

Identifying Prescription Patterns and Iron Supplementation With Chinese Herbal Medicine for Uterine Myoma in Taiwan: A Social Network Analysis of the Chang Gung Research Database

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Research

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Abstract

Background: Uterine myoma is a common gynecological disease in women of reproductive age. Owing to surgery and treatment-related complications, many patients opt for alternative therapy, such as traditional Chinese medicine (TCM). However, there is no standard treatment protocol for TCM. This study aimed to investigate the prescription patterns of TCM for uterine myoma and compare differences between the Chang Gung Research Database (CGRD) and the National Health Insurance Research Database (NHIRD).

Methods: Data of 217040 patients newly diagnosed with uterine myoma between 2005 and 2014 were retrieved from the CGRD using the International Classification of Diseases, Ninth Revision, Clinical Modification code for myoma and related symptoms. We analyzed patient demographics, frequencies and average daily doses of prescribed Chinese herbal formulas and single herbs, and iron supplementation doses. Associations between Chinese herbal formulas and single herbs commonly used for uterine myoma were analyzed by association rule mining (ARM) and social network analysis (SNA).

Results: In total 45,436 patients used TCM. Most participants (49.1%) were aged 30–44 years. Jia-Wei-Xiao-Yao-San (28.2%; average daily dose 4.85 g) and Xiang-Fu (22.0%; average daily dose 1.10 g) were the most frequently prescribed herbal formula and single herb, respectively. Additionally, the Si-Wu-Tang decoction was often used for uterine fibroids. Common prescription patterns and herbal pairs were identified. Western medicine (WM) outpatient visits (12 ± 19.6) and iron supplement prescriptions (prescription code PLB001M, 62.5 ± 115.3 pills; PLB012M, 24.6 ± 78 pills) were more prevalent in the combined therapy group than in the WM-only group (outpatient visits: 5.9 ± 6.7 times; iron supplements: PLB001M, 48.3 ± 98.4 pills; PLB012M, 20.9 ± 67.5) in the CGRD.

Conclusions: We characterized the prescription patterns for uterine myoma in the CGRD. Chinese herbal medicine prescriptions may aim to improve anemia related to hypermenorrhea caused by uterine myoma. Ours is the first study of TCM myoma treatment within the CGRD, and we compared our findings to the TCM NHIRD myoma study results. ARM and SNA of TCM prescription patterns provide an evidence base to inform medical education and medical decision-making.

Background

Uterine myoma is the most common benign uterine tumor in females, originating from uterine smooth muscle tissues.[1] Its incidence is higher in black women and increases with age.[2–4] Myoma growth may be stimulated by estrogen and progesterone[5]; thus, this condition is prevalent among women of reproductive age [6, 7] and its occurrence decreases in postmenopausal women.[8] Multiple risk factors, including early menarche, nulliparity, consumption of alcohol or caffeine, obesity, and hypertension, may induce or aggravate uterine myoma.

Most patients with uterine myoma are asymptomatic[4, 9]; thus, uterine myoma is often an accidental finding during routine health examinations or ultrasound exams. Approximately 25% of patients complain about discomfort, including from abnormal uterine bleeding (i.e., menorrhagia or metrorrhagia), pelvic

pain, and compression symptoms of the rectum or bladder (i.e., constipation or frequent urination).[10] Other patients may complain about infertility, recurrent abortions, or complications during childbirth.[11, 12] The uterine myoma, especially submucosal myoma or large intramural myoma, may structurally interfere with placental implantation, fetus growth so that increase the risk of spontaneous abortion, fetal malpresentation and subsequent cesarean section rate, placenta previa, preterm birth, and peripartum hemorrhage.[12, 13]

Asymptomatic patients or those with minor symptoms of uterine myoma may be prescribed conservative medical treatments, including gonadotropin-releasing hormone (GnRH) analogs, selective estrogen receptor modulators, the anti-progestin agent mifepristone, the selective progesterone receptor modulator ulipristal acetate, and aromatase inhibitors.[9, 14] More aggressive treatments include minimally invasive methods or surgical interventions. Patients who do not want to preserve their fertility or uterus may undergo hysterectomy, while those who prefer to preserve their fertility may choose laparoscopic myomectomy.[15] Non-invasive high-frequency magnetic resonance-guided focused ultrasound surgery [16] or uterine artery embolization [17] may also be considered. Due to the high prevalence of this condition, considerable medical expenses are incurred in treating uterine fibroids.[4]

Alternative therapy may be considered during the conservative treatment when surgical complications or high medical costs are a concern.[18] Traditional Chinese medicine (TCM) is one type of alternative therapy. TCM physicians use herbal medicine and acupuncture to treat myoma, which may reduce pain, menstrual flow, and the size of the myoma. Due to its efficacy, convenience, and low economic cost, TCM therapy is gradually becoming more popular worldwide. Previous studies have identified TCM prescription patterns,[19] demonstrating that TCM doctors diagnose and treat myoma using different combinations of formulas and medicinal herbs. TCM prescription methodology is complicated and varies from doctor to doctor. Thus, it is challenging to generalize standard quantitative treatment models and medical guidelines.

Chang Gung Memorial Hospitals form the largest medical system in Taiwan. There are seven main branch hospitals located in Keelung, Taipei, Linkou, Taoyuan, Yunlin, Chiayi, and Kaohsiung. In 2015, Chang Gung Memorial Hospitals served 1336901 outpatients, accounting for approximately 6.1% of the entire Taiwanese population.[20] The Chang Gung Research Database (CGRD) may thus be representative for the study of disease diagnosis or medical treatment models in Taiwan.

Yen et al. analyzed TCM prescription patterns for the treatment of myoma in the National Health Insurance Research Database (NHIRD) in Taiwan.[21] The NHIRD encompasses local clinics and hospital data and is thus more heterogeneous than the CGRD, which encompasses mainly medical center data. Differences between the NHIRD and CGRD have not been previously compared. By analyzing the CGRD, our study identified a TCM network for examining myoma TCM treatment and demonstrated core formulas and medicinal combinations. We compared CGRD and NHIRD data to determine differences in medical centers regarding TCM medical treatments for the whole population, which could aid in improving the quality of TCM medical treatment.

Methods

Data source

In this retrospective review study, we used de-identified patients from the CGRD, based on myoma patient data from seven branches of Chang Gung hospitals, with medical data dating between January 1, 2005, and December 31, 2014. The ethics approval committee waived the requirement for informed patient consent due to the retrospective nature of the study. Following the study methodology presented by Yen et al., this study used International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to screen specific patients with uterine myoma and related symptoms.[21] After the initial screen to exclude erroneous data, we identified 217,040 newly diagnosed myoma patients. Further analyses of these data were conducted according to prescription patterns (i.e., TCM-only, Western medicine [WM]-only, and combined therapy groups). Medical data recorded in the CGRD were different from the data recorded in NHIRD. Specifically, the CGRD records outpatient visits within Chang Gung hospitals, while the NHIRD records outpatient visits from hospitals and local clinics. However, detailed data for each prescription could be obtained from the CGRD, including outpatient visits to hospitals, doctors, laboratory or image examination results, and prescribed medications. Thus, the CGRD may provide a more detailed and specific analysis dataset than the NHIRD.[20]

Study subjects and data enrollment

The study protocol was approved by the Institutional Review Board of the Chang Gung Memorial Foundation (approval number 201900089B0C501). Patient data were selected according to the screen flow chart shown in Fig. 1. Outpatient medical records from 2005 to 2015 were selected if the diagnosis column showed newly diagnosed myoma or related symptoms based on ICD-9-CM diagnosis codes (i.e., 218: uterine leiomyoma; 617: endometriosis; 625.3: dysmenorrhea; 625.4: premenstrual tension syndrome; 626: disorders of menstruation and other abnormal bleeding from the female genital tract; 628: female infertility). This ICD-9-CM diagnosis code classification was the same as in the study by Yen et al., which allowed comparisons with the CGRD database. Patients with missing and erroneous data were excluded, as were male patients. Patients who never received TCM treatment were grouped as TCM non-users (i.e., the WM-only group; n = 171,604), while those who had been prescribed TCM at least once were grouped as TCM users (n = 45,436). TCM users were further divided into TCM-only (n = 32,146) or combined therapy groups (n = 13,290) according to whether WM was prescribed.

Analysis methods

TCM prescription network analysis

This study used association rule mining (ARM) and social network analysis (SNA) methods to analyze CGRD outpatient TCM prescription data obtained in Taiwan from 2005–2014 and to determine core treatments as well as connections between formulas and medicines. ARM and SNA have previously been implemented to analyze TCM prescription patterns [22, 23]. Three factors of ARM were analyzed: 1) high

support (> 1%), indicating that the TCM prescription combinations were more prevalent among all possible combinations; 2) high confidence (> 30%); and 3) high lift (> 1), indicating a strong connection between TCM prescriptions, i.e., the herbs were frequently prescribed as a pair. Common TCM prescription combinations were shown in the SNA to graphically demonstrate the TCM prescription network.

Iron supplementation

There are two forms of outpatient oral iron supplements prescribed within the CGRD; 300 mg ferrous gluconate B (+ vitamin B1 10 mg + vitamin C 30 mg/tab; code: PLB001M) and 460 mg ferrous fumarate (+ vitamin B12 + folic acid/tab; code: PLB012M). We determined if these two forms of iron supplements were prescribed at each outpatient visit in the CGRD through outpatient charge codes. The TCM group data was divided into TCM-only (n = 32,146) and combined therapy groups (n = 13,290), according to the presence or absence of WM treatment. We then compared iron supplementation in the WM-only and combined therapy groups.

Statistical analyses

All iron supplement data, as well as data regarding participant characteristics, are expressed as means \pm standard deviations (SD). Nonparametric Mann-Whitney U-tests were used to analyze the above data, and the statistical significance level was set as a two-tailed $p < 0.05$. SPSS statistical software version 19.0 (IBM, Armonk, New York, USA) was used to examine descriptive statistics and to conduct the Mann-Whitney U-tests.

Results

According to the selection criteria (Fig. 1), we identified 217,040 newly diagnosed female patients who visited the Chang Gung hospitals between 2005 and 2014. Table 1 shows the distribution of medical and demographic characteristics among these patients. The largest patient age group comprised patients aged 30–44 years (n = 106,466, 49.1%). The vast majority of these patients visited the Linkou (36.2%), Taipei (29.1%), and Kaohsiung (15.9%) branches of the Chang Gung hospitals. The accumulated number of outpatient visits per patient gradually decreased as follows: 1–5 visits (56.1%), 6–10 visits (20.4%), 11–20 visits (14.2%), 21–40 visits (6.9%), and > 40 visits (2.4%), with an average of 8.4 outpatient visits per patient.

Characteristics of patients newly diagnosed with uterine myoma in the Chang Gung Research Database (2005–2014)

Characteristics	N	%
Total number of outpatients	217,040	100.0
Age of patients (years)		
13–29	70,855	32.6
30–44	106,466	49.1
45–55	35,927	16.6
> 55	3792	1.7
Hospital branch		
Keelun	24,443	11.3
Taipei	63,262	29.1
Linkou	78,474	36.2
Taoyuan	70	< 0.1
Yunlin	2	< 0.1
Chiayi	16,193	7.5
Kaohsiung	34,596	15.9
Outpatient visits per patient		
1–5	121,854	56.1
6–10	44,242	20.4
11–20	30,819	14.2
21–40	14,995	6.9
>40	5,130	2.4
Average number of outpatient visits per patient	8.4	

(Table 1)

We observed a total of 353,348 TCM prescriptions. Overall, 793 formulas (mixture of multiple medicinal herbs) and 298 medicinal herbs were used (i.e., a total of 1,091 Chinese herbal medicines [CHMs]). CHMs are the foundations of TCM prescriptions. Each TCM prescription uses a different combination of CHMs. Thus, we used SNA and ARM to analyze the TCM prescriptions to determine the general structure patterns of these prescriptions and to deduce the general treatment logic of TCM doctors, which may help junior TCM doctors gain valuable experience. Figure 2 shows the distribution of CHM prescriptions for the

treatment of uterine myoma, with an average of 7.5 CHMs per prescription. Many prescriptions were combined with 6–8 medicines, with respective proportions of 14.1% (6 medicines), 18.8% (7 medicines), and 13.2% (8 medicines). The top 10 prescribed formulas are shown in Table 2, with an average daily dose ranging from 1.71 to 4.87 g/day. The top three formulas were Jia-Wei-Xiao-Yao-San (99,762, 28.2%), Zou-Gui-Wan (46,474, 13.2%), and Gui-Zhi-Fu-Lin-Wan (40,520, 11.5%). The top 10 medicinal herbs used in the prescriptions are shown in Table 3, with an average daily dose ranging from 1.10 to 1.70 g/day. The top three medicinal herbs were Xiang-Fu (77,814, 22.0%), Yan-Hu-Suo (44,794, 12.7%), and Dan-Shen (33,120, 12.2%).

Table 2
The 10 most common herbal formulas for patients with uterine myoma

No.	Herbal formula	Indications in TCM use	Prescription frequency N (%)	Average daily dose (g/day)
1	Jia-Wei-Xiao-Yao-San	Anxiety, irritability, depression, and increased menstrual flow or uterine blood	99,762 (28.2)	4.85
2	Zou-Gui-Wan	Impotence, spontaneous emissions, infertility, lightheadedness, tinnitus, lower back or knee soreness, night sweats, and dry mouth and throat	46,474 (13.2)	4.85
3	Gui-Zhi-Fu-Ling-Wan	Masses in the abdomen (women only), amenorrhea due to blood stasis, menses with abdominal pain, and persistent uterine bleeding	40,520 (11.5)	4.54
4	Wen-Jing-Tang	Irregular menses, continuous or extended menstrual flow, bleeding or spotting between cycles, and coldness in the lower abdomen	36,438 (10.3)	4.69
5	Dang-Gui-Shao-Yao-San	Continuous mild cramping pain over the abdomen, urinary difficulty, and slight edema	32,277 (9.1)	4.87
6	Gui-Pi-Tang	Palpitations, insomnia, anxiety, reduced appetite, and chronic bleeding syndromes	31,604 (8.9)	4.38
7	Ma-Zi-Ren-Wan	Constipation with hard stools that were difficult to expel and frequent urination	29,014 (8.2)	1.71
8	Zhi-Bo-Di-Huang-Wan	Hot flush and tidal fever, vertigo, tinnitus, and dryness of the skin and mucus membrane	25,288 (7.2)	4.44
9	Xue-Fu-Zhu-Yu-Tang	Depression or low spirits, insomnia, restless sleep, irritability, and extreme mood swings	24,176 (6.8)	4.77
10	Shao-Fu-Zhu-Yu-Tang	Lower abdominal pain/distension with or without palpable masses, frequent menstruation with dark or purple blood, abdominal uterine, and bleeding with pain	23,518 (6.7)	4.80
TCM, traditional Chinese medicine				
Total number of prescriptions = 353,348				

Table 3
The 10 most prescribed medicinal herbs for patients with uterine myoma

No.	Single herb	Scientific name	Major effect	Prescription frequency N (%)	Average daily dose (g/day)
1	Xiang-Fu	<i>Rhizoma Cyperi</i>	Disperse stagnated liver qi	77,814 (22.0)	1.10
2	Yan-Hu-Suo	<i>Rhizoma Corydalis</i>	Relieve pain and regulate qi	44,794 (12.7)	1.33
3	Dan-Shen	<i>Radix Salviae Miltiorrhizae</i>	Promote blood circulation by removing blood stasis	43,120 (12.2)	1.34
4	Yi-Mu-Cao	<i>Herba Leonuri</i>	Regulate menstruation, and diuresis to alleviate edema	40,970 (11.6)	1.50
5	Xu-Duan	<i>Dipsaci Radix</i>	Enhance liver yin and kidney yin, and strengthen muscles and the skeletal system	32,453 (9.2)	1.20
6	Du-Zhong	<i>Eucommiae Cortex</i>	Enhance liver yin, kidney yin, and tocolysis	30,957 (8.8)	1.26
7	Nu-Zhen-Zi	<i>Ligustri Lucidi Fructus</i>	Invigorate the liver and the kidney, and improve blurred vision	26,527 (7.5)	1.22
8	Chuan-Xoing	<i>Rhizoma Ligustici</i>	Conduct qi, and promote blood circulation	24,714 (7.0)	1.35
9	Tu-Si-Zi	<i>Semen Cuscutae</i>	Tonify the kidneys, nourish essence, and nourish the liver to improve vision	24,467 (6.9)	1.29
10	Huang-Qi	<i>Radix Astragali</i>	Tonify qi	23,650 (6.7)	1.69
Total number of prescriptions = 353,348					

The top 10 combinations of TCM prescription data based on ARM are shown in Table 4. Among the prescription combinations, we observed the strongest support for Xiang-Fu and Jia-Wei-Xiao-Yao-San (7%). Confidence in differentiating between combinations of the decoctions Chuan-Xoing, Dang-Gui, and Shu-Di-Huang was elevated because these herbs were used in the preparation of the regular Si-Wu-Tang decoction.

Table 4

Top 10 most commonly prescribed Chinese herbal medicine pairs in outpatient departments

Rank	Herbal pair		Support %	Confidence %	Lift
1	Xiang-Fu	Jia-Wei-Xiao-Yao-San	6.6	30.3	1.1
2	Yan-Hu-Suo	Xiang-Fu	5.7	45.5	2.1
3	Zou-Gui-Wan	Xiang-Fu	5.1	80.2	10.7
4	Han-Lian-Cao	Nu-Zhen-Zi	4.9	37.5	1.7
5	Dan-Shen	Xiang-Fu	4.5	36.3	1.7
6	Chuan-Xoing (decoction pieces)	Dang-Gui (decoction pieces)	3.9	97.8	21.0
7	Dan-Shen	Jia-Wei-Xiao-Yao-San	3.9	31.5	1.1
8	Wen-Jing-Tang	Xiang-Fu	3.8	37.0	1.7
9	Shu-Di-Huang (decoction pieces)	Chuan-Xoing (decoction pieces)	3.7	96.9	20.7
10	Wu-Ling-Zhi	Pu-Huang	3.7	90.1	15.9
Total number of prescriptions = 353,348					

Using SNA, we evaluated the connections between each pair of herbal medicines and categorized multiple clusters. Each cluster was further divided into subgroups with high connectivity to distinguish herbal treatment effects. Figure 3 presents the TCM prescription network of all TCM prescriptions. In the network, the size of the node represents the prescription frequency. The bigger the node, the more frequently this medicine was prescribed. The size of the line represents the frequency of prescription of the two medicines connected by the line. A thicker line indicates that the medicine pair was prescribed more frequently. There were three clear clusters, including the decoction cluster of Si-Wu-Tang (i.e., the four nodes of Shu-Di-Huang, Chuan-Xoing, Dang-Gui, and Bai-Shao). These four medicines are all decoction pieces with very thick interconnected lines. The SNA demonstrates a very strong connection between the four decoction medicines; thus, these four medicines were likely prescribed as a group for many patients.

The other two clusters were from the non-decoction herbal powder group. One cluster of the herbal powder group is formed by two medicinal herbs, Nu-Zhen-Zi and Han-Lian-Cao, with a strong association observed between the two medicines. Another cluster of the herbal powder group presents the primary nodes Jia-Wei-Xiao-Yao-San, Xiang-Fu, Zou-Gui-Wan, and Yan-Hu-Suo. The lines connecting these nodes are thick, indicating that the connectivity of each pair is strong. Other herbal medicines surrounding the primary nodes (Wen-Jing-Tang, Dan-Shen, and Gui-Zhi-Fu-Ling-Wan) may be considered as secondary nodes. These secondary nodes were scattered outside the primary nodes and the interconnection lines

were fairly strong. Secondary node medicines may be prescribed accompanying primary node medicines aiming to strengthen the efficacy of the master node group. Dang-Gui-Shao-Yao-San and Pu-Huan surround Yan-Hu-Suo, similar to the secondary node medicines. There were strong connections between Dang-Gui-Shao-Yao-San/Yan-Hu-Suo and Yi-Mu-Cao/Jia-Wei-Xiao-Yao-San.

Table 5 presents iron supplementation data. Based on descriptive statistical analysis, the distributions of the input variables were observed to have similar patterns, with extremely positively skewed distributions. Therefore, the Mann-Whitney U test is the most appropriate test to compare the means of the input variables between these two groups of patients (i.e., to test whether the means are equal). All three outcomes inferred a higher level of iron supplementation in the combined therapy group than in the WM-only group. The percent of patients taking iron supplements was similar in TCM non-users (6.5% for WM-only, 6.7% in the combined therapy group). However, WM outpatient department visits (12 ± 19.6 vs. 5.9 ± 6.7) and both PLB001M and PLB012M prescribed per patient were showed statistically significant increase in the combined therapy group when compared to the WM-only group.

Table 5
Iron supplementation analysis

	WM-only n = 171,604	Combined therapy n = 13,290	Statistics (two-tailed U-test)
Patients with iron supplementation, n (%)	11,225 (6.5%)	896 (6.7%)	
WM outpatient visit number	5.9 (6.7)	12 (19.6)	p < 0.0001
PLB001M pills prescribed per patient	48.3 (98.4)	62.5 (115.3)	p < 0.0001
PLB012M pills prescribed per patient	20.9 (67.5)	24.6 (78.0)	p < 0.0001
WM, Western medicine			
The last three data rows are shown as means and standard deviations, and Nonparametric Mann-Whitney U-tests was used for test.			

Discussion

This study analyzed CGRD medical records of newly diagnosed uterine leiomyoma patients presenting within the Chang Gun hospital system between 2005 and 2014. We found that patients in the 30–44-year age group comprised the main treatment group (49.1%). This finding confirms the results of a nationwide population-based study in Taiwan conducted in 2002–2010.(21) However, in the CGRD study, the second most common group were patients between 13 and 29 years of age, who were thus considerably younger than in Yen et al.'s study (among patients 45–55 years of age). We also found a declining trend in the number of outpatient visits per patient in the CGRD study (with groupings ranging from 1–5 visits to > 40 visits), compared to the bimodal distribution in Yen et al.'s NHIRD study (> 40 or 1–5 visits). The CGRD encompasses hospital data, whereas the NHIRD data mainly includes local clinics (89.7% in Yen et al.'s

study). This difference may imply that younger patients tend to seek medical treatment in hospitals rather than in local clinics, whereas, for long-term treatment (i.e., > 40 visits), patients tend to visit local clinics rather than hospitals due to medical accessibility. It is convenient for patients to visit local clinics if frequent outpatient follow-ups are needed.

Chang Gung has seven main branches of hospitals in Taiwan; the Linkou Chang Gung Hospital is the largest branch. From the study, we found that most patients visited the Linkou, Taipei, and Kaohsiung branches of the Chang Gung hospital system. The urban population densities of the neighborhoods for these three branches are the highest in Taiwan; thus, our finding is consistent with our previous findings on the average population densities of these cities (i.e., New Taipei City, 1,947/km²; Taipei City, 9818/km²; Taoyuan City, 1819/km²; Kaohsiung City, 940/km²; the average population density of Taiwan is 282/km²). The number of CHMs per prescription shown in Fig. 2 revealed that the most common number of formula/medicinal herbs combinations in a prescription was seven combined medicines. This finding is similar to a previous study on CHM treatment of endometriosis in the NHIRD.[22]

In traditional Chinese theory, uterine myoma is classified as an abdominal mass disease with the etiologies of blood stasis, qi stagnation, qi and blood insufficiency, and cold-dampness stagnation. These TCM etiologies and related TCM patterns are commonly described in Chinese publications presenting TCM clinical studies.[19] The corresponding methods of TCM treatment for uterine myoma were invigorating blood circulation and eliminating stasis, dispersing liver and regulating qi, supply qi and blood, and warming meridian to expel cold-dampness. Most of the top 10 formulas and medicinal herbs are shown in Tables 2 and 3 and have these treatment effects. These TCM etiologies and Zheng descriptions are very different from current WM clinical manifestation descriptions and translations are needed for communication. For example, qi stagnation and blood stasis may relate to the clinical manifestations of heavy menstrual flow, blood clots, uterine myoma masses, and dysmenorrhea. The traditional herbal formula Gui-Zi-Fu-Ling-Wan can invigorate blood, eliminate blood stasis, and reduce fixed abdominal myoma masses, and can thus be widely used in treating uterine fibroids.[24]

Tables 2 and 3 present the top 10 prescribed formulas and medicines. The most frequent formula for uterine myoma treatment in the CGRD was Jia-Wei-Xiao-Yao-San; this formula was the second most frequently prescribed formula in the NHIRD.[21] The treatment effect of Jia-Wei-Xiao-Yao-San is dispersing liver and regulating qi. This medicine is used for qi stagnation Zheng of myoma patients. The second most frequently prescribed formula in our study was Zou-Gui-Wan, though it was not one of the top 10 formulas in Yen et al.'s NHIRD study. Zou-Gui-Wan, the effect of which is to nourish yin and tonify the kidneys, is not commonly used for the treatment of uterine myoma but is frequently prescribed for infertility. This may imply that, in the Chang Gung hospitals, Zou-Gui-Wan is prescribed among women of reproductive age with uterine myoma complicated with infertility or recurrent abortions. This is consistent with the fact that the myoma patients in our CGRD study were younger than in Yen et al.'s NHIRD study. The third most frequently prescribed formula in our study was Gui-Zhi-Fu-Lin-Wan, the effect of which was to invigorate blood circulation and eliminating stasis. This was the most frequently prescribed formula in Yen et al.'s study. When combined with Western medical treatment, Gui-Zhi-Fu-Lin-Wan has

synergistic efficacy for the treatment of myoma.[25] Gui-Zhi-Fu-Lin-Wan is also prescribed in endometriosis, and it was the most frequently prescribed formula for endometriosis in Tsai et al.'s NHIRD study in Taiwan.[22]

The most frequently prescribed single herb for the treatment of myoma in the CGRD study was Xian-fu (*Rhizoma Cyperi*), with the treatment effect of dispersing liver and regulating qi. It was the third most frequently prescribed single herb in Yen et al.'s study. Xian-fu has been found to have antioxidant, anti-inflammatory, and potentially neural protective effects.[26] The second most frequently prescribed single herb in our study was Yan-Hu-Suo (*Rhizoma Corydalis*), which was the fifth most frequently prescribed single herb in Yen et al.'s study. Yan-Hu-Suo has an analgesic effect and may be used to treat dysmenorrhea in myoma patients. The compound L-tetrahydropalmatine, which is extracted from Yan-Hu-Suo, has good anesthetic and analgesic effects.[27, 28] This may imply that the myoma patients in the CGRD study had more pain than those in the NHIRD study, and this may be the reason that Yan-Hu-Suo was prescribed more frequently. The third most frequently prescribed single herb in our study was Dan-Shen, which was the sixth most commonly prescribed single herb in Yen et al.'s study. Yi-Mu-Cao (*Herba Leonuri*) was the fourth most commonly prescribed single herb in both our study and Yen et al.'s study. Yi-Mu-Cao, also termed the Chinese Motherwort, has treatment effects of invigorating blood circulation and eliminating blood stasis, and inducing diuresis for removing edema; it is most commonly prescribed for dysmenorrhea, postpartum abdominal pain, and hypermenorrhagia. A recent study of the unique alkaloid, leonurine, found in Yi-Mu-Cao, showed that it has antioxidant, anti-apoptotic, and anti-inflammatory effects and may improve micro-circulation.[29] Thus, treatment effects of Yi-Mu-Cao may include invigorating blood circulation and eliminating blood stasis in ischemic heart disease and cardiac fibrosis. These findings may provide scientific evidence informing TCM treatment logic. Taken together, it appears that the patients in our study complained most about anxiety and infertility problems, and thus Jia-Wei-Xiao-Yao-San, Xiang-Fu, and Zou-Gui-Wan were prescribed frequently. The patients in our study also expressed more pain symptomology, so that herbs with analgesic effects (i.e., Yan-Hu-Suo, and Yi-Mu-Cao) were more commonly prescribed. The effects discussed above may account for the differences observed between our study and that of Yen et al.

ARM can help discover frequent prescription combinations of formulas and single herbs, which may help uncover hidden treatment theories and inform medical education and medical decision-making. The confidence between the decoction pieces of Chuan-Xiong, Dang-Gui, Shu-Di-Huang, and Bai-Sao was much higher (> 90%) than that of other herbal powders, which implies that these four decoction medicines were frequently prescribed as a group. In TCM clinical practice, these four decoctions form the Si-Wu-Tang formula, whose function is to tonify blood and promote menstruation. In TCM clinical practice, the Si-Wu-Tang decoction may treat menorrhagia and hypermenorrhagia of myoma patients with anemia symptoms.[30] In phenylhydrazine-induced hemolytic anemia in rats, extracts of Si-Wu-Tang exhibited hemopoietic effects,[31] which may provide evidence for TCM clinical practice.

The other medicine combinations with high confidence are common TCM herbal treatments for pain in gynecologic disease. For example, in Table 4, the confidence levels of combination values for Yan-Hu-

Suo/Xiang-Fu as well as Wu-Lin-Zhi/Pu-Huang were > 40%. These two combinations may have synergistic effects for promoting qi to activate blood and analgesia and can thus be used in treating dysmenorrhea or benign gynecology tumors (i.e., myoma, endometrioma, adenomyosis). In addition, the combination of Yan-Hu-Suo/Xiang-Fu has high support and confidence, implying that this herbal pair is frequently used to treat myoma. The combination of Zou-Gui-Wan and Xiang-Fu can have synergistic effects for treating infertility. Combining Nu-Zhen-Zi with Han-Lian-Cao forms a new combination, termed Er-Zhi-Wan. Its function is to tonify the liver and kidney yin and it may be prescribed for hypermenorrhagia in chronic anemia patients. The support of each herbal pair showed the prevalence of the combination in treating myoma. TCM herbal pairs may exhibit synergistic effects, such as those of the common herbal pair *Radix notoginseng* and *Radix Salivae Miltiorrhizae*, which are used in TCM for invigorating blood circulation and eliminating stasis. The biological basis of this combination includes a complex network of activities involving apoptosis, superoxide dismutase, intercellular adhesion molecule-1, etc.[19]

SNA can help visualize and clarify treatment logic and medical decision-making. Results of SNA may determine physicians' general treatment logic and medication prescription tendency. For example, SNA can help visualize the core combination of medicines for the treatment of uterine fibroids (i.e., Xiang-Fu/Dan-Shen/Jia-Wei-Xiao-Yao-San/Yan-Hu-Suo/Zuo-Gui-Wan). This may help educate TCM physicians, especially younger TCM physicians, in TCM clinical reasoning for treating uterine fibroids and may shorten and simplify physician training and continuing medical education.

Another clinical reasoning example may be deduced from the iron supplement data. Menorrhagia and hypermenorrhagia among myoma patients may lead to iron deficiency anemia[9, 32]; thus, iron supplementation is frequently necessary for these patients. Because the iron supplements were prescribed during WM outpatient visits, they can only be analyzed in the WM-only group or the combined therapy group. As seen in Table 5, the ratio of patients receiving iron supplementation was similar in the WM-only (6.5%) and combined therapy groups (6.7%). However, the WM OPD visit number and PLB001M/PLB012M pills prescribed per patient were statistically significantly higher in the combined therapy group. This may imply that these patients searched for combined therapies due to severe anemia related to uterine fibroids and thus visited WM physicians more frequently to receive iron supplements. This may be consistent with the finding that the Si-Wu-Tang cluster seen in the SNA analysis of our study is frequently prescribed to treat severe anemia. A previous study [33] demonstrated that Chinese medicine may reduce conventional WM medicine consumption and annual medical costs in treating uterine fibroids owing to its low cost. TCM may thus be employed in future combined therapies in the Chang Gung Memorial Hospitals.

Despite our findings and the substantial strengths of this study, the present study has some limitations. First, although our study used the same ICD-9 codes as the Yen et al. NHIRD study, the patient medical record time span in Yen et al.'s NHIRD study (2002–2010) differed from ours (2005–2014). Thus, these studies need to be compared with caution. Only 6 years of data were matched (2005–2014), i.e., data in CGRD were also included in NHIRD. Second, although imaging findings and laboratory data could be

obtained from the CGRD, we could not analyze these findings because the data fluctuated with the menstruation cycle. Similarly, manual extraction of myoma size data from the ultrasound reports is challenging, costly, and beyond the scope of the current study. Thus, treatment efficacy for reducing myoma size could not be evaluated.

Conclusions

To our knowledge, this is the first study of TCM myoma treatment within the CGRD. We compared our findings to those of the TCM NHIRD myoma study. Prescription patterns examined through ARM and SRA may inform physicians' treatment logic and will help educate TCM physicians. We also demonstrate that iron supplementation differed in the combined therapy and WM-only groups, which may imply severe iron deficiency anemia. Doctors in the medical center may consider combining TCM prescription and iron supplements to treat severe anemia. The data from the CGRD is inherently different from the NHIRD in terms of population and patient characteristics; thus, the prescription patterns are expected to differ. The promotion of combined therapy for myoma patients may help clarify treatment effects in future research, and may thus inform medical guidelines and an evidence base for medical decision-making.

Abbreviations

ARM: Association rule mining

CGRD: Chang Gung Research Database

CHM: Chinese herbal medicine

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

NHIRD: National Health Insurance Research Database

OPD: outpatient department

SNA: social network analysis

TCM: Traditional Chinese medicine

WM: Western medicine

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Institutional Review Board of Chang Gung Memorial Foundation: approval number 201900089B0C501) and with the 1964 Helsinki

Declaration and its later amendments or comparable ethical standards. The ethics approval committee waived the requirement for informed patient consent due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Chang Gung Research Database 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 however available from the authors upon reasonable request and with permission of Institutional Review Board of the Chang Gung Memorial Foundation..

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SL Kuo analyzed and interpreted the traditional Chinese medicine (TCM) data and was a major contributor in writing the manuscript. WC Chen analyzed and interpreted the gynecology-related data. MC Kao were consulted for TCM interpretation. HY Lin gathered the data, informed the discussion, and drafted graphs. YI Chiang performed statistical analysis. WJ Wu performed the ARM/SNA data extraction as well as manuscript review and editing. MJ Chiu provided TCM pharmacy funding acquisition and WJ Wu and MJ Chiu contributed to the study design. All authors read and approved the final manuscript.

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Figures

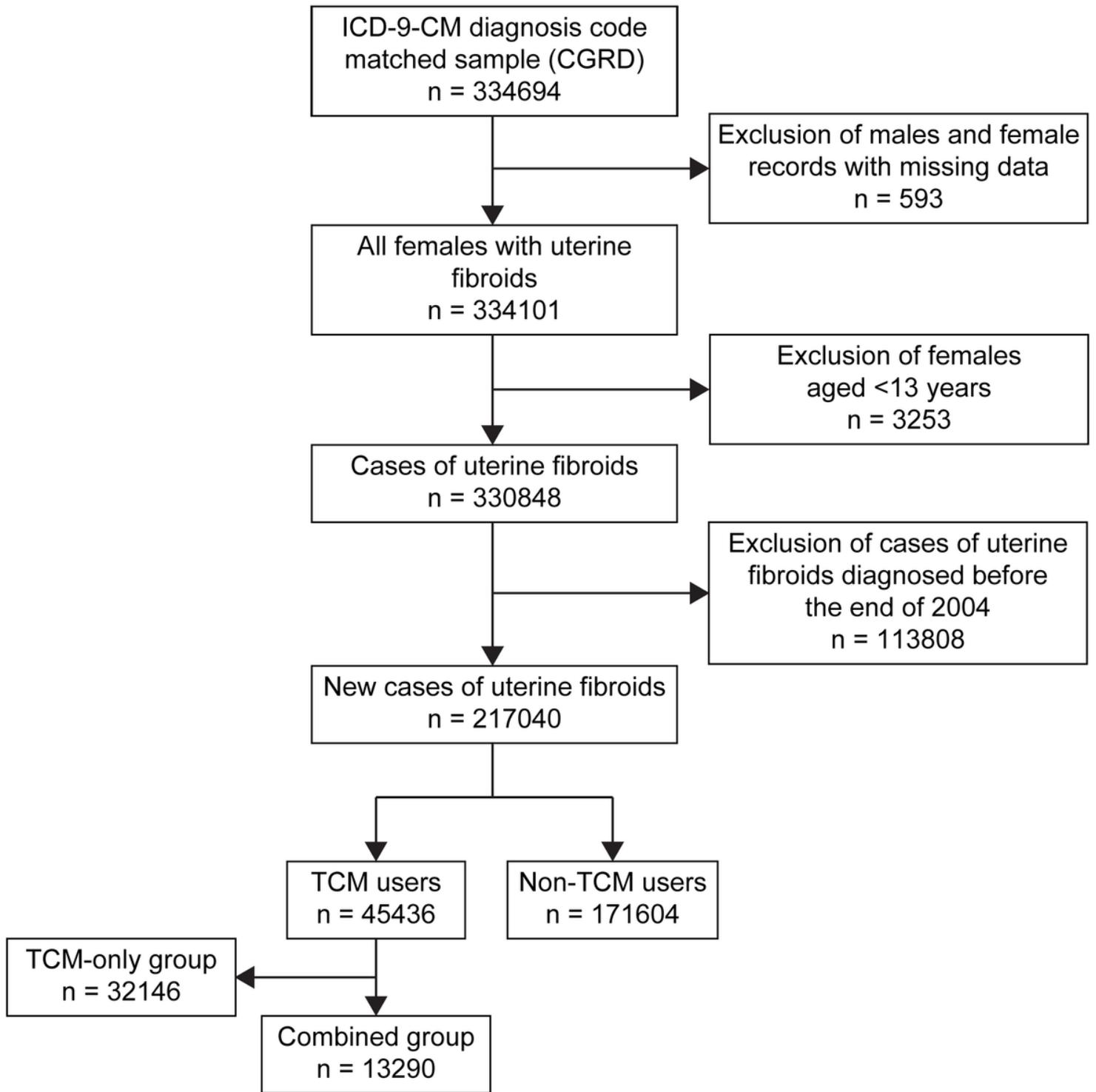


Figure 1

Flow chart of participants selected from the CGRD in Taiwan. CGRD, Chang Gung Research Database; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; TCM, traditional Chinese medicine

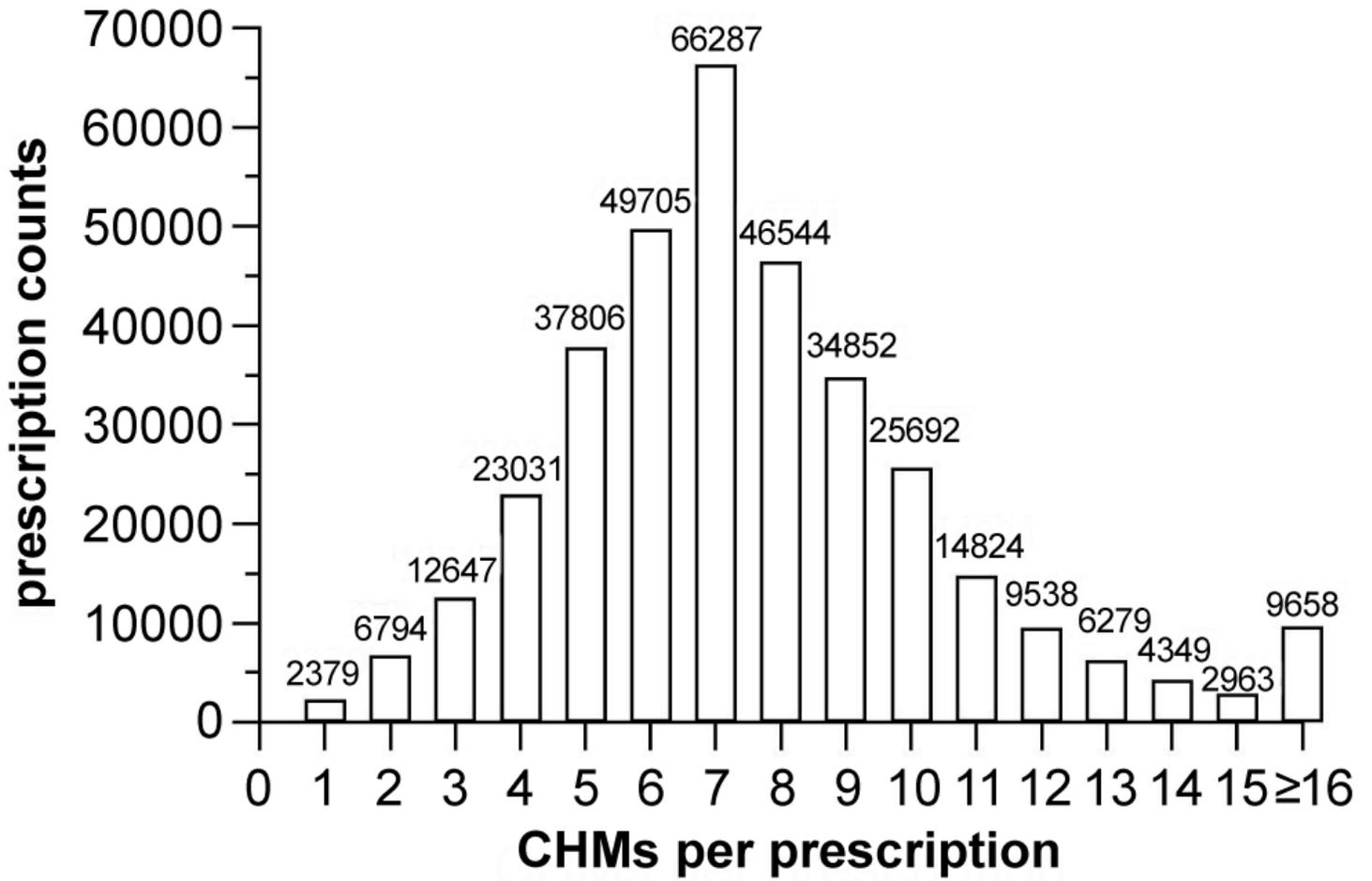


Figure 2

Distribution of Chinese herbal medicines (CHMs) per prescription for the treatment of uterine myoma.

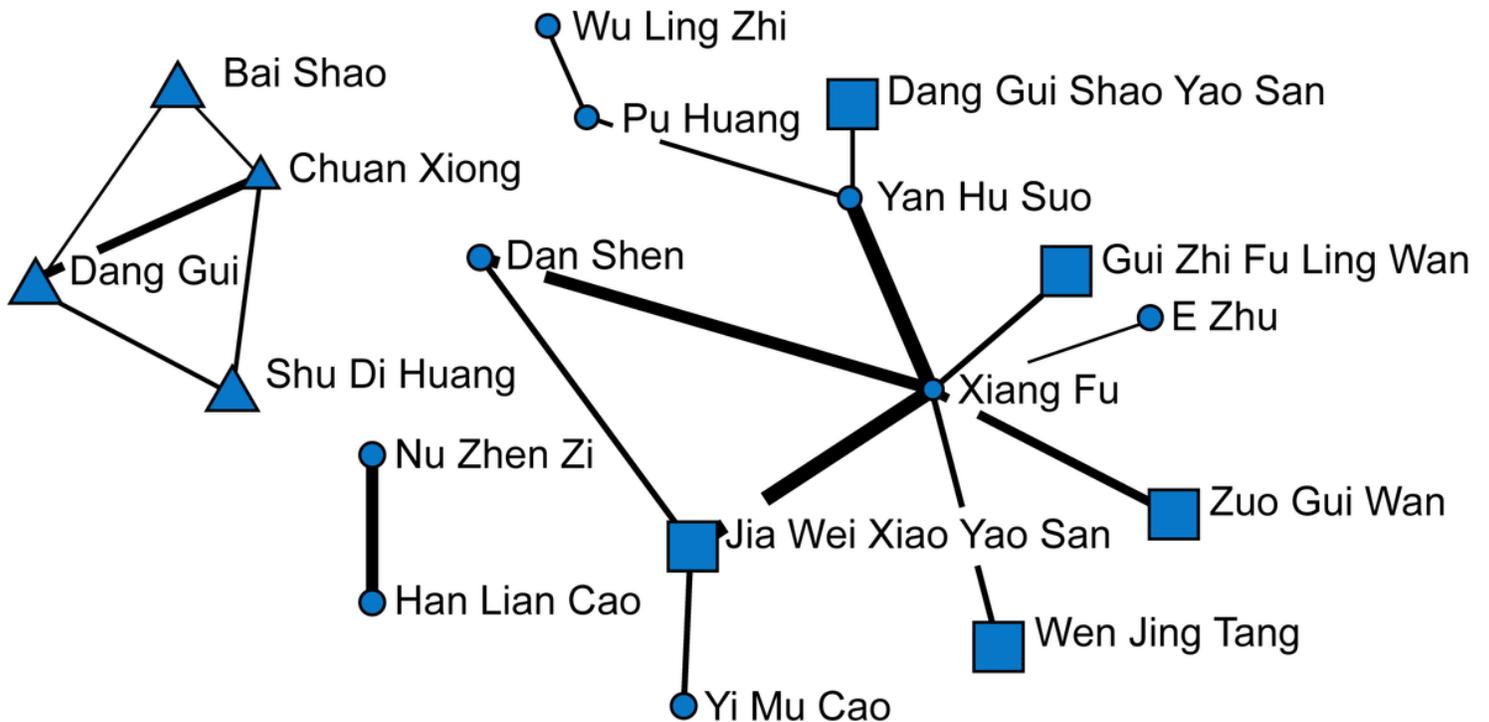


Figure 3

Social network analysis of Chinese medicine prescriptions for patients with uterine fibroids. The □ symbol represents the powder form of the formula. The △ symbol represents the decoction piece of the single herb. The ● symbol of represents the powder form of the single herb.