Observational Study

Medicine

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Role of traditional Chinese medicine on fracture, hospitalization, and total mortality risks in patients with hyperthyroidism and osteoporosis

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Abstract

Previous studies have confirmed that hyperthyroidism is one of the common causes of secondary osteoporosis and can aggravate the disease severity in patients with osteoporosis. This study is mainly based on the Taiwan National Health Insurance Database and through big data analysis shows that combining traditional Chinese medicine (TCM) treatment can help the health of patients with hyperthyroidism and osteoporosis. There were 4980 patients who received TCM treatment and 19,920 controls who did not receive TCM treatment selected from Taiwan National Health Insurance Database in a 4:1 ratio of gender, age, and index year. Cox proportional hazards analyzes were performed to compare fracture, inpatient, and all-cause mortality over an average follow-up period of 15 years. A total of 4745/5823/3487 enrolled subjects (19.06%/23.39%/14.00%) suffered fractures/hospitalization/all-cause death which TCM group was 452/987/511 (15.10%/19.82%/10.26%); control group was 3993/4836/2976 (20.05%/24.28%/14.94%). Cox proportional hazards regression analysis showed that subjects in the TCM group had lower fractures, hospital mortality, and all-cause mortality (adjusted HR = 0.563; 95% confidence intervals [CI] = 0.392–0.680, $P < .001$; adjusted HR = 0.614; 95% CI = 0.474–0.714, $P < .001$; adjusted HR = 0.691; 95% CI = 0.569–0.792, $P < .001$). Kaplan–Meier analysis showed that the cumulative risk of fracture, hospitalization and death were lower in TCM group with significant differences (all log-rank $P < .001$). The analysis of this study shows that patients with hyperthyroidism and osteoporosis even with comorbidity of atrial fibrillation, atrial flutter, or heart failure combined with TCM treatment are associated with a lower risk of fractures, hospitalization, or all-cause death, providing clinicians with a treatment option.

Abbreviations: Af = atrial fibrillation, AF = atrial flutter, BMD = bone mineral density, CCI = Charlson comorbidity index, CI = confidence intervals, HR = hazard ratios, ICD = International Classification of Diseases, NHI = National Health Insurance, SD = standard deviations, TCM = traditional Chinese medicine, TNHID = Taiwan National Health Insurance Database.

Keywords: hyperthyroidism, osteoporosis, Taiwan National Health Insurance Database, traditional Chinese medicine

1. Introduction

Osteoporosis refers to the reduction of bone mass and the weakening of bone structure, causing bones to be fragile and prone to further fractures.[1] Primary osteoporosis is caused by aging and occurs in older men and postmenopausal women,[2] while secondary osteoporosis is often caused by drugs or other diseases.[3] The population in Taiwan is gradually aging, so the treatment of osteoporosis is an issue that cannot be ignored.

Y-CH, C-HL, and W-CC contributed equally to this work.

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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About 30% of postmenopausal women and 50% to 80% of elderly men[4,5] are found to have osteoporosis caused by other diseases. The causes of secondary osteoporosis include drugs, chronic inflammation, kidney disease, and endocrine diseases.[3] Hyperthyroidism is one of the common causes of secondary osteoporosis among endocrine diseases.[6] Thyroxine controls metabolic functions throughout the body, and in the case of bones, affects bone development and maximum bone mass.[7] Hyperthyroidism will produce too much thyroxine, causing the bone turnover to accelerate and the bone remodeling cycle to become shorter. However, the regeneration of bone does not keep up with the resorption of old bone tissue, so every time that a period of bone remodeling can cause bone loss.[8] A comprehensive analysis of 25 studies showed that if patients with hyperthyroidism are not well controlled, they will have a significant decrease in bone density and an increased risk of hip fractures. If patients with hyperthyroidism are treated, bone density will be significantly improved.[9]

If only drugs for osteoporosis are given without simultaneously treating the underlying disease, the effect of treating osteoporosis will be worse than expected.[10] Therefore, analgesics, anti-inflammatory drugs, calcium supplements, etc are sometimes added, but these treatments sometimes cause patients to experience adverse reactions such as gastrointestinal inflammation, ulcers, and kidney injury. Due to the occurrence of these adverse effects, the treatment methods of traditional Chinese medicine (TCM) have gradually attracted the attention and choice of the public.[11] However, there are relatively few studies discussing whether combined TCM treatment can reduce the risk of fracture, hospitalization, and death in patients with hyperthyroidism and osteoporosis. Therefore, this study mainly used big data analysis through the Taiwan National Health Insurance Database (TNHID) has proven that combining TCM treatment can be helpful for patients with hyperthyroidism and osteoporosis.

2. Materials and methods

2.1. Data source

Patients with hyperthyroidism and osteoporosis were included from TNHID. We used data from the TNHID from 2000 to 2015 to investigate whether combined TCM treatment could reduce fractures, hospitalizations, or all-cause mortality in patients with hyperthyroidism and osteoporosis over a 15-year follow-up period. TNHID uses the International Classification of Diseases (ICD), 9th Revision, Clinical Modification (ICD-9-CM) to record categorical diagnoses. All diagnoses of

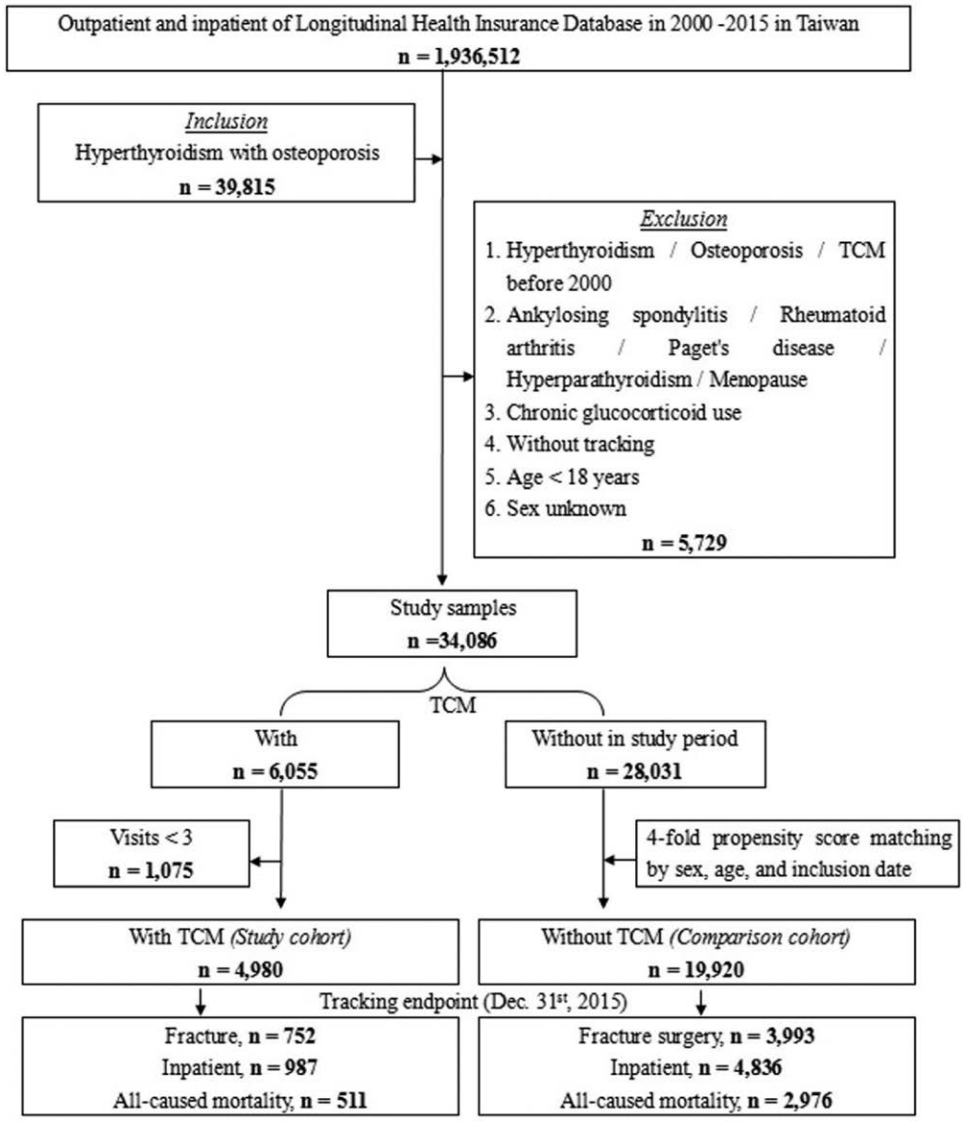

Figure 1. The flowchart of study.

hyperthyroidism and osteoporosis were made by specialist physicians. Taiwan National Health Insurance (NHI) Program launched in 1995, and as of 2009 it had contracted with 97% of medical providers in Taiwan. The NHI randomly reviewed records related to every 100 outpatient visits and every 20 hospitalizations to verify the accuracy of diagnoses. As of today, there are many studies confirming the accuracy and effectiveness of TNHID diagnosis.[12–14]

2.2. Research design and sample participants

Our study used a retrospective matched cohort design. From January 1, 2000, to December 31, 2015, diagnoses of osteoporosis and hyperthyroidism were selected based on the codes ICD-9-CM 733.XX (osteoporosis) and ICD-9-CM 242.XX (hyperthyroidism), respectively. Based on these ICD-9-CM codes, each enrolled patient had at least 3 recorded outpatient visits during the study period, and patients who received <3 TCM treatments and were younger than 18 years were excluded. The catastrophic illness registry has collected each type of catastrophic disease including all malignant diseases. Covariates included Charlson comorbidity index (CCI) minus osteoporosis, hyperthyroidism, sex, and age. We also included common comorbidities of hyperthyroidism, such as atrial fibrillation (Af) (427.31), atrial flutter (AF) (427.32), and heart failure (HF) (428.xx), in the analysis. The CCI online calculation tool can predict the 10-year survival rate of patients with multiple comorbidities. TCM includes concentrated preparations of scientific Chinese medicine and decoctions. Scientific Chinese medicine is covered by the NHI and is included in the NHI database. In contrast, decoctions are not covered by NHI and therefore are not recorded in the database. Commonly used medications for the treatment of hyperthyroidism and osteoporosis were also analyzed (as in Table S1, Supplemental Digital Content, https://links.lww.com/MD/O941). The patients' registered insurance fees by monthly income were categorized as high > NTD$40,000 (USD$1250), middle NTD$20,000–40,000 (USD$625–1250), and low < NTD$20,000 (USD$625).

2.3. Outcome measures

All study participants were followed from index date to hospitalization or death until the end of 2015 under the NHI scheme.

2.4. Statistical analysis

All statistical analyzes were performed using SPSS software version 22 for Windows (SPSS Inc., Chicago, IL). Chi-square and *t* tests were used to evaluate the distribution of categorical and continuous variables, respectively. Multivariable Cox proportional hazards regression analysis was used to determine the risk of fracture, hospitalization, or death in patients with hyperthyroidism and osteoporosis treated with TCM. Statistical analysis results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). Differences in risk of fracture, hospitalization, or death between groups receiving and not receiving TCM were estimated using the Kaplan–Meier method and the log-rank test. Statistical significance was determined using a two-tailed test with a *P* value <.05.

2.5. Ethics

Our study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Institutional Review Board of Tri-Service General Hospital (TSGH) approved our study and waived the need for individual written informed consent (TSGH IRB No. B-110-17).

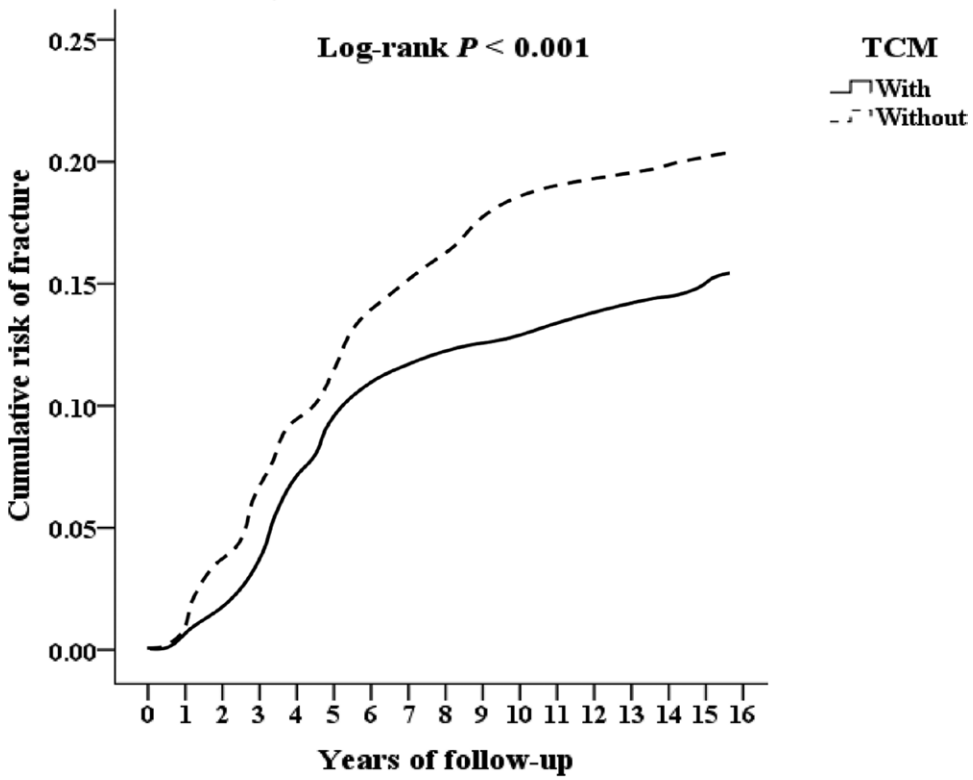

Figure 2. Kaplan–Meier for cumulative risk of fracture among hyperthyroidism with osteoporosis aged 18 and over stratified by TCM with log-rank test. TCM = traditional Chinese medicine.

3. Results

We included 39,815 patients with hyperthyroidism and osteoporosis, excluding those who had been diagnosed with hyperthyroidism, osteoporosis or received TCM treatment before 2000, and were known to have bone metabolism diseases, including ankylosing spondylitis, rheumatoid arthritis,

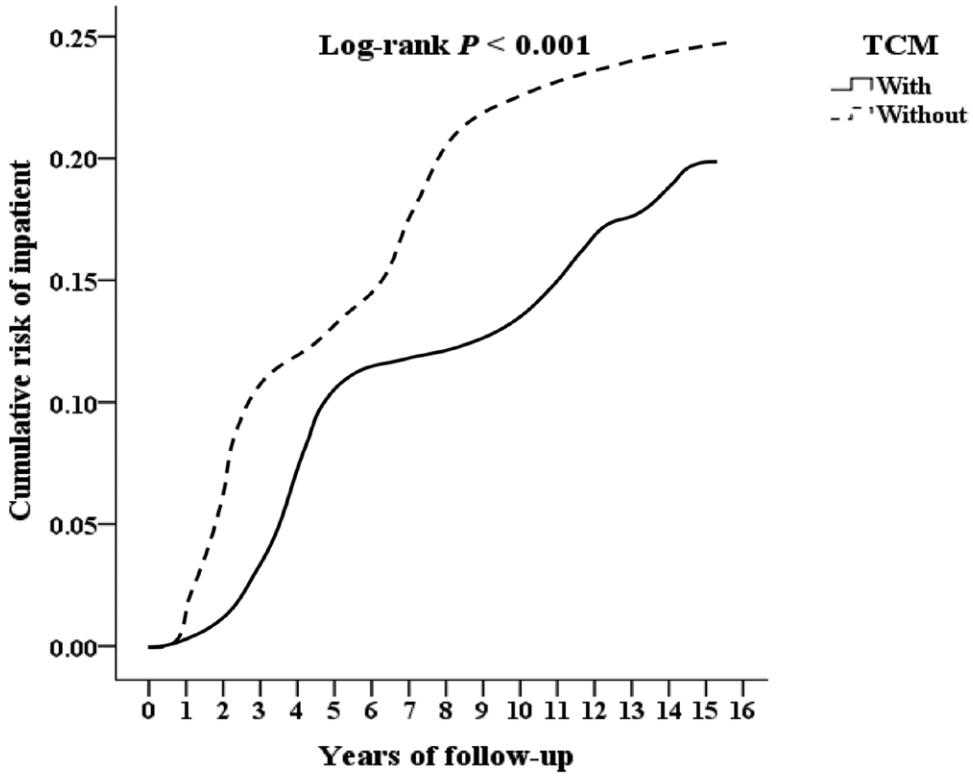

Figure 3. Kaplan–Meier for cumulative risk of inpatient among hyperthyroidism with osteoporosis aged 18 and over stratified by TCM with log-rank test. TCM = traditional Chinese medicine.

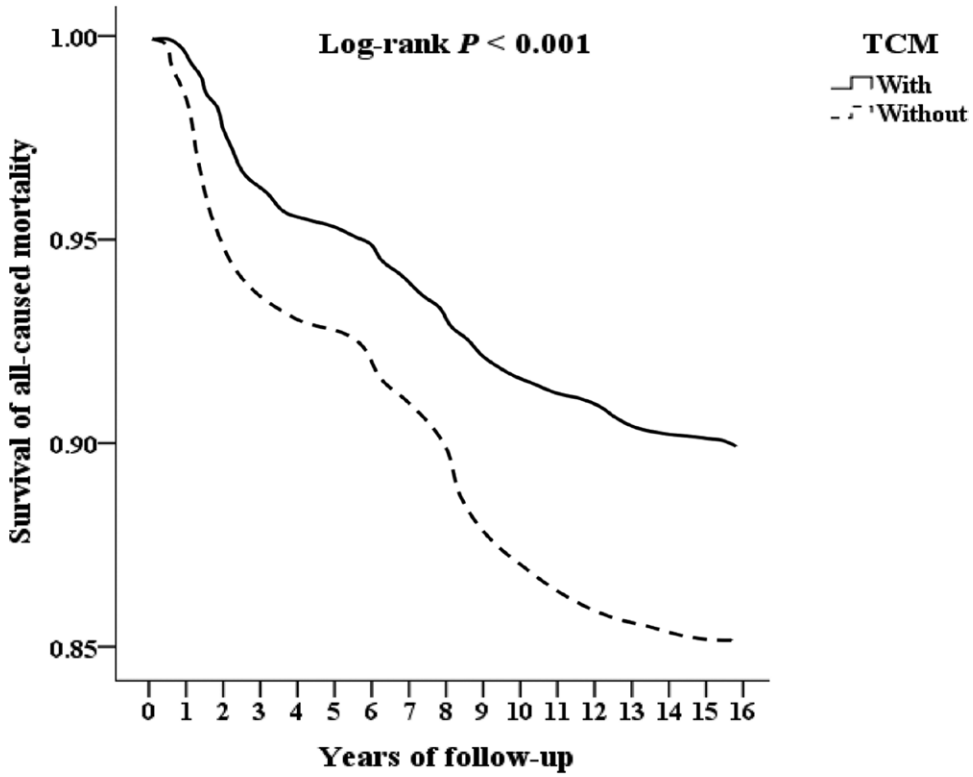

Figure 4. Kaplan–Meier for survival of all-caused mortality among hyperthyroidism with osteoporosis patients aged 18 and over stratified by TCM with log-rank test. TCM = traditional Chinese medicine.

Paget, and parathyroid function. There were 5729 patients with postmenopausal women, patients with long-term steroid use, no follow-up records, patients younger than 18 years old, and patients of unknown gender. Finally, 34,086 patients were included. There were 6055 people who received TCM treatment, and 1075 people who had less than 3 outpatient follow-up visits were excluded. Finally, there were 4980 patients who received TCM treatment. There were 28,031 people who did not receive TCM treatment, and 19,920 people who did not receive TCM treatment were included in the control group by matching gender, age, and inclusion date with a 4:1 propensity score. There were 752 fracture surgeries, 987 hospitalizations, and 511 deaths that received TCM treatment. Among those who did not receive TCM treatment, there were 3993 fracture surgeries, 4836 hospitalizations, and 2976 deaths, as shown in Figure 1. Kaplan–Meier analysis showed that the cumulative risk of fracture, hospitalization, and death in patients who received TCM treatment was lower than that of patients who did not receive TCM treatment, with statistical significance (all log-rank $P < .001$), as shown in Figures 2 to 4.

Table 1 presents the baseline characteristics of the study population, including sex, age, low income status, comorbidities such as Af, AF, and HF, treatments for hyperthyroidism and osteoporosis, as well as disease severity. Among the 24,900 patients with both hyperthyroidism and osteoporosis, 16,040 (64.42%) were female and 8860 (35.58%) were male, with a mean age of 45.88 ± 15.57 years. There were no significant differences between the TCM treatment group and the control group in terms of gender, age, low income status, comorbidities (Af, AF, and HF), and treatments for hyperthyroidism and osteoporosis. However, regarding catastrophic illness and CCI_R, the TCM treatment group exhibited significantly greater disease severity compared to the control group ($P < .05$).

Table 2 shows the end of the follow-up period, the rates of fracture surgery, hospitalization, and all-cause mortality were lower in the TCM group compared to the control group. A total of 4745 subjects (19.06%) underwent surgical treatment for fractures, including 752 in the TCM group and 3993 in the control group (15.10% vs 20.05%, $P < .001$). Overall, 5823 patients (23.39%) were hospitalized, comprising 987 in the TCM group and 4836 in the control group (19.82% vs 24.28%, $P < .001$). There were 3487 deaths (14.00%) during follow-up, with 511 in the TCM group and 2976 in the control group (10.26% vs 14.94%, $P < .001$). There were no significant differences between the TCM and control groups in terms of gender, age, low income, comorbidities (Af, AF, and HF), and treatments for hyperthyroidism and osteoporosis. However, regarding catastrophic illness and CCI_R, the TCM treatment group exhibited significantly greater disease severity compared to the control group ($P < .001$).

Table 3 shows factors affecting Cox regression of fracture, hospitalization, and all-cause mortality. Among patients undergoing fracture, we found that patients treated with TCM had a lower proportion of fractures, with an adjusted HR of 0.563 (95% CI = 0.392–0.680, $P < .001$). For those with higher fracture proportions, the adjusted HR for men was 1.172 (95% CI = 1.017–1.342, $P = .041$), and the adjusted HR for patients aged 50 to 59 years was 1.359 (95% CI = 1.111–1.598, $P < .001$), the adjusted HR for patients over 60 years old was 1.414 (95% CI = 1.127–1.634, $P < .001$), and the adjusted HR for low-income patients was 1.215 (95% CI = 1.090–1.417, $P = .005$), and the adjusted HR for those with catastrophic

Table 1

Characteristics of study in the baseline.

TCM	Total		With		Without		
Variables	**n**	**%**	**n**	**%**	**n**	**%**	***P***
Total	24,900		4980	20.00	19,920	80.00	
Sex							.999
Male	8860	35.58	1772	35.58	7088	35.58	
Female	16,040	64.42	3208	64.42	12,832	64.42	
Age (years)	45.88 ± 15.57		45.66 ± 19.27		45.93 ± 19.64		.384
Age groups (years)							.999
18–49	13,890	55.78	2778	55.78	11,112	55.78	
50–59	4120	16.55	824	16.55	3296	16.55	
≧60	6890	27.67	1378	27.67	5512	27.67	
Low-income							.836
Without	23,955	96.20	4794	96.27	19,161	96.19	
With	945	3.80	186	3.73	759	3.81	
Catastrophic illness							.001
Without	20,785	83.47	4079	81.91	16,706	83.87	
With	4115	16.53	901	18.09	3214	16.13	
Atrial fibrillation (Af)							.718
Without	24,597	98.78	4917	98.73	19,680	98.80	
With	303	1.22	63	1.27	240	1.20	
Atrial Flutter (AF)							.497
Without	24,681	99.12	4932	99.04	19,749	99.14	
With	219	0.88	48	0.96	171	0.86	
Heart failure (HF)							.550
Without	24,741	99.36	4945	99.30	19,796	99.38	
With	159	0.64	35	0.70	124	0.62	
Anti-osteoporosis therapy (Tx)							.855
Without	7031	28.24	1401	28.13	5630	28.26	
With	17,869	71.76	3579	71.87	14,290	71.74	
Anti-hyperthyroidism Tx							.285
Without	5177	20.79	1008	20.24	4169	20.93	
With	19,723	79.21	3972	79.76	15,751	79.07	
CCI_R	1.02 ± 1.05		1.10 ± 1.16		1.01 ± 1.04		<.001

P: Chi-square/Fisher exact test on category variables and *t* test on continue variables.

Illness was 1.452 (95% CI = 1.271–1.694, $P < .001$) with higher risk. The adjusted HR for patients with Af/AF/HF were 1.215/1.420/1.632 (95% CI = 1.090–1.417/1.104–1.792/1.359–1.964, all $P < .001$), respectively. The adjusted HR of CCI was 1.215 (95% CI = 1.151–1.340, $P < .001$). Patients who also received TCM treatment had a lower risk of hospitalization with an adjusted HR of 0.614 (95% CI = 0.474–0.714, $P < .001$). The proportion of hospitalizations was higher in men, with an adjusted HR of 1.201 (95% CI = 1.067–1.293, $P = .017$), and in patients aged 50 to 59 years, with an adjusted HR of 1.190 (95% CI = 1.032–1.313, $P = .032$). The adjusted HR for patients over 60 years old was 1.443 (95% CI = 1.200–1.696, $P < .001$), and the adjusted HR for low-income patients was 1.126 (95% CI = 1.107–1.298, $P < .001$). The adjusted HR for patients with catastrophic Illness was 1.442 (95% CI = 1.135–1.667, $P < .001$), and adjusted HR for patients with Af/AF/HF were 1.403/1.597/2.065 (95% CI = 1.100–1.725/1.264–1.831/1.763–2.398, all $P < .001$), respectively. The adjusted HRs for patients with osteoporosis/hyperthyroidism were 1.432/1.420 (95% CI = 1.038–1.879/1.022–1.863, $P = .031/0.039$), respectively and those with higher CCI adjusted HR was 1.147 (95% CI = 1.056–1.224, $P < .001$). In terms of all-cause mortality, patients who received TCM treatment had an adjusted HR of 0.691 (95% CI = 0.569–0.792, $P < .001$), and had a lower mortality rate. All-cause mortality was higher in men, with an adjusted HR of 1.217 (95% CI = 1.040–1.418, $P = .030$), and in patients aged 50 to 59 years, with an adjusted HR of 1.270 (95% CI = 1.065–1.498, $P = .018$). The adjusted HR for patients over 60 years old was 1.444 (95% CI = 1.223–1.650, $P < .001$), and the adjusted HR for low-income patients was 1.201 (95% CI = 1.102–1.358, $P < .001$), and the adjusted HR for patients with catastrophic Illness was 1.495 (95% CI = 1.275–1.765, $P < .001$). The adjusted HRs for patients with Af/AF/HF were 1.424/1.689/2.151 (95% CI = 1.127–1.760/1.301–1.988/1.804–2.462, all $P < .001$), respectively. The adjusted HRs for patients with osteoporosis/hyperthyroidism who received treatment were 1.645/1.792 (95% CI = 1.284–2.007/1.303–2.139, all $P < .001$), and those with higher CCI adjusted HR was 1.149 (95% CI = 1.099–1.211, $P = .001$).

Table 4 further illustrates that the proportion of fractures in patients receiving TCM treatment has a lower adjusted HR of 0.563 (95% CI = 0.392–0.680, $P < .001$). Regardless of gender, age, catastrophic illness, Af/AF/HF patients, osteoporosis/hyperthyroidism patients received treatment, and CCI those fractures in patients receiving TCM treatment that proportions were all low (all $P < .001$). Table 5 goes on to show

Table 2

Characteristics of study in the endpoint.

TCM	Total		With		Without		
Variables	**n**	**%**	**n**	**%**	**n**	**%**	***P***
Total	24,900		4980	20.00	19,920	80.00	
Fracture							<.001
Without	20,155	80.94	4228	84.90	15,927	79.95	
With	4745	19.06	752	15.10	3993	20.05	
Inpatient							<.001
Without	19,077	76.61	3993	80.18	15,084	75.72	
With	5823	23.39	987	19.82	4836	24.28	
All-caused mortality							<.001
Without	21,413	86.00	4469	89.74	16,944	85.06	
With	3487	14.00	511	10.26	2976	14.94	
Sex							.999
Male	8860	35.58	1772	35.58	7088	35.58	
Female	16,040	64.42	3208	64.42	12,832	64.42	
Age (years)	56.65 ± 20.71		56.26 ± 20.24		57.65 ± 20.83		.135
Age groups (years)							.915
18–49	13,493	54.19	2711	54.44	10,782	54.13	
50–59	4152	16.67	829	16.65	3323	16.68	
≧60	7255	29.14	1440	28.92	5815	29.19	
Low-income							.685
Without	23,911	96.03	4777	95.92	19,134	96.05	
With	989	3.97	203	4.08	786	3.95	
Catastrophic illness							<.001
Without	20,748	83.33	4063	81.59	16,685	83.76	
With	4152	16.67	917	18.41	3235	16.24	
Af							.442
Without	24,577	98.70	4910	98.59	19,667	98.73	
With	323	1.30	70	1.41	253	1.27	
AF							.364
Without	24,668	99.07	4928	98.96	19,740	99.10	
With	232	0.93	52	1.04	180	0.90	
HF							.336
Without	24,730	99.32	4941	99.22	19,789	99.34	
With	170	0.68	39	0.78	131	0.66	
Anti-osteoporosis Tx							.833
Without	7015	28.17	1397	28.05	5618	28.20	
With	17,885	71.83	3583	71.95	14,302	71.80	
Anti-hyperthyroidism Tx							.750
Without	5054	20.30	1003	20.14	4051	20.34	
With	19,846	79.70	3977	79.86	15,869	79.66	
CCI_R	1.03 ± 1.07		1.10 ± 1.17		1.02 ± 1.04		<.001

P: Chi-square/Fisher exact test on category variables and *t* test on continue variables.

that the hospitalization rate of patients who received TCM treatment was lower adjusted HR 0.614 (95% CI = 0.474–0.714, $P < .001$). Regardless of gender, age, catastrophic illness, Af/AF/HF patients, osteoporosis/hyperthyroidism patients received treatment and CCI, the hospitalization rate of patients who received TCM treatment that proportions were all low (all $P < .001$). Table 6 further illustrates that patients who receive TCM treatment have lower all-cause mortality, with an adjusted HR of 0.691 (95% CI = 0.569–0.792, $P < .001$). Regardless of gender, age, catastrophic Illness, Af/AF/HF patients, osteoporosis/hyperthyroidism patients received treatment and CCI, patients who receive TCM treatment that all-cause mortality were lower among treated patients (all $P < .001$).

Table 7 shows the factors of prognosis among different TCM subgroups by using Cox regression and Bonferroni correction for multiple comparisons. The factors analyzed include different types of TCM treatments such as using herbal formulae only, acupuncture only, TCM traumatology only, herbal formulae + acupuncture and herbal formulae + TCM traumatology, and analyzed treatments using either herbal formulae, acupuncture or TCM traumatology. Regardless of which single or combined TCM treatment modality was used, patients had a statistically significant reduction in risk of fractures, hospitalization, or death compared with patients who did not use TCM treatment. Otherwise due to decoctions are not covered by NHI and therefore are not recorded in the database. More information about the definition of herbal prescriptions can be found in Table S1, Supplemental Digital Content, https://links.lww.com/MD/O941.

4. Discussion

This study is the first to use a large database to explore whether TCM treatment can effectively reduce the risk of fractures, hospitalization and death in patients with hyperthyroidism and osteoporosis those even with comorbidity of Af, AF or HF. From the results of the study, we know that TCM treatment is a treatment option that can assist in reducing the harm to human health caused by hyperthyroidism combined with osteoporosis. This study found that the factors affecting the Cox regression of fracture, hospitalization and all-cause mortality were higher in men, patients over 50 years old, higher disease severity and higher CCI. However, after receiving TCM treatment, regardless of gender, age, disease severity and CCI, the above risks of fractures, hospitalization and all-cause mortality were significantly reduced.

Osteoporosis is a chronic bone disease throughout the body[1] which starting from the age of 35, adults will lose about 0.5% to 1% of their bone mass every year as they age.[15] From the age of 50, the loss will be faster, with a loss of about 1% to 3% every year.[5] Due to bone reduced, the bone pores become larger and looser, causing the bones to be fragile and easily broken, thus increasing the risk of fractures.[16] The World Health Organization defines osteoporosis as bone mineral density (BMD) at any site (T-score) 2.5 or more standard deviations (SD) lower than in younger adults, while osteopenia is defined as BMD > 1 SD and < 2.5 SD below the mean endpoint for young adults.[17] Osteoporosis is the second most prevalent disease in the world, after cardiovascular disease.[18] Since it is a silent disease, it should be prevented as early as possible and proper calcium supplementation should be provided. Once

Table 3

Factors of outcomes by using Cox regression.

Outcomes	Fracture				Inpatient				All-caused mortality			
Variables	aHR	95% CI	95% CI	*P*	aHR	95% CI	95% CI	*P*	aHR	95% CI	95% CI	*P*
TCM												
Without	Reference				Reference				Reference			
With	0.563	0.392	0.680	< .001	0.614	0.474	0.714	< .001	0.691	0.569	0.792	<.001
Sex												
Male	1.172	1.017	1.342	.041	1.201	1.067	1.293	.017	1.217	1.040	1.418	.030
Female	Reference				Reference				Reference			
Age groups (years)												
18–49	Reference				Reference				Reference			
50–59	1.359	1.111	1.598	< .001	1.190	1.032	1.313	.032	1.270	1.065	1.498	.018
≧60	1.414	1.127	1.634	< .001	1.443	1.200	1.696	< .001	1.444	1.223	1.650	<.001
Low-income												
Without	Reference				Reference				Reference			
With	1.215	1.090	1.417	.005	1.126	1.107	1.298	< .001	1.201	1.102	1.358	<.001
Catastrophic illness												
Without	Reference				Reference				Reference			
With	1.452	1.271	1.694	< .001	1.442	1.135	1.667	< .001	1.495	1.275	1.765	<.001
Af												
Without	Reference				Reference				Reference			
With	1.303	1.006	1.678	.047	1.403	1.100	1.725	< .001	1.424	1.127	1.760	<.001
AF												
Without	Reference				Reference				Reference			
With	1.420	1.104	1.792	< .001	1.597	1.264	1.831	< .001	1.689	1.301	1.988	<.001
HF												
Without	Reference				Reference				Reference			
With	1.632	1.359	1.964	< .001	2.065	1.763	2.398	< .001	2.151	1.804	2.462	<.001
Anti-osteoporosis Tx												
Without	Reference				Reference				Reference			
With	0.862	0.450	1.265	.549	1.432	1.038	1.879	.031	1.645	1.284	2.007	<.001
Anti-hyperthyroidism Tx												
Without	Reference				Reference				Reference			
With	0.743	0.317	1.101	.688	1.420	1.022	1.863	.039	1.792	1.303	2.139	<.001
CCI_R	1.215	1.151	1.340	< .001	1.147	1.056	1.224	< .001	1.149	1.099	1.211	.001

aHR = adjusted hazard ratio, CI = confidence interval.

diagnosed, it should be treated early to ensure the therapeutic effect of osteoporosis.[19]

Osteoporosis is divided into primary osteoporosis and secondary osteoporosis according to the cause of occurrence.[15] In Taiwan, according to the National Nutrition and Health Status Survey from 2005 to 2008, the prevalence rate of osteoporosis in postmenopausal women over 50 years old was 38.3%.[20] According to the 2008 to 2011 Osteoporosis Society of the Republic of China survey, the prevalence rate of osteoporosis among middle-aged and elderly people over 50 years old is 31% which is a disease that cannot be ignored and harms health.[21] Secondary osteoporosis may be caused by physical constitution, nutritional status, smoking, drinking, lack of exercise, or even drug factors or acquired diseases.[22] In particular, some endocrine diseases, such as hyperthyroidism, lead to easy bone loss and osteoporosis.[23]

The ultimate goal of preventing and treating osteoporosis is to reduce the occurrence of fractures. Drugs for the treatment of osteoporosis have been proven in clinical trials to reduce the occurrence of fractures and those can be divided into anti-bone loss drugs based on their mechanism of action, such as bisphosphonates and selective estrogen receptors, modulators, RANKL monoclonal antibodies, etc. Drugs that promote osteogenesis, such as parathyroxine and drugs with combined anti-bone loss and pro-osteogenesis effects, such as strontium ranelate.[24] Clinicians prescribe appropriate osteoporosis drugs based on the patient's bone density test results and the degree of fracture occurrence. No matter what kind of drug is used, treatment will take more than a year to truly achieve the effect of reducing fractures.[25] It is not advisable to stop the drug too early and more importantly, only by supplementing appropriate calcium and vitamin D3 every day can the best effect of the drug be exerted.[26]

Multiple studies have shown that hyperthyroidism, both endogenous (due to Graves' disease) and exogenous (especially due to long-term levothyroxine therapy), significantly increases the risk of osteoporosis in postmenopausal women.[23] People with secondary osteoporosis such as untreated hyperthyroidism have significantly reduced bone density and an increased risk of fractures.[27] In adults, hyperthyroidism shortens bone turnover time and leads to poor bone mineralization, with a loss of approximately 10% to 20% of bone mineral density, especially in cortical bone.[28] People with hyperthyroidism tend to destroy bone more quickly and regenerate bone more slowly than people without hyperthyroidism, and treating hyperthyroidism itself can reduce the risk of osteoporosis.[23] Hyperthyroidism predisposes to cardiovascular complications such as Af, AF, and HF. Studies have shown that patients with heart failure who have hyperthyroidism have a 60% higher risk of death than those with normal thyroid function.[29] In addition, controlling atrial fibrillation is very important in the treatment of hyperthyroidism because it can reduce and prevent the risk of death caused by thromboembolic events.[30] If osteoporosis is caused by an aggravation of hyperthyroidism, in addition to the original standard treatment, are there other treatments to reduce related complications?

The treatment of TCM is quite common in the Chinese world. TCM is good at conditioning and is often used to assist Western medicine in the treatment of related diseases, such as cancer or chronic diseases.[31] There is no record of osteoporosis in the ancient books of TCM. According to the theoretical inheritance, most osteoporosis is classified as "bone failure" which the categories such as "bone paralysis and "bone dryness."[32] The syndrome manifestations of secondary osteoporosis mainly come from the syndrome of the primary disease which the clinical

Table 4

Factors of fracture stratified by variables listed in the table by using Cox regression and Bonferroni correction for multiple comparisons.

TCM	With			Without (Reference)			With vs without (Reference)			
Stratified	Events	PYs	Rate	Events	PYs	Rate	aHR	95% CI	95% CI	*P*
Total	752	47,739.20	1575.23	3993	191,743.52	2082.47	0.563	0.392	0.680	<.001
Sex										
Male	279	16,989.44	1642.20	1435	68,226.88	2103.28	0.634	0.489	0.737	<.001
Female	473	30,749.76	1538.22	2558	123,516.64	2070.98	0.603	0.466	0.702	<.001
Age groups (years)										
18–49	404	25,988.15	1554.55	2157	103,784.25	2078.35	0.607	0.469	0.706	<.001
50–49	125	7946.38	1573.04	669	31,986.11	2091.53	0.611	0.471	0.710	<.001
≧60	223	13,804.67	1615.40	1167	55,973.16	2084.93	0.630	0.485	0.732	<.001
Low-income										
Without	719	45,793.17	1570.10	3834	184,177.72	2081.69	0.612	0.473	0.712	<.001
With	33	1946.03	1695.76	159	7565.80	2101.56	0.655	0.505	0.762	<.001
Catastrophic illness										
Without	610	38,948.95	1566.15	3337	160,423.75	2080.12	0.611	0.472	0.711	<.001
With	142	8790.25	1615.43	656	31,319.77	2094.52	0.627	0.483	0.729	<.001
Af										
Without	741	47,069.95	1574.25	3942	189,308.21	2082.32	0.553	0.382	0.670	<.001
With	11	669.25	1643.63	51	2435.31	2094.19	0.584	0.407	0.706	<.001
AF										
Without	744	47,246.39	1574.72	3956	190,010.90	2081.99	0.560	0.388	0.679	<.001
With	8	492.81	1623.34	37	1732.62	2135.49	0.566	0.394	0.683	<.001
HF										
Without	746	47,385.78	1574.31	3966	190,482.53	2082.08	0.542	0.371	0.664	<.001
With	6	353.42	1697.70	27	1260.99	2141.17	0.590	0.411	0.713	<.001
Anti-osteoporosis Tx										
Without	214	13,365.95	1601.08	1131	54,077.00	2091.46	0.570	0.395	0.688	<.001
With	538	34,373.25	1565.17	2862	137,666.52	2078.94	0.561	0.390	0.677	<.001
Anti-hyperthyroidism Tx										
Without	177	9613.99	1841.07	821	33,994.14	2415.12	0.567	0.392	0.685	<.001
With	575	38,125.21	1508.19	3172	157,749.38	2010.78	0.558	0.388	0.674	<.001

aHR = adjusted hazard ratio, CI = confidence interval, PYs = person-years; rate: per 100,000 PYs.

treatment of osteoporosis should focus on nourishing the kidneys, nourishing liver yin, strengthening the spleen and replenishing qi, and promoting blood circulation and removing blood stasis.[33] Previous research literature has pointed out that TCM treatment of osteoporosis can effectively improve bone density and improve clinical symptoms such as pain and joint swelling.[34] According to statistics from the TNHID, it was also found that patients with osteoporosis can effectively reduce the probability of fractures after receiving TCM treatment.[35] Therefore, the efficacy of TCM in treating osteoporosis has a certain empirical basis. Most randomized controlled trials of TCM focus on clinical trials in postmenopausal women with osteoporosis.[36] It was found that QL1206 effectively increased BMD of the lumbar spine, total hip, and femoral neck in postmenopausal women with osteoporosis, and rapidly reduced bone turnover markers,[37] the combined treatment of warming yang and activating blood circulation moxibustion and oral calcium bone decoction can significantly relieve the pain of patients with osteoporosis and improve the bone density of patients with osteoporosis.[38]

Hyperthyroidism belongs to the category of "gall disease" in TCM, which a type of disease characterized by swelling and lumps on both sides of the Adam apple in the front of the neck as the main clinical feature.[39] Combined treatment of traditional Chinese and Western medicine has its advantages. The active ingredients of TCM can effectively relieve the symptoms of hyperthyroidism, reduce the side effects of antithyroid drugs, and reduce the chance of recurrence of the disease.[40] The ingredients of TCM have attracted more and more attention from modern medicine which mechanism of action of the active ingredients of TCM is different from that of existing treatment projects.[41] A large number of high-quality randomized controlled trials research and in-depth exploration are still needed to confirm the efficacy and clarify the exact mechanism. Since there have been no large-scale studies in the past to explore the clinical efficacy of combining TCM to treat patients with hyperthyroidism and osteoporosis those even with comorbidity of Af, AF, or HF, we used the TNHID and it seems that when combined with TCM to treat such patients, there is a relatively low effectiveness risk of fracture, hospitalization, and all-cause mortality.

Some studies have shown that Erxian Decoction has an anti-osteoporosis effect similar to estrogen and can inhibit the bone resorption activity of osteoclasts[42]; Icariin can promote the osteogenic differentiation of bone marrow mesenchymal stem cells and promote osteogenesis by regulating multiple signaling pathways (such as BMP/Smads, Wnt/β-catenin), while inhibiting the formation and function of osteoclasts[43]; Eucommia Ulmoides Oliv has the effect of inhibiting bone resorption and promoting osteogenesis, which may be through stimulating the secretion of growth hormone to regulate bone growth and development.[32] Although the results show that TCM may have certain benefits in increasing bone density, due to limitations in research quality and sample size, further clinical and basic research is needed to confirm its efficacy and mechanism of action.

This study also has some limitations. First, this is a study using a database, and we cannot effectively know the patient's height, weight, blood test reports such as thyroid function and thyroid autoimmune antibodies, bone density test, dual-energy X-ray absorptiometry values and the used related Chinese herbal medicine names. Second, this is a database of patients seeking medical treatment in Taiwan. The information obtained only describes the situation in Taiwan and cannot be extrapolated to all ethnic groups. Third, this study cannot infer

Table 5

Factors of inpatient stratified by variables listed in the table by using Cox regression and Bonferroni correction for multiple comparisons.

TCM	With			Without (Reference)			With vs without (Reference)			
Stratified	Events	PYs	Rate	Events	PYs	Rate	aHR	95% CI	95% CI	*P*
Total	987	51,847.39	1903.66	4836	207,427.11	2331.42	0.614	0.474	0.714	<.001
Sex										
Male	362	18,448.56	1962.21	1728	73,807.47	2341.23	0.631	0.486	0.733	<.001
Female	625	33,398.83	1871.32	3108	133,619.64	2326.01	0.605	0.467	0.704	<.001
Age groups (years)										
18–49	527	28,224.65	1867.16	2610	112,273.18	2324.69	0.604	0.466	0.703	<.001
50–49	165	8630.29	1911.87	808	34,602.27	2335.11	0.617	0.475	0.716	<.001
≧60	295	14,992.45	1967.66	1418	60,551.66	2341.80	0.632	0.488	0.735	<.001
Low-income										
Without	943	49,727.62	1896.33	4644	199,237.86	2330.88	0.612	0.472	0.712	<.001
With	44	2119.77	2075.70	192	8189.25	2344.54	0.666	0.513	0.775	<.001
Catastrophic illness										
Without	802	42,273.11	1897.19	4050	173,740.92	2331.06	0.612	0.472	0.712	<.001
With	185	9574.28	1932.26	786	33,686.19	2333.30	0.624	0.481	0.725	<.001
Af										
Without	972	51,118.63	1901.46	4774	204,792.71	2331.14	0.605	0.462	0.710	<.001
With	15	728.76	2058.29	62	2634.40	2353.48	0.658	0.508	0.765	<.001
AF										
Without	976	51,306.13	1902.31	4792	205,551.20	2331.29	0.612	0.470	0.711	<.001
With	11	541.26	2032.30	44	1875.91	2345.53	0.652	0.503	0.758	<.001
HF										
Without	979	51,441.04	1903.15	4804	206,062.89	2331.33	0.609	0.468	0.708	<.001
With	8	406.35	1968.75	32	1364.22	2345.66	0.631	0.487	0.734	<.001
Anti-osteoporotic Tx										
Without	273	14,544.17	1877.04	1364	58,500.74	2331.40	0.605	0.467	0.704	<.001
With	714	37,303.22	1914.04	3472	148,926.37	2331.43	0.617	0.479	0.720	<.001
Anti-hyperthyroidism Tx										
Without	198	10,442.02	1896.18	983	42,182.98	2331.43	0.612	0.472	0.710	<.001
With	789	41,405.37	1905.55	3853	165,244.13	2331.42	0.616	0.478	0.718	<.001

aHR = adjusted hazard ratio, CI = confidence interval, PYs = person-years; rate: per 100,000 PYs.

Table 6

Factors of all-caused mortality stratified by variables listed in the table by using Cox regression and Bonferroni correction for multiple comparisons.

TCM	With			Without (Reference)			With vs without (Reference)			
Stratified	Events	PYs	Rate	Events	PYs	Rate	aHR	95% CI	95% CI	*P*
Total	511	71,783.35	711.86	2976	303,196.62	981.54	0.691	0.569	0.792	<.001
Sex										
Male	188	25,542.97	736.01	1062	107,884.48	984.39	0.713	0.586	0.817	<.001
Female	323	46,240.38	698.52	1914	195,312.14	979.97	0.679	0.559	0.779	<.001
Age groups (years)										
18–49	271	39,077.35	693.50	1608	164,109.28	979.83	0.675	0.555	0.774	<.001
50–49	86	11,949.80	719.68	497	50,578.36	982.63	0.699	0.575	0.800	<.001
≧60	154	20,756.20	741.95	871	88,508.98	984.08	0.719	0.592	0.823	<.001
Low-income										
Without	489	68,856.05	710.18	2857	291,231.35	981.01	0.690	0.568	0.791	<.001
With	22	2927.30	751.55	119	11,965.27	994.55	0.720	0.594	0.825	<.001
Catastrophic illness										
Without	416	58,565.49	710.32	2492	253,956.72	981.27	0.690	0.568	0.791	<.001
With	95	13,217.86	718.72	484	49,239.90	982.94	0.698	0.574	0.798	<.001
Af										
Without	503	70,774.73	710.71	2938	299,346.36	981.47	0.684	0.562	0.783	<.001
With	8	1008.62	793.16	38	3850.26	986.95	0.766	0.631	0.878	<.001
AF										
Without	505	71,033.82	710.93	2949	300,456.98	981.50	0.670	0.558	0.771	<.001
With	6	749.53	800.50	27	2739.64	985.53	0.774	0.637	0.888	<.001
HF										
Without	506	71,222.25	710.45	2956	301,202.74	981.40	0.662	0.543	0.762	<.001
With	5	561.10	891.11	20	1993.88	1003.07	0.846	0.697	0.970	.035
Anti-osteoporosis Tx										
Without	141	20,141.07	700.06	839	85,511.38	981.16	0.680	0.554	0.779	<.001
With	370	51,642.28	716.47	2137	217,685.24	981.69	0.695	0.573	0.793	<.001
Anti-hyperthyroidism Tx										
Without	102	14,460.26	705.38	605	61,658.96	981.20	0.685	0.562	0.785	<.001
With	409	57,323.09	713.50	2371	241,537.66	981.63	0.693	0.571	0.794	<.001

aHR = adjusted hazard ratio, CI = confidence interval, PYs = person-years; rate: per 100,000 PYs.

causal relationships and it can only explain possible related causes and literature searches. These require the design of relevant prospective studies in the future, which may be able to solve the relevant research and test limitations. Furthermore, scientific Chinese medicine is covered by NHI, it is recorded in the NHI database. However, decoctions are not covered by NHI, so they are not recorded in the database. This represents a limitation when studying TCM treatments and conducting related research and analysis.

5. Conclusion

Osteoporosis is one of the most common metabolic bone diseases which is the second most important epidemic in the world and hyperthyroidism will lead to an increased risk of osteoporosis. To prevent or treat osteoporosis that is important for people with osteoporosis to reduce the risk to their health. This study hopes to provide clinicians with information on how to combine TCM treatment with patients with hyperthyroidism and osteoporosis those even with comorbidity of Af, AF, or HF to reduce the risk of fractures, hospitalization, or death.

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Table 7

Factors of prognosis among different TCM subgroups by using Cox regression and Bonferroni correction for multiple comparisons.

Prognosis	TCM subgroup		Population	Events	PYs	Rate	aHR	95% CI	95% CI	*P*
Fracture surgery	Without TCM		19,920	3993	191,743.52	2082.47	Reference			
	With TCM		4980	752	47,739.20	1575.23	0.563	0.392	0.680	<.001
		Herbal formulae only	3736	572	35,795.12	1597.98	0.571	0.399	0.691	<.001
		Acupuncture only	218	34	2094.23	1623.51	0.581	0.404	0.701	<.001
	With TCM	TCM traumatology only	165	30	1690.71	1774.40	0.635	0.440	0.767	<.001
		Herbal formulae + Acupuncture	479	62	4532.11	1368.02	0.489	0.340	0.592	<.001
		Herbal formulae + TCM traumatology	382	54	3627.03	1488.82	0.532	0.370	0.644	<.001
		Herbal formulae	4597	688	43,954.26	1565.26	0.560	0.390	0.676	<.001
	With TCM	Acupuncture	697	96	6626.34	1448.76	0.518	0.361	0.625	<.001
		TCM traumatology	547	84	5317.74	1579.62	0.565	0.393	0.682	<.001
Inpatient	Without TCM		19,920	4836	207,427.11	2331.42	Reference			
	With TCM		4980	987	51,847.39	1903.66	0.614	0.474	0.714	<.001
		Herbal formulae only	3736	742	38,686.97	1917.96	0.619	0.479	0.721	<.001
		Acupuncture only	218	42	2235.04	1879.16	0.605	0.470	0.706	<.001
	With TCM	TCM traumatology only	165	41	2063.12	1987.28	0.641	0.493	0.744	<.001
		Herbal formulae + Acupuncture	479	84	4918.76	1707.75	0.551	0.425	0.643	<.001
		Herbal formulae + TCM traumatology	382	78	3943.50	1977.94	0.639	0.491	0.738	<.001
		Herbal formulae	4597	904	47,549.23	1901.19	0.613	0.470	0.715	<.001
	With TCM	Acupuncture	697	126	7153.80	1761.30	0.568	0.440	0.662	<.001
		TCM traumatology	547	119	6006.62	1981.15	0.639	0.492	0.741	<.001
All-caused mortality	Without TCM		19,920	2976	303,196.62	981.54	Reference			
	With TCM		4980	511	71,783.35	711.86	0.691	0.569	0.792	<.001
		Herbal formulae only	3736	384	53,809.85	713.62	0.695	0.573	0.796	<.001
		Acupuncture only	218	23	3096.12	742.87	0.721	0.596	0.828	<.001
	With TCM	TCM traumatology only	165	20	2609.00	766.58	0.745	0.614	0.851	<.001
		Herbal formulae + Acupuncture	479	46	6810.47	675.43	0.657	0.540	0.750	<.001
		Herbal formulae + TCM traumatology	382	38	5457.91	696.24	0.675	0.558	0.769	<.001
		Herbal formulae	4597	468	66,078.23	708.25	0.688	0.566	0.792	<.001
	With TCM	Acupuncture	697	69	9906.59	696.51	0.676	0.551	0.769	<.001
		TCM traumatology	547	58	8066.91	718.99	0.698	0.573	0.802	<.001

With TCM had 7 subtypes: herbal formulae only, acupuncture only, TCM traumatology only, herbal formulae + acupuncture, herbal formulae + TCM traumatology, acupuncture + TCM traumatology (Not seen in this study), and herbal formulae + acupuncture + TCM traumatology (Not seen in this study), herbal formulae was including herbal formulae only, herbal formulae + acupuncture, and herbal formulae + TCM traumatology. Not seen in this study: herbal formulae + acupuncture + TCM traumatology. Acupuncture was including acupuncture only and herbal formulae + acupuncture. Not seen in this study: acupuncture + TCM traumatology and herbal formulae + acupuncture + TCM traumatology. TCM traumatology was including TCM traumatology only and herbal formulae + TCM traumatology. Not seen in this study: acupuncture + TCM traumatology and herbal formulae + acupuncture + TCM traumatology.

aHR = adjusted hazard ratio, CI = confidence interval, PYs = person-years; rate: per 100,000 PYs.

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