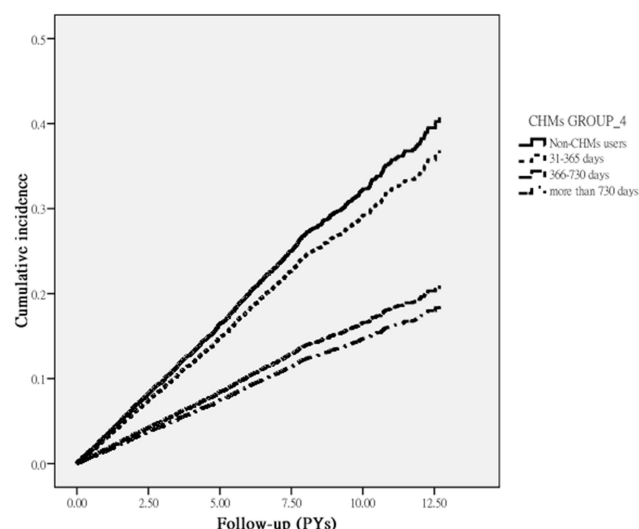**Note**: *Model adjusted for sex, age, urbanization level, monthly income, and comorbidities.

Figure 2 Cumulative incidence of fracture among RA subjects with and without use of CHMs (Log rank test, p<0.001).

CHMs group was commensurate with the non-CHMs group. Results obtained by this study of RA patients showed that, compared with patients who did not use CHMs therapy, the fracture risk in RA patients treated with CHMs was lower by 20%. Of note, those receiving CHMs for more than two years had a substantial reduced risk of fracture. The dose-dependent response suggests causation between CHMs use and reduction of fracture risk. Proposed mechanisms by which the prescribed herbal products protect against incident osteoporotic fracture may involve the regulation of inflammatory response,[12] and increasing the bone mineral density via regulating the mitogen-activated protein kinase (MAPK) signaling pathway;[19] both of these possible mechanisms appear to be beneficial in attenuating osteoporosis to prevent following fragility fracture.

Moreover, regardless of gender, younger patients benefited more from CHMs treatments than older patients in terms of risk prevention of fracture risk. This suggests that younger people who may experience fewer coexisting medical conditions, have a more positive attitude toward their medical conditions, or have better psychosocial and coping resources to rely upon than do older patients.[20] These characteristics in younger adults may superimpose the protective effect of CHMs on bone health. Additionally, females benefited more from CHMs treatment than males. Previous studies demonstrated that estrogen was one of the main hormones that influenced the growth cycle and reabsorption of bone by inhibiting the activation of osteoclastogenesis and mesenchymal cell differentiation,[21–23] which were known to induce bone fragility.

Further, the present study pointed out the specific CHMs products that were likely to be associated with reduced risk of fracture for RA patients. Among the commonly used single-product CHMs to treat RA, five herbs were observed to lower the risk of fracture. First, the use of Yan-Hu-Suo was associated with a 25% reduced risk of fracture. Traditionally, Yan-Hu-Suo was used to relieve pain caused by stagnation of blood and Qi (energy). A recent study showed that l-tetrahydropalmatine, a major compound purified from this formula, significantly suppresses the receptor activator of nuclear factor κB ligand (RANKL)-activated NF-κB and MAPK pathway.[24] This pathway involves the inhibition of osteoclastogenesis and regulation of osteoblast differentiation and osteogenic formation.[25]

The present study also showed that use of Bei-Mu and Da-Huang may lessen the risk of fracture among RA subjects. These prescriptions were previously shown to have a

Table 3 Incidence and Fracture 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)
	Fracture Event	PYs	Incidence	Fracture Event	PY	Incidence		
Sex								
Female	477	13105.75	36.40	369	13074.36	28.22	0.77 (0.67–0.88)	0.80[Ō] (0.71–0.92)
Male	121	5050.60	23.96	112	4793.57	23.36	0.97 (0.75–1.25)	0.93[Ō] (0.72–1.20)
Age								
≤ 50	186	8212.65	22.65	145	8572.22	16.92	0.75 (0.60–0.93)	0.72* (0.58–0.88)
>50	412	9943.70	41.43	336	9295.72	36.15	0.87 (0.75–1.00)	0.88* (0.76–1.02)

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

Table 4 The Top Ten Single Chinese Herbs and Chinese Herbal Formula Used Among the Studying Participants

CHMs Name	Ingredients or Generic Name
Single-herb products	
Hai-Piao-Xiao	*Sepiella maindroni* de Rochebrune
Ye-Jiao-Teng	*Polygonum multiflorum* Thunb.
Yan-Hu-Suo	*Corydalis yanhusuo* (Y.H.Chou & Chun C.Hsu) W.T.Wang ex Z.Y.Su & C.Y.Wu
Ge-Gen	*Pueraria lobata* (Willd.) Ohwi
San-Qi	*Panax notoginseng* (Burkill) F.H.Chen
Bei-Mu	*Fritillaria thunbergii* Miq.
Da-Huang	*Rheum palmatum* L.
Tian-Hua-Fen	*Trichosanthes kirilowii* Maxim.
Dan-Shen	*Salvia miltiorrhiza* Bunge
Fu-Zi	*Aconitum carmichaeli* var. carmichaeli
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)
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)
Shao-Yao-Gan-Cao-Tang	Bai-Shao (Radix Paeoniae Alba; *Paeonia lactiflora* Pall.), Gan-Cao (Radix Glycyrrhizae; *Glycyrrhiza uralensis* Fisch.)
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.)
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.), Ge-Gen (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.)

(Continued)

Table 4 (Continued).

CHMs Name	Ingredients or Generic Name
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.)
Gui-Zhi-Shao-Yao-Zhi-Mu-Tang	Gui-Zhi (Ramulus Cinnamomi; *Cinnamomum cassia* (L.) J.Presl), Ma-Huang (Herba Ephedrae; *Ephedra sinica* Stapf), Fu-Zi (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.)
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), Chuan-Xiong (Rhizoma Chuanxiong; *Ligusticum striatum* DC.), Gan-Cao (Radix Glycyrrhizae; *Glycyrrhiza uralensis* Fisch.)
Zhi-Gan-Cao-Tang	Gan-Cao (Radix Glycyrrhizae; *Glycyrrhiza uralensis* Fisch.), Ren-Shen (Radix Ginseng; *Panax ginseng* C.A.Mey.), Gui-Zhi (Ramulus Cinnamomi; *Cinnamomum cassia* (L.) J.Presl), Di-Huang (Radix Rehmanniae; *Rehmannia glutinosa* (Gaertn.) DC.), Mai-Men-Dong (Radix Ophiopogonis; *Ophiopogon japonicus* (Thunb.) Ker Gawl.), E-Jiao (Colla Corii Asini; *Equus asinus* L.), Huo-Ma-Ren (Semen Cannabis; *Cannabis sativa* L.), Sheng-Jiang (Rhizoma Zingiberis Recens; *Zingiber officinale* Roscoe), Da-Zao (Fructus Jujubae; *Ziziphus jujuba* Mill.)
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.), Sheng-Jiang (Rhizoma Zingiberis Recens; *Zingiber officinale* Roscoe), Da-Zao (Fructus Jujubae; *Ziziphus jujuba* Mill.), Gan Cao (Radix Glycyrrhizae; *Glycyrrhiza uralensis* Fisch.)

pronounced anti-arthritic effect by inhibiting the production of inflammatory mediators, such as TNF-a, IL-6 and IL-8.[26,27] Furthermore, through the induction of matrix metalloproteinase (MMPs) generations and osteoclast activation, these inflammatory mediators were shown to moderate the production of bone marrow, resulting in hypo-development of the skeleton and bone brittleness,[13,14] thereby increasing susceptibility to fracture.

Another herbal product shown to be effective in lessening fracture risk is Dan-Shen. One recent in vivo study indicated that Dan-Shen may possess an anti-osteoporosis effect by suppressing trabecular bone loss and osteoclastogenesis.[28] Meanwhile, Dan-Shen significantly regulates cytokine secretion and reduces oxidative stress,[29] and accordingly, promotes bone regeneration and lessens the chance of inflammation-induced osteoporosis. In addition, the use of Fu-Zi demonstrated positive therapeutic effects against risk of fracture. Using a rodent model, Kim and colleagues found that Fu-Zi markedly promoted the proliferation

rate of mouse bone marrow mesenchymal stem cells up to 122.24% compared to untreated cells,[30] which may implicate the possible mechanism responsible for the positive effect of Fu-Zi observed in the present study.

With regard to the commonly prescribed multi-herb products, Jia-Wei-Xiao-Yao-San, Gan-Lu-Yin, and Shu-Jing-Huo-Xue-Tang were all found to reduce the risk of incident fracture in RA patients. Both human and animal studies have disclosed that these remedies decreased the level of IL-6 or TNF-α via the suppression of nuclear factor kappa beta (NF-κB) activation.[31–33] In addition to being a crucial transcription mediator regulating the induction of the inflammatory response, NF-κB was considered a potent mediator of inflammatory osteolysis, thereby contributing to enhanced osteoclastogenesis to exacerbate bone loss. Accordingly, numerous studies have exploited NF-κB as a target for bone therapies in addition to mitigating the effect of inflammatory disorders.[34]
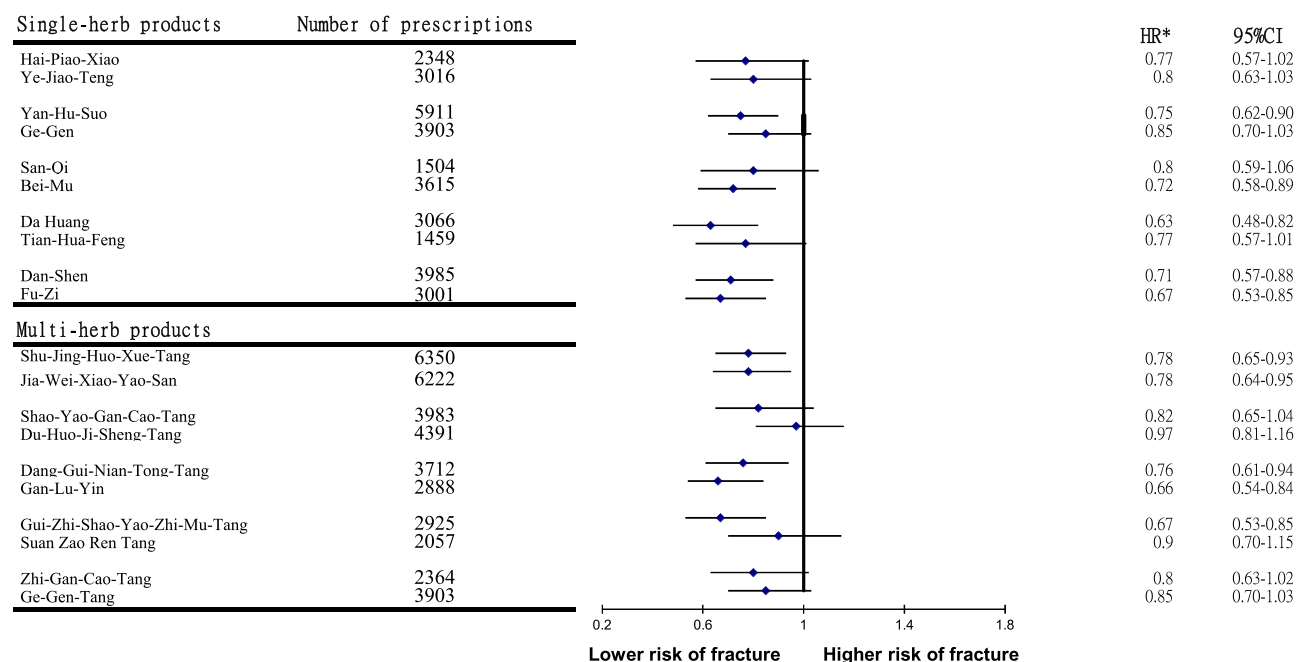
Single-herb products	Number of prescriptions	HR*	95%CI
Hai-Piao-Xiao	2348	0.77	0.57-1.02
Ye-Jiao-Teng	3016	0.8	0.63-1.03
Yan-Hu-Suo	5911	0.75	0.62-0.90
Ge-Gen	3903	0.85	0.70-1.03
San-Qi	1504	0.8	0.59-1.06
Bei-Mu	3615	0.72	0.58-0.89
Da Huang	3066	0.63	0.48-0.82
Tian-Hua-Feng	1459	0.77	0.57-1.01
Dan-Shen	3985	0.71	0.57-0.88
Fu-Zi	3001	0.67	0.53-0.85
Multi-herb products			
Shu-Jing-Huo-Xue-Tang	6350	0.78	0.65-0.93
Jia-Wei-Xiao-Yao-San	6222	0.78	0.64-0.95
Shao-Yao-Gan-Cao-Tang	3983	0.82	0.65-1.04
Du-Huo-Ji-Sheng-Tang	4391	0.97	0.81-1.16
Dang-Gui-Nian-Tong-Tang	3712	0.76	0.61-0.94
Gan-Lu-Yin	2888	0.66	0.54-0.84
Gui-Zhi-Shao-Yao-Zhi-Mu-Tang	2925	0.67	0.53-0.85
Suan Zao Ren Tang	2057	0.9	0.70-1.15
Zhi-Gan-Cao-Tang	2364	0.8	0.63-1.02
Ge-Gen-Tang	3903	0.85	0.70-1.03

0.2   0.6   1   1.4   1.8

Lower risk of fracture   **Higher risk of fracture**

Figure 3 Risk of fracture in relation to the top ten most-used single-herb and multi-herb products among studying participants. *Model adjusted for age, sex, urbanization level, monthly income, and comorbidities.

Findings of the present study also indicated that the prescription of Dang-Gui-Nian-Tong-Tang diminished vulnerability to fracture. The extract of Angelica sinensis, a major ingredient purified from Dang-Gui-Nian-Tong-Tang, has been shown to elevate bone turnover markers and increase bone mineral density, indicating bone cell proliferation.[35,36] Echoing a previous report, the present study also revealed that Gui-Zhi-Shao-Yao- Zhi-Mu-Tang is one of the commonly used decoctions for RA.[9] The decoction produced protective effects on fracture risk, possibly through influencing the calcification of bone by osteoblast reproduction and reducing the inflammatory mediator levels that were associated with synovial inflammation and bone destruction.[37]

Although the findings of the present study have an appreciable level of clinical and research significance, several limitations should be considered. First, given the detection of a positive association between CHMs use and lower risk of fracture, the use of retrospective analysis of cross-sectional data usually limits the inference of causality. Also, retrospective cohort design may have misclassification bias that can influence measurement, just as in the use of ICD-9-CM diagnostic codes only. To minimize this bias, we enrolled only persons with new-onset fracture or RA, and only after the patients had at least 3 outpatient visits, reporting consistent diagnoses or at least one inpatient admission. The clarification of the diagnosis of RA was further verified by the catastrophic illness certificate. Meanwhile, it should also be noted that the NHI of Taiwan randomly reviews the charts and audits medical charges to verify the accuracy of claims.[15] Second, in the LHID database detailed information of family history, educational level, and laboratory data were not accessible in LHID database, which may have restricted our capacity to accurately determine patients' health status. Thus, research addressing these variables is worthy of further investigation. Third, since a reliable index of RA severity was unavailable from the LHID, and failure to control for this factor may bias the findings, we performed two sensitivity analyses to mitigate this concern. First, we limited the analysis to only those patients with no comorbidities. Second, we added to the analysis prescription of biological agents, taken for six months or longer, which is a common surrogate used for RA severity in the administrative claims data.[11,38] These sensitivity analyses revealed that disease severity was not likely to alter the veracity of our findings that adding CHMs to conventional therapy reduced the risk of fracture in RA patients. Fourth, due to the use of a cohort study design, rather than a randomized controlled trial, inferences regarding the beneficial effect of CHMs on reducing fracture risk are likely limited due to unmeasured or unknown confounders. Therefore, caution should be

taken 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. One strength was that this nationwide register-based study had the opportunity to fully access records of hospital diagnoses and prescription claims; minimal risk of selection bias and attrition during follow-up. The study also sampled a large population of both men and women, which provided sufficient power to conduct detailed analyses, especially given the relatively low incidence of RA in the population.

Conclusions

This is the largest population-based cohort study based on Taiwan's national health database designed to determine the association between the use of CHMs and the risk of incident fracture in RA patients. Longer duration of incorporating CHMs into routine treatment for RA patients was found to significantly reduce the risk of fracture by 53%. Results of this study may serve as a reference to help healthcare providers when planning and implementing therapeutic interventions that seek to improve the overall health of patients with RA. Further prospective randomized trials are recommended to clarify whether the association revealed in this study supports a causal link.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval for the version to be published; and agreed to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to declare.

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