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ORIGINAL ARTICLE

Association of use of Chinese herbal medicines and the risk of fracture in patients with osteoporosis: a population-based cohort study

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Abstract

Summary After utilizing a large population-based claims database and the application of propensity score match approach to reduce the confounding effects, we found that the use of Chinese herbal medicines (CHMs) was related to the lower risk of sequent osteoporotic fracture by 27% among the individuals with osteoporosis. The predominant effect was observed in those receiving CHMs for more than two years.

Introduction Osteoporosis (OS) is a highly disabling condition that can lead to fragility fracture, thus posing greater burdens of functional limitations for the affected individuals. It is unclear if the use of Chinese herbal medicines (CHMs) could reduce the risk of fracture due to OS. This study aimed to investigate the association of CHMs and the subsequent osteoporotic fracture risk among OS patients.

Methods This longitudinal cohort study used the Taiwanese National Health Insurance Research Database to identify 250,699 newly diagnosed OS patients aged 20 years or older between 1998 and 2010. We recruited 103,325 CHM users following the onset of OS (CHM users) and randomly selected 103,325 subjects without CHM usage as controls (non-CHM users) by propensity score matching according to the demographic characteristics and comorbidities at enrollment. All enrollees were followed until the end of 2012 to record the incidence of osteoporotic fracture. We applied the Cox proportional hazard regression model to compute the hazard ratio (HR) of the risk of osteoporotic fracture.

Results During the 15-year follow-up period, 7208 CHM users and 11,453 non-CHM users sustained osteoporotic fracture, with an incidence rate of 9.26 and 12.96, respectively, per 1000 person-years. We found that CHM users had a significantly reduced risk of osteoporotic fracture compared to non-CHM users (adjusted HR 0.73; 95% confidence interval [CI] = 0.70–0.75). Those treated with CHMs for longer than 730 days had a lower fracture risk by 54%. Some commonly used CHMs, such as Yan hu suo (Rhizoma Corydalis), Huang Qin (Scutellaria Baicale), Jie Geng (*Platycodon grandifloras*), Xiang Fu (*Cyperus rotundus*), Hai

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Piao Xiao (Cuttlebone Sepium), Jia-Wei-Xiao-Yao-San, Ge-Gen-Tang, Shao-Yao-Gan-Cao-Tang, and Du-Huo-Ji-Sheng-Tang, are related to the lower risk of fracture.

Conclusions The use of CHMs was associated with lower risk of osteoporotic fracture for OS patients, suggesting that it could be integrated into conventional therapy to prevent subsequent bone fracture.

Keywords Chinese herbal medicines · Cohort study · Osteoporosis · Osteoporotic fracture

Introduction

Osteoporosis (OS) is a bone disease characterized by thinning and deterioration of bone tissue and loss of density [1], which may induce the enhanced bone fragility and the onset of fracture [2]. According to the report by the International Osteoporosis Foundation, it estimates that OS may cause more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 s [3]. Notably, over two-fold higher risk of mortality after fracture has been documented, especially in hip fracture [4]. So, its economic burden cannot be ignored. In the United States, the total cost of treating OS-related fractures was estimated at $19 billion in 2005 and is expected to surge over three times by 2040 [5, 6]. Though there have been significant advances of pharmacological interventions against OS, some adverse side effects, including nausea, joint aches, pain, or carcinoma, may increase the likelihood of non-adherence to treatment [7, 8]. In view of these concerns, it is of therapeutic interest to explore alternative treatments with fewer side effects to improve the therapeutic efficacy.

With fewer side effects, Chinese herbal medicines (CHMs) have been one of the mainstream therapies in Asian countries [9]. For example, it was widely used for those with some critical illnesses, including dementia [10], hepatocellular carcinoma [11], and vertigo [12], or for symptom management in cancer palliative care [13]. Based on the traditional Chinese medicine (TCM) theory, OS is believed to occur due to the deficiency of Shen (kidney) essence, which plays a decisive role in nourishing the bone and strengthening the skeleton [14, 15]. Several Chinese herbal formulae, such as kidney-stabilizing herbs, have been proven to exert bone-protecting effects for those with OS by relieving the Shen-Jing deficiency (kidney essence) syndrome [16, 17]. However, to our knowledge, there is still a paucity of information concerning the long-term effect of CHMs against the onset of osteoporotic fracture, especially for those with high susceptibility of this disease, namely OS individuals.

To address this gap in the extant literature, we employed a nationwide population-based database to assess the risk of bone fracture among OS patients who either received or did not receive CHMs, which may help clarify its effect on the prognosis of bone fracture and serve as a reference for instituting more efficient treatments for OS patients.

Methods

Data source

The subjects of this cohort study were retrieved from a national representative sample of the Longitudinal Health Insurance Database [18], which is managed by the National Health Insurance Administration and provided for public access. Taiwan launched a single-payer NHI program in 1995, covering more than 25 million enrollees, representing approximately 98% of the population in Taiwan [18]. The LHID, a subdataset of the NHI program, is made up of 1 million randomly sampled patients. Data on patients who were alive in 2000 were collected from medical records of these individuals for the time period of 1996 to 2012. Because a multistage stratified systematic sampling method was used, no statistically significant differences regarding sex or age were observed between the 1 million insured individuals and the general population. This database contains all NHI enrollment files, claims data, and a prescription drug registry and provides comprehensive utilization information for the subjects covered by the insurance program. To date, more than 400 published papers have used this database as the basis for their studies [18]. This study was conducted in accordance with the Helsinki Declaration, and it was evaluated and approved by the local Institutional Review Board and Ethics Committee of Buddhist Dalin Tzu Chi Hospital (No. B10004021-2).

Study population

Newly diagnosed patients with OS during the period of January 1, 1998, to December 31, 2010, were identified (Fig. 1). To be included, patients with OS had to have at least three ambulatory or inpatient claims with diagnosis of ICD-9-CM code 733.0. Index date was defined as the date of the first diagnosis of OS. Exclusion criteria included patients younger than 20 years, those who had a diagnosis of osteoporotic fracture prior to OS diagnosis, or patients who were followed for less than one year. Based on a former approach [19, 20], the main event of interest, osteoporotic fracture, included any fracture except those of the skull, face, fingers, or toes, and was defined by the time an osteoporotic fracture (ICD-9-CM codes 733.1 and 805-to-829) or fracture-related surgery first appeared

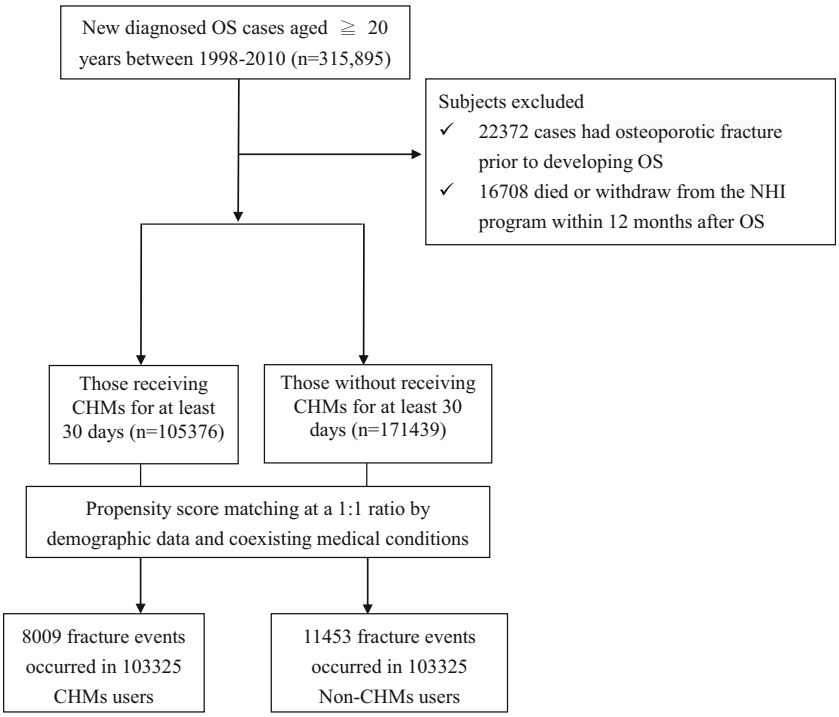

Fig. 1 Flowchart of selection and follow-up of study subjects

in the inpatient or outpatient claim records, which contained ICD-9-CM codes 78.1 (application of external fixation device), 78.4 (other repair or plastic operation on bone), 78.5 (internal fixation of bone without fracture reduction), 78.9 (insertion of bone growth stimulator), 79 (reduction of fracture and dislocation), and 81 (repair and plastic operations on joint structures). Thereafter, the enrollees who received CHM treatment due to OS for more than 30 days were identified as the CHMs, and the remaining cases were classified as no-CHM users [12]. Propensity score approaches were then applied to reduce confounding effects by the indication of the CHM treatment. We used a 1:1 propensity score match by sex, age (per 5 years), comorbidities, and the year in which OS was first diagnosed through multiple logistic regression analysis. Ultimately, equal numbers of patients in the CHMs and no-CHM cohorts were analyzed in this study. Additionally, to decrease the immortal time bias, since delay in first time use of CHMs following OS onset may induce overestimation of the intervention's beneficial effect, the index date of the follow-up period for OS patients with CHM usage was assigned to the first date of the initiation of the CHM treatment, whereas the index date of the follow-up period for OS subjects who were classified as non-CHM users was assigned to the date of the first OS diagnosis [21–23]. The end date of the follow-up period for both groups was assigned as the date of the earliest of one of the following: a diagnosis of fracture, the date of withdrawal from the insurance program, or the date of December 31, 2012.

Demographic variables and disease characteristics

Demographic variables considered in this study included patient's age, gender, income (for estimating insurance payments), and urbanization level of the subject's residential area. The subjects' monthly incomes were stratified into the following 3 levels: ≤ New Taiwan Dollar (NTD) 17,880; NTD 17,881–NTD 43,900; and ≥ NTD 43,901. Urbanization levels were divided into the following 3 strata: urban (levels 1–2), suburban (levels 3–4), and rural (levels 5–7) areas. Level 1 refers to the "most urbanized" communities, and level 7 refers to the "least urbanized" communities [24]. Disease characteristics included the presence of a chronic disease, and these characteristics were evaluated by using the established Charlson-Deyo comorbidity index (CCI) [25] and based on individual medical records one year prior to initial cohort entry. Additionally, anti-osteoporotic medication usage was stratified into two groups according to whether the subjects received calcium supplements, vitamin D, calcitonin, bisphosphates, selective estrogen receptor modulators (SERMs), sex hormones, strontium, or RANKL inhibitors for more than six months after the index date.

Statistical analysis

The demographic data and disease characteristics of the CHM users and non-CHM users were compared using chi-square test and Student's T-test as appropriate. Incidence rate of fracture is presented as number of cases per 1000 person-years (PYs). The Cox proportional hazard regression analysis was

then applied to compute the hazard ratio (HR) with 95% confidence intervals of fracture risk in association with CHM use. To test the robustness of the relationship between CHM use and the subsequent fracture risk, we divided the CHM users into the following four subgroups: the first group used CHMs for 30 to 180 days, the second group used CHMs for 181 to 365 days, the third group used CHMs for 366 to 730 days, and the fourth group used CHMs for more than 730 days. Additionally, the Kaplan-Meier failure estimates of fracture risk were plotted and differences between the four groups (including non-users) were examined by the log-rank test. Analysis stratified by age and gender using Cox proportional hazard regression was also conducted to assess the HR of fracture among those who received and did not receive CHMs. Assumptions of the proportional hazards model were verified by using plots of log (−log (survival) function) vs log (time) and Schoenfeld residuals vs time. All analyses were conducted using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA), at a $p < 0.05$ statistically significant level.

Results

The CHM user and non-CHM user cohorts provided data for 103,325 and 103,325 patients, respectively. After matching procedure with propensity score, there was no significant difference between the two groups in age, sex, monthly income, residential area, medication usage, and CCI score, indicating the two groups to be comparable on these characteristics (Table 1).

Among all eligible subjects with OS, 19,462 first episodes of fracture occurred in 11,453 non-CHM users and 8009 in CHM users, during the follow-up periods of 883,528.87 and 864,945.94 PYs, respectively. The incidence rate of fracture was lower in CHM users than in non-CHM users (12.96 vs 9.26, respectively, per 1000 PYs), with an adjusted HR of 0.73 (95% CI = 0.70–0.75) (Table 2). Of note, those who used CHMs for more than two years had a 54% decreased risk of fracture (95% CI = 0.39–0.50). Based on Kaplan-Meier survival curve and log-rank test results, the data also supported a statistically significant difference regarding the survival rate of free from fracture across the groups during the follow-up period. Those receiving CHMs for more than two years had significantly lower incidence rate of fracture than those not receiving CHMs ($p < 0.001$) (Fig. 2).

Table 3 presents the results from this analysis, stratified by age and gender. Both female and male patients receiving CHMs had a lower risk of fracture with an adjusted HR of 0.72 (95% CI = 0.70–0.77) and 0.76 (95% CI = 0.72–0.79), respectively. Collectively, the significant beneficial effects of CHMs were observed among the younger subjects, irrespective of gender. In female subjects, decreases in adjusted HR were greater for CHM users aged ≦ 50 years (adjusted HR 0.62; 95% CI = 0.58–0.66); in male subjects, the effect of CHMs in reducing the fracture risk was also more prominent for those aged ≦ 50 years, with an adjusted HR of 0.61 (95% CI = 0.56–0.65).

Table 1 Demographic data and selected comorbidities of the study subjects

Variables	Non-CHM users $n = 103,325$ (%)	CHM users $n = 103,325$ (%)	P value
Age (yr)			0.96
≤ 50	68,539 (70.6)	68,549 (70.7)	
> 50	28,478 (29.4)	28,468 (29.3)	
Mean (SD)	41.76 (13.1)	41.70 (13.7)	0.89
Gender			0.99
Female	67,681 (69.8)	67,681 (69.8)	
Male	29,336 (30.2)	29,336 (30.2)	
Monthly income			0.96
Low	53,101 (54.7)	53,165 (54.8)	
Median	39,856 (41.1)	39,928 (41.2)	
High	4060 (4.2)	3924 (4.0)	
Residential area			0.30
Urban	57,632 (59.4)	57,584 (59.4)	
Suburban	15,961 (16.5)	15,961 (16.5)	
Rural	23,424 (24.1)	23,472 (24.1)	
Medication usage			0.23
Yes	85,657 (82.9)	85,453 (82.7)	
No	17,668 (17.1)	17,872 (17.3)	
CCI			0.06
Mean (SD)	1.40 (4.3)	1.43 (4.3)	

CHMs, Chinese herbal medicines; SD, standard deviation; CCI, Charlson-Deyo comorbidity index

The most commonly prescribed Chinese medicine products for OS patients are also summarized in Table 4. Nine Chinese medicine products were found to lessen the subsequent risk of fracture, including Yan Hu Suo (Rhizoma Corydalis), Huang Qin (Scutellaria Baicale), Jie Geng (*Platycodon grandifloras*), Xiang Fu (*Cyperus rotundus*), Hai Piao Xiao (Cuttlebone Sepium), Jia-Wei-Xiao-Yao-San, Ge-Gen-Tang, Shao-Yao-Gan-Cao-Tang, and Du-Huo-Ji-Sheng-Tang.

Discussion

To our knowledge, no research had been done to assess the relationship between CHM use and subsequent fracture risk in OS patients. This is the first population-based cohort study to apply large nationwide claims-based data to address this concern, allowing for more robust validation of findings regarding the clinical benefits of CHMs for OS patients.

Table 2 Risk of osteoporotic fracture for OS subjects with and without CHMs

Patient group	Event	PYs	Incidence	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Non-CHM users	11,453	883,528.87	12.96	1	1
CHM users	8009	864,945.94	9.26	0.71 (0.69–0.74)	0.73 (0.70–0.75)
CHM use within 30–180 days	5465	536,445.48	10.18	0.79 (0.77–0.82)	0.81 (0.79–0.84)
CHM use within 181–365 days	1427	167,898.95	8.50	0.66 (0.62–0.69)	0.68 (0.64–0.72)
CHM use within 366 to 730 days	765	102,833.82	7.44	0.57 (0.53–0.61)	0.58 (0.54–0.62)
CHM use for more than 730 days	352	58,067.7	6.06	0.46 (0.41–0.51)	0.46 (0.39–0.50)

[a] Model adjusted for age, gender, urbanization level, monthly income, medication usage, and CCI score

This study cleared up the risk of bone fracture that was reduced by nearly 30% in the patients who received CHMs, as compared to those who were non-CHM users. It is also instructive that those using CHMs for more than 730 days experienced a 54% decreased risk of developing fracture. This dose-response relation may indicate a causal link between CHM use and a decrease in the predisposition for fracture. No previous studies have been reported to directly determine the long-tern impact of CHMs on fracture risk among OS cases, thus rendering a comparison of results impossible. However, the positive therapeutic effect of CHMs observed in this study is pertinent to the earlier report and further adds to the growing body of literature on this topic [17, 26]. Based on the TCM theory, OS was related to deficiency of Shen essence. Several components in the Chinese herbal formulas, such as icariin, flavones, glycosides, and organic acids, were proven to significantly increase the bone mineral density of lumbar vertebrate through promoting growth and repair of bone, thus preventing skeletal disorders from worsening [27].

Additionally, we discovered a more dominant effect of CHMs on fracture risk in younger subjects, irrespective of gender, and this finding appears compatible with those of previous studies that showed a significant association between use of CHMs and the risk of events of interest (e.g., hepatocellular carcinoma and stroke) among younger patients [11, 12]. It is possible that younger subjects may have fewer coexisting medical conditions or possess better medical knowledge, in addition to demonstrating more positive attitudes towards medical impairments [28], thus enhancing the preventive impact of CHMs on fracture risk.

An additional contribution of this work is the list of Chinese herbal products that were beneficial in reducing fracture risk. For example, among the commonly prescribed multi-herb products, we noted that Du-Huo-Ji-Sheng-Tang could decrease the subsequent risk of fracture by 38%. A former study reported that the ingredient Du-Huo-Ji-Sheng-Tang is helpful in boosting the osteogenic activity by activating the estrogen receptor alpha, thus stimulating osteoblast

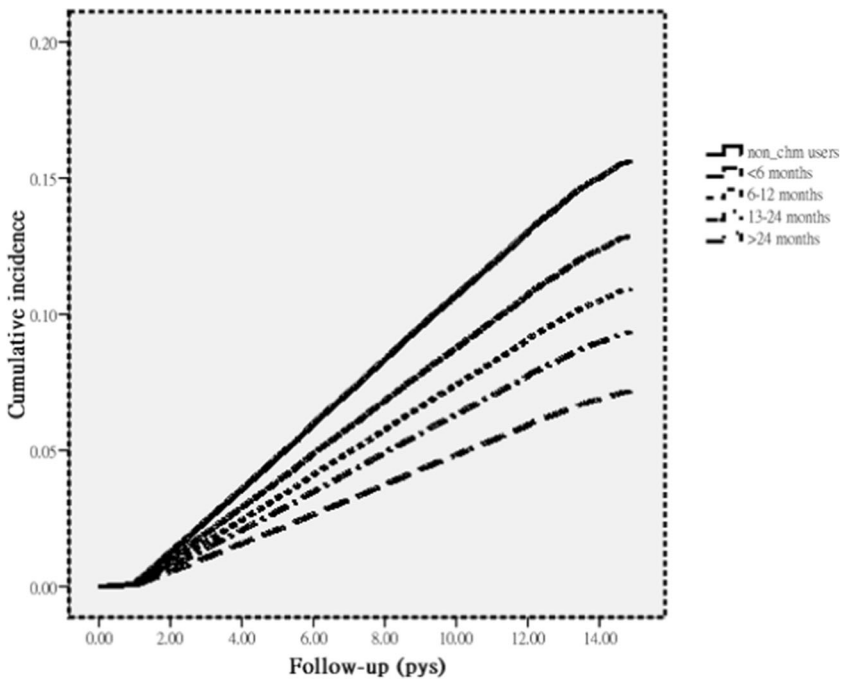

Fig. 2 Comparison of Kaplan-Meier failure estimates of fracture onset among the four groups

Table 3 Incidence and fracture risk for OS patients with and without CHMs in the stratification of sex and age

Variables	Non-CHM users			CHM users			Crude HR (95% CI)	Adjusted HR (95% CI)
	Case	PYs	Incidence	Case	PYs	Incidence		
Female								
<= 50	3347	431,654.82	7.75	2116	437,197.31	4.84	0.62 (0.57–0.66)	0.62[a] (0.58–0.66)
> 50	4518	167,808.36	26.92	3336	157,087.06	21.24	0.77 (0.74–0.82)	0.78[a] (0.75–0.82)
All	7865	599,463.18	13.12	5452	594,284.37	9.17	0.73 (0.70–0.78)	0.72[b] (0.70–0.77)
Male								
<= 50	2000	163,611.67	12.22	1206	159,302	7.57	0.60 (0.59–0.65)	0.61[a] (0.56–0.65)
> 50	1588	120,454.02	13.18	1351	111,359.57	12.13	0.91 (0.84–0.98)	0.93[a] (0.86–0.99)
All	3588	284,065.69	12.63	2557	270,661.57	9.45	0.75 (0.71–0.77)	0.76[b] (0.72–0.79)

[a] Model adjusted for urbanization level, monthly income, medication usage, and CCI score

[b] Model adjusted for age, urbanization level, monthly income, medication usage, and CCI score

differentiation to synthesize the bone-specific extracellular matrix proteins necessary for mineralization [29].

The positive effect of Jia-Wei-Xiao-Yao-San on the susceptibility of fracture was also found in this study. Finding from a murine model reported that Jia-Wei-Xiao-Yao-San could prevent natural and surgical menopausal bone loss by increasing bone density and altering bone histomorphology [30]. Meanwhile, this formula showed good compliance with treatment regimen and appeared to be medically safe for relief of climacteric symptoms among postmenopausal women [31]. In agreement with a prior report [32], Ge-Gen-Tang was found to be related to reduced risk of fracture onset. It was inferred that

Table 4 Risk of fracture in relation to the top 10 used single-herb and multi-herb products for OS patients

Chinese herbal name	Total prescribed visits	Mean prescribed days per visit	Daily dose (g)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Single-herb products					
Yan Hu Suo	223,158	7.3	8.1	0.59 (0.51–0.67)	0.62 (0.54–0.66)
Da Huang	191,721	7.0	6.0	0.79 (0.61–0.97)	0.81 (0.63–1.01)
Huang Qin	186,290	7.6	10.2	0.65 (0.60–0.69)	0.65 (0.62–0.68)
Jie Geng	178,859	6.1	8.0	0.62 (0.52–0.68)	0.64 (0.53–0.70)
Bei Mu	162,273	6.9	7.9	0.71 (0.66–0.75)	0.73 (0.65–0.77)
Bai Zhi	141,125	7.2	8.8	0.77 (0.40–1.11)	0.77 (0.43–1.12)
Xiang Fu	130,179	7.2	8.4	0.60 (0.55–0.68)	0.62 (0.57–0.69)
Ge Gen	116,428	8.4	8.4	0.91 (0.79–1.10)	0.90 (0.71–1.13)
Hai Piao Xiao	100,321	6.7	6.7	0.62 (0.59–0.68)	0.64 (0.61–0.72)
Chuan Qi	91,213	9.7	9.1	1.09 (0.90–1.19)	1.10 (0.92–1.17)
Multi-herb products					
Jia-Wei-Xiao-Yao-San	249,937	6.4	8.9	0.64 (0.54–0.69)	0.67 (0.62–0.71)
Shu-Jing-Huo-Xie-Tang	182,456	6.1	8.3	0.96 (0.91–1.06)	0.97 (0.91–1.10)
Ge-Gen-Tang	179,924	6.4	10.4	0.70 (0.66–0.75)	0.73 (0.69–0.77)
Chuan-Xiong-Cha-Tiao-San	148,659	6.3	9.5	0.68 (0.54–0.97)	0.69 (0.55–1.01)
Shao-Yao-Gan-Cao-Tang	135,609	6.2	7.8	0.64 (0.44–0.97)	0.68 (0.47–0.98)
Yin-Qiao-San	123,028	6.6	8.0	0.87 (0.79–1.08)	0.88 (0.77–1.06)
Ping-Wei-San	122,931	5.0	6.5	0.86 (0.76–1.09)	0.90 (0.75–1.05)
Gan-Lu-Yin	119,756	5.6	6.3	0.66 (0.48–0.97)	0.68 (0.47–1.01)
Du-Huo-Ji-Sheng-Tang	109,832	4.8	5.9	0.61 (0.56–0.66)	0.62 (0.60–0.67)
Long-Dan-Xie-Gan-Tang	88,927	5.1	4.2	1.03 (0.95–1.11)	1.04 (0.96–1.11)

[a] Model adjusted for age, gender, urbanization level, monthly income, medication usage, and CCI score

its major ingredient, Ge Gen, might ameliorate bone loss via down-regulating bone turnover markers, such as plasma alkaline phosphatase and osteocalcin [33]. Additional evidence showed that Ge Gen could be used to treat bone loss caused by estrogen deficiency [32, 34]. Accordingly, we recommend that Jia-Wei-Xiao-Yao-San and Ge-Gen-Tang may be considered in treating bone diseases in elderly females.

Another commonly used multi-herb product, Shao-Yao-Gan-Cao-Tang, was also found to be related to the lower risk of fracture. We speculated that this prescription had a pronounced anti-arthritic effect by inhibiting the production of inflammatory mediators that played an important role in the induction of matrix metalloproteinase generation and osteoclast activation [35, 36], thus lowering the vulnerability to fracture.

With regard to the commonly used single-herb products, we observed that those who used Yan Hu Suo were at a lower risk of having fracture. An in vitro study described that this remedy inhibited osteoclast proliferation through the increase of mitochondrial pro-apoptotic protein expression and up-regulation of caspase activity [37], which may account for the positive effect of Yan Hu Suo on the reduction of fracture events. Another single-drug prescription, Jie Geng, has been shown to significantly reduce the risk of fracture as well. We inferred that this product was related to the upregulation of alkaline phosphatase and the expression of osteogenic marker genes, such as runt-related transcription factor 2, which is a transcription factor closely associated with osteoblast phenotype [16].

We noted that Xiang Fu (*Cyperus rotundus*) is not only a commonly used prescription medication but also can attenuate fracture risk. This single-herb product was beneficial in reducing the mRNA expression of osteoclast-associated genes, such as the receptor activator of nuclear factor κ B, carbonic anhydrase II, cathepsin K, and tartrate-resistant acid phosphatase [38], all of which may cause accelerated bone loss. In addition, this study showed that Huang Qin could lessen the lower risk of fracture. A prior ovariectomized rat model showed that baicalin, a main ingredient of Huang Qin, enhances the activity of alkaline phosphatase [39], which played an important role in the mineralization of bones. Similar to previous reports [40, 41], the findings of the present study indicated the preventive effect of Hai Piao Xiao on the reduction of fracture risk. It could be argued that this product promotes the repair of bone defect by stimulating osteogenesis [41], which in turn reduces the risk of onset of bone disease.

Despite the clinical and research implications suggested by the present study, there are some important limitations to consider. First, coding error of disease is always a possibility in an administrative database. To minimize this bias, we only enrolled subjects with OS or osteoporotic fracture, and only after the patients had either at least three outpatient visits, reporting consistent diagnoses, or after they had at least one inpatient admission. It should also be noted that the NHI of Taiwan randomly samples claims from hospitals, interviews patients, and reviews medical charts to verify the accuracy of medical records [18]. Second, information on health behaviors, coping strategies and resources, physical activity, or dietary intake was not available from the claims data, therefore confounding effects by indication may exist. Nonetheless, given the magnitude and statistical significance of the observed effect in this large-scale cohort study, these limitations were not likely to have compromised our findings. Future research is, however, needed to better assess if the present findings are replicable across diverse groups of individuals, after considering the uncontrolled variables of the present study. Third, we were unable to contact the enrolled patients directly regarding their use of Chinese herbal products, due to the anonymity of identification numbers in the database. However, over 95% of the dose frequencies in Chinese herbs are typically used for only one week in clinical practice; so, those who continued to receive the same prescription for a longer period of time were, therefore, likely to have used the prescribed medication [42]. Fourth, prescriptions for medications issued before 1996 were not reflected in our data analysis. This omission could possibly result in underestimation of the cumulative frequencies and may have weakened the effect of the specified herbal products. Fifth, although our study revealed a substantial benefit resulting from the use of CHMs with OS patients, it must be recognized that these patients were not randomly categorized into users and non-users. Therefore, caution should be exerted when interpreting the findings, especially regarding daily drug dosage. 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. Notwithstanding these limitations, the strengths of this study must also be acknowledged and these include the immediate availability of data, the comprehensiveness of the database, and the statistical power derived from the sample's large size.

Conclusion

This is the first large-scale nationwide cohort study to investigate the effect of CHMs on the risk of osteoporotic fractures among OS patients. The findings could serve as a reference to further determine the association of CHM products with the development of various bone fractures. We found that the integration of CHMs during treatment of OS was beneficial to lessen osteoporotic fracture risk by 25%. Results of this study may serve as a reference for healthcare providers to establish more effective therapeutic interventions that seek to improve the prognosis of individuals with OS.

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Compliance with ethical standards

Conflicts of interest Chen WJ, Livneh H, Hsieh MH, Yeh CC, Yeh MH, Lu MC, Chien JT, and Tsai TY declare that they have no conflict of interest.

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