Data mining in Xu Runsan's Traditional Chinese Medicine practice: treatment of chronic pelvic pain caused by pelvic inflammatory disease

Liu Liuqing, Yang Fang, Xin Ling, Jing Yan

Liu Liuqing, First Clinical Medical School of Beijing University of Chinese Medicine, Beijing 100700, China
Yang Fang, Jing Yan, Traditional Chinese Medicine Gynecology Department, China-Japan Friendship Hospital, Beijing 100029, China
Xin Ling, First Affiliated Hospital of Anhui University of Chinese Medicine, Hefei 230001, China.
Correspondence to: Prof. Jing Yan, Traditional Chinese Medicine Gynecology Department, China-Japan Friendship Hospital, Beijing 100029, China. jingy1959@sina.com
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Abstract

OBJECTIVE: To research the Traditional Chinese Medicine (TCM) practice of Professor Xu Runsan for treatment of chronic pelvic pain (CPP) caused by sequelae of pelvic inflammatory disease (SPID) by data mining.

METHODS: The medical records of inpatients at China-Japan Friendship Hospital confirmed to have CPP caused by SPID were collected (274 visits in total). The data extracted from the medical records were analyzed by frequency statistics, correlation analyses, cluster analyses, and complex network analyses.

RESULTS: The most frequently used medicines were warm medicines, bitter medicines, and medicines distributed to the liver meridian. The most common medicinal combinations were Chishao (Radix Paeoniae Rubra) plus Huangqi (Radix Astragali Mongolici) plus Sanqi (Radix Notoginseng) and Ezhu (Rhizoma Curcumae Phaeocaulis); Guizhi (Ramulus Cinnamomi) plus Fuling (Poria) and Chishao (Radix Paeoniae Rubra); and Chaihu (Radix Bupleuri Chinensis) plus Zhishi (Fructus Aurantii Immaturus) and Gancao (Radix Glycyrrhiza). The most frequently used medicines were divided into four groups according to their efficacy; i.e., medicines that could (a) warm meridians and free collateral vessels, (b) regulate Qi and free collateral vessels, (c) fortify the spleen and nourish blood and Qi, and (d) tonify Qi and activate blood. The most commonly used formulations were Guizhi Fuling Pill and Sini Powder. The core medicines extracted based on complex network analyses were Chishao (Radix Paeoniae Rubra), Sanqi (Radix Notoginseng), Huangqi (Radix Astragali Mongolici), Danshen (Radix Salviae Miltiorrhizae), Ezhu (Rhizoma Curcumae Phaeocaulis), Gancao (Radix Glycyrrhiza), Chaihu (Radix Bupleuri Chinensis), Guizhi (Ramulus Cinnamomi), Shuizhi (Hi-rudo), Fuling (Poria), and Zhishi (Fructus Aurantii Immaturus).

CONCLUSION: According to the TCM practice of Professor Xu, treatment of CPP caused by SPID should focus on dissolving stasis and obstructions using medicines that can activate blood, resolve stasis, regulate Qi, and dissipate adhesions. His prescriptions are often based on Guizhi Fuling Pill and Sini Powder. More blood-activating, stasis-resolving, or tonifying medicines could be used according to the accompanying symptoms or symptom patterns identified.

Keywords: Pelvic pain; Pelvic inflammatory disease; Drugs, Chinese herbal; Cluster analysis; Complex network analysis
INTRODUCTION

Pelvic inflammatory disease (PID) is one of the most common diseases in women of reproductive age. PID is characterized by infection and inflammation of the upper genital tract. Without appropriate and timely treatment, PID can cause several long-term sequelae (tubal infertility, ectopic pregnancy, and chronic pelvic pain), which are termed sequelae of PID (SPID, previously termed chronic PID). One of the clinical features of SPID, chronic pelvic pain (CPP), can lead to certain physiological dysfunction and psychological problems. Western Medicine has limited methods for treating CPP due to SPID because of the essential pathologic changes that occur: tissue destruction, inflammatory exudation, tissue hyperplasia, and formation of adhesions and scars. CPP is not an infectious inflammation; thus, it is not sensitive to antibiotic treatment. Finite evidence supports the use of nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, gabapentin, and serotonin-norepinephrine reuptake inhibitors for chronic pelvic pain, while evidence-based therapy still remains limited. Laparoscopic adhesiolysis can temporarily relieve pelvic and abdominal pain. However, sufficient evidence of the efficacy of this treatment is lacking, and such treatment can cause more complications. Traditional Chinese Medicine (TCM) emphasizes treatment based on identification of symptom patterns. Clinical studies have suggested that TCM can satisfy some unmet medical needs in patients with CPP and alleviate pain by improving their mental state and quality of life. Professor Xu Runsan (hereafter referred to as "Xu") from China-Japan Friendship Hospital (Beijing, China) is one of 500 well-known TCM practitioners in China. He has engaged in clinical research and treatment of TCM for over 70 years with a wealth of clinical experience, and now he still keeps working at the advanced age of 93 years old. Xu has studied CPP caused by SPID for many decades and has accumulated considerable experience in its treatment. From the perspective of TCM theory, Xu proposes that the basic pathogenesis of SPID is blood stasis in the conception vessel and thoroughfare vessel. Hence, he has proposed the therapeutic principle of activating blood and dredging the collateral vessels. Under his leadership, the TCM Gynecology Department in China-Japan Friendship Hospital has achieved good outcomes in treating SPID and relieving CPP based on a TCM approach. Most of Xu’s studies have been subjective theoretical summaries that lack real data. Thus, illustration of TCM theory using information from actual cases analyzed by objective means is important. Although one study of Xu’s experience in using medications for treating SPID did have data support, the statistical analysis method was relatively simple: it involved the counting of medications and formulations but lacked analyses of the associations between medicines. Thus, the study had limitations in revealing the characteristics of medication use and the hypotheses formulated by Xu, necessitating more in-depth studies with diversified data-mining methods. In the present study, we applied data mining to Xu’s TCM practice for treating CPP caused by SPID.

MATERIALS AND METHODS

Medical records

The medical records of patients diagnosed with CPP caused by SPID who were admitted to the TCM Gynecology Department of China-Japan Friendship Hospital and whose medicines were prescribed by Xu from 1 January 2014 to 31 December 2017 were collected.

Diagnostic criteria for SPID

The diagnostic criteria for SPID were determined by referring to the relevant content regarding SPID in the Guidelines for the Diagnosis and Treatment of Common Diseases in Gynecology of Traditional Chinese Medicine issued by the China Association of Chinese Medicine in 2012. Medical history: the patients’ medical history included PID or recurrent PID, infertility, acute pelvic infection, or acute appendicitis. Symptoms: the main manifestations were abdominal pain and/or lumbosacral pain, possibly accompanied by leukorrhea, irregular menstruation, low-grade fever, fatigue, or other systemic manifestations. Signs: physical examination showed (a) retroversion, retroflexion, and limited activity of the uterus possibly accompanied by tenderness; (b) palpable cords, flaky thickening, tenderness, or a cystic mass on one or both sides of the uterus; and (c) cervical pain or thickening and tenderness of the uterosacral ligaments if the pelvic connective tissue was inflamed.

Diagnostic criteria for CPP

The diagnostic criteria for CPP were based on the definition of chronic pelvic pain in Chronic Pelvic Pain (edited by Chen Baicheng and Zhang Jing). The minimum diagnostic criterion for CPP was pain in the pelvis and its surrounding tissues as the main symptom with a duration of ≥ 6 months.

Inclusion criteria

The medical records of patients who satisfied all of the following criteria were included in the study: (a) the above-stated diagnostic criteria for SPID were met, (b) the above-stated diagnostic criteria for CPP were met, (c) accurate and complete medical records were available, and (d) Chinese medicines had been prescribed by Xu.

Exclusion criteria

The medical records of patients with one or more of the following conditions were excluded from the study:
(a) endometriosis, adenomyosis, pelvic congestion, tuberculous PID, gynecological tumors, or other gynecological diseases that might cause chronic pain; (b) diseases of other systems (e.g., digestive, motor, or urinary) that could also induce pelvic and lumbosacral pain; (c) infertility and a desire for fertility during the treatment; (d) fewer than two hospitalizations or no relief of symptoms (e.g., abdominal or lumbosacral pain) as indicated in the medical records; (e) pregnancy or lactation; (f) severe primary diseases of the cardiovascular, digestive, urinary, immune, or hematologic systems; and (g) cancer, psychoses or cognitive impairment.

Collection and screening of patients
A total of 104 patients met the inclusion criteria according to their medical records. After screening of patients using the exclusion criteria, 56 patients’ medical records were retained. Each patient, after being questioned and examined by Xu at each ward round, was prescribed a specific prescription according to the patient’s current symptoms, signs, tongue features, and pulse. In this way, 274 prescriptions were made among these 56 patients. To facilitate the statistical analyses, a new prescription was regarded as a new visit. Finally, the medical records of 274 visits were included in the present study.

Establishment of database
The basic information in the medical records (patient age, complaints, prescriptions, and medicines) was extracted and inputted into a “cases collection system”.

Data pretreatment
The medicines entered into the database were standardized according to the standard name of the medicine recorded in the Pharmacopoeia of the People’s Republic of China (2015).

Data quantification
The assignment of medicines was performed using a binary method (appearance vs absence). If the medicine appeared, it was recorded as “1”; otherwise, it was recorded as “0”.

Frequency statistics
Frequency statistics for medicines and prescriptions were calculated with a clinical data multidimensional retrieval query and display system for TCM formulations. The basic formulation used in each prescription was recorded. If the prescription was a combination of more than one basic formulation, the name of each formulation was recorded. If it was a self-composed prescription (prescriptions without a fixed medicine or formulation), it was recorded as “Zini Fang” (in Pinyin).

Characteristics of medicines
The characteristics of medicines were based on the TCM theory of property, flavor, and meridian tropism. The properties of medicines were classified as “cold”, “hot”, “warm”, “cool”, or “mild”. The flavors of medicines were classified as “sour”, “bitter”, “sweet”, “pungent”, or “salty”. The final parameter was meridian tropism. The frequency of each property, flavor, and meridian was counted. The characteristics of the medicines were verified according to the 2015 edition of the Pharmacopoeia of the People’s Republic of China.

Correlation analyses
Correlation analyses were conducted using SPSS Clementine 11.1 (IBM Corp., Armonk, NY, USA). We used the Apriori algorithm to model and acquire the support, confidence, and lifting degree of the data. Samples with high confidence, high support, and a lifting degree of > 1 were selected as frequently used medicinal combinations. We set the minimum confidence as 85% and the minimum support as 40%. Only combinations satisfying the minimum thresholds for support and confidence were selected and analyzed. Based on Xu’s prescribing habits, we set the Former Item as two medicines to obtain a medicine combination with three or more medicines, while the default of the Latter Item was one medicine.

Cluster analyses
Cluster analyses were conducted using SPSS statistics 20.0 (IBM Corp., Armonk, NY, USA). Similarity between variables was detected by Pearson’s correlation coefficient, and similar data were classified into one class. Hence, we categorized the medicines according to classes, and medicines in the same class were regarded as a group.

Complex network analyses
Complex network analyses were conducted with Liquorice software (Digitas Liquorice, Cape Town, Western Cape, South Africa). We analyzed the rules of medicine combinations to obtain the core medicines using the Java rich client platform and complex network (or social network) analytical methods.

RESULTS
The age range of the study cohort was 24 to 50 years (mean, 32 years) (Figure 1). The shortest course of CPP caused by SPIID was 6 months, and the longest was approximately 20 years.

Medicines and formulations
Of the 274 prescriptions included in the present study, 180 medicines were used. The medicines in these 274 prescriptions were recorded 3334 times in total. The mean number of medicines per prescription was 12.17.
Frequency of medicines
Seventeen medicines had a frequency of use of >20%. Table 1 shows the 17 medicines used most frequently. Chishao (Radix Paeoniae Rubra) was used most frequently (210 times, 76.64%).

Properties of medicines
All medicines (except the rarely used medicines not included in the Pharmacopoeia of the People’s Republic of China) were classified according to their properties based on the four Qi theory of TCM. The frequency of use of each medicine in each category was counted separately (Table 2, Figure 2). The frequently used medicines stated above were also classified by the same method (Table 3, Figure 3). Among all medicines and frequently used medicines, warm medicines accounted for the largest proportion (approximately 45%) and cold medicines accounted for approximately 30%.

Flavors of medicines
The occurrence of each flavor among all medicines (except the rarely used medicines not included in the Pharmacopoeia of the People’s Republic of China) was counted separately. The frequency of each flavor of the frequently prescribed medicines stated above was calculated by the same method. Among all medicines and the most frequently used medicines, "bitter" and "sweet" were the flavors with the highest frequency, followed by pungency (Table 4).

Meridian tropism of medicines
The meridian tropism of all medicines (except the rarely used medicines not included in the Pharmacopoeia...
Percentage did not add up to 100 because of rounding up of values. The final property in each category among the most frequently used medicines; proportion: frequency in each category/total frequency; frequency: sum of use of each medicine with a certain medicine in the present study contained 281 formulations. The names of the formulations used in prescriptions written in all visits were recorded. The prescriptions of the People’s Republic of China was counted. The frequency of each meridian was calculated separately. The liver meridian appeared much more frequently than the others (2099 times), followed by the spleen meridian (1567 times) (Figure 4).

Table 2 Properties of medicines

<table>
<thead>
<tr>
<th>Medicinal property</th>
<th>Frequency (times)</th>
<th>Occurrence frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm</td>
<td>1507</td>
<td>45.42</td>
</tr>
<tr>
<td>Cold</td>
<td>916</td>
<td>27.61</td>
</tr>
<tr>
<td>Mild</td>
<td>751</td>
<td>22.63</td>
</tr>
<tr>
<td>Hot</td>
<td>107</td>
<td>3.22</td>
</tr>
<tr>
<td>Cool</td>
<td>37</td>
<td>1.12</td>
</tr>
<tr>
<td>Total</td>
<td>3318</td>
<td>100</td>
</tr>
</tbody>
</table>

Notes: warm: warm medicines; cold: cold medicines; mild: mild medicines; cool: cool medicines. Frequency: sum of use of each medicine with a certain property in each category among all medicines; occurrence frequency: frequency in each category/total frequency.

Figure 2 Proportional distribution of different medicinal properties among all medicines Warm: warm medicines; cold: cold medicines; mild: mild medicines; hot: hot medicines; cool: cool medicines.

Figure 5 lists the formulations used that had a frequency of > 1.5%. The most common formulations were Guizhi Fuling pill (95 times, 34.67%) and Sini powder (85 times, 31.02%).

Correlation analyses

SPSS Clementine 11.1 (IBM Corp., Armonk, NY, USA) was used for the correlation analyses. Combinations with support of ≥ 40% and confidence of ≥ 85% with two medicines as the Former Item and one medicine as the Latter Item were selected. The medicines most frequently used as a combination were Chishao (Radix Paeoniae Rubra), Huangqi (Radix Astragali Mongolic), Sanqi (Radix Notoginseng), Ezhu (Rhizoma Curcumae Phaeocaulis), Guizhi (Ramulus Cinnamomum), and Fuling (Poria) (Table 6).

Cluster analyses

According to the frequency statistics of the medicines mentioned above, the 17 most frequently used medicines (frequency of > 20%) were selected for cluster analyses (Figure 6). According to the combination processes shown in Figure 6, the combinatory relationship of medicines in each category was reasonable according to the theory of TCM when those medicines were classified into four categories (Table 6).

Complex network analyses

Complex network analyses of all medicines were carried out. The 11 medicines closest to the core were finally selected. As shown in Figure 7, the core medicines were Chishao (Radix Paeoniae Rubra), Sanqi (Radix Notoginseng), Huangqi (Radix Astragali Mongolic), Danshen (Radix Salviae Miltiorrhizae), Ezhuhu (Rhizoma Curcumae Phaeocaulis), Gancao (Radix Glycyrrhizae), Chaihu (Radix Bupleuri Chinensis), Guizhi (Ramulus Cinnamomum), Shuizhi (Hirudo), Fuling (Poria), and Zhishi (Fructus Aurantii Immaturus). These medicines comprised the core formulation used for the treatment of CPP caused by SPID.

DISCUSSION

Characteristics of medicines

In the present study, warm medicines were used most...
frequently for treatment of CPP caused by SPID. Warm medicines can heat the blood and increase the blood circulation, thus helping to resolve stasis and relieve pain caused by cold and stagnation. What’s more, some medicines, such as Huangqi (Radix Astragali Mongolici), Baizhu (Rhizoma Atractylodis Macrocephalae), and Danggui (Radix Angelicae Sinensis), are both warm and sweet; those medicines can be warming and nourishing, thus reinforcing healthy Qi (also called “anti-pathologic Qi”) and helping to eliminate pathogenic factors.

Bitter and pungent medicines were used frequently in the present study. Pungent medicines have upward and outward effects of dispersing, whereas bitter medicines have downward effects such as purgation. Using pungent medicines and bitter medicines in combination can dissolve stagnation of Qi and blood. This allows Qi and blood to circulate smoothly, which can relieve pain. Sweet medicines were also used in the present study. In general, sweet medicines not only relieve spasms and pain but also reinforce healthy Qi to treat the pain caused by weakness.

The 17 most frequently used medicines in the present study included 7 medicines that can promote blood cir-

### Table 4 Flavors of medicines

<table>
<thead>
<tr>
<th>Medicinal Flavor</th>
<th>Frequency in all medicines (times)</th>
<th>Medicinals (number of medicinals)</th>
<th>Frequency in frequently used medicines (times)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitter</td>
<td>1891</td>
<td>Chishao (Radix Paeoniae Rubra), Sanqi (Radix Notoginseng), Ezhu (Rhizoma Curcumae Phaeocaulis), Danshen (Radix Salviae Moldi) (3), Chaishi (Radix Bupleuri Chinesis), Shuizhi (Hirudo), Zhishi (Fructus Aurantii Immaturus), Baizhu (Rhizoma Atractylodis Macrocephalae), Taoren (Semen Persicae), Chuanxuduan (Radix Dipsaci Apetoidis) (10)</td>
<td>1240</td>
</tr>
<tr>
<td>Sweet</td>
<td>1537</td>
<td>Sanqi (Radix Notoginseng), Huangqi (Radix Astragali Mongolici), Fuling (Poria), Gancao (Radix Glycyrrhiza), Guizhi (Ramulus Cinnamomi), Baizhu (Atractylodis Macrocephalae Rhizoma), Taoren (Semen Persicae), Danggui (Angelicae Sinensis Radix) (8)</td>
<td>987</td>
</tr>
<tr>
<td>Pungent</td>
<td>1276</td>
<td>Ezhu (Rhizoma Curcumae Phaeocaulis), Guizhi (Ramulus Cinnamomi), Chaishi (Radix Bupleuri Chinesis), Zhishi (Fructus Aurantii Immaturus), Danggui (Radix Angelicae Sinensis), Weilingxian (Radix et Rhizoma Clematidis Chinesis), Chuanxuduan (Radix Dipsaci Apetoidis) (7)</td>
<td>668</td>
</tr>
<tr>
<td>Salty</td>
<td>423</td>
<td>Shuizhi (Hirudo), Mul (Concha Ostreae), Weilingxian (Radix et Rhizoma Clematidis Chinesis) (3)</td>
<td>225</td>
</tr>
<tr>
<td>sour</td>
<td>221</td>
<td>Zhishi (Fructus Aurantii Immaturus)</td>
<td>103</td>
</tr>
</tbody>
</table>

Note: frequency: sum of use of each medicine with a certain flavor in each category among the 17 most frequently used medicines.
The total proportion of these two types of medicines accounted for > 50% of the most frequently used medicines, which reflects the importance attached by Xu to treating blood stasis in the collateral vessels for relief of CPP.

Some tonifying and replenishing medicines also accounted for a large proportion of medicines used. These medicines included those that can replenish Qi [Sanqi (Radix Notoginseng), Huangqi (Radix Astragali Mongolici), Gancao (Radix Glycyrrhiza)], and Baizhu (Rhizoma Atractylodis Macrocephalae), nourish blood [Danggui (Radix Angelicae Sinensis) and Danshen (Radix Salviae Miltiorrhizae)], tonify the spleen [Fuling (Frustra Poria)], and tonify the kidney [Chuanxu (Radix Paeoniae Rubra)]

These findings suggest that in addition to dissolving blood stasis in collateral vessels, Xu also pays attention to reinforcing healthy Qi. This strategy can help to alleviate pain associated with deficiency syndromes and improve blood and Qi circulation to remove stasis and stagnation.

### Medicines used in combination

The medicinal combinations frequently used to treat CPP caused by SPID were identified through correlation analyses and cluster analyses. These medicinal combinations were classified into three groups. The first group comprised Chishao (Radix Paeoniae Rubra), Huangqi (Radix Astragali Mongolici), Sanqi (Radix Notoginseng), and Ezhu (Rhizoma Curcumae Phaeocaulis). Those four medicines, especially the first three, are often used in combination with one another. Ch-
ishao (Radix Paeoniae Rubra) can clear heat to cool the blood and dissolve stasis. Huangqi (Radix Astragali Mongolici), which is warm in property and sweet in flavor, can tonify Qi. Sanqi (Radix Notoginseng) can promote blood circulation to remove blood stasis and nourish Qi and blood. The combination of these three medicines can resolve stasis and strengthen healthy Qi. Moreover, a combination of cold and warm medicines can reduce the bias of the medicinal property and extend the range of applications. When adding Ezhu (Rhizoma Curcumae Phaeocaulis), which has the action of breaking blood, dispelling stasis, and enhancing the effect of attacking pathologic factors, the combination can dissipate binds and resolve stasis.

The second group comprised Guizhi (Ramulus Cinnamomomi), Chishao (Radix Paeoniae Rubra), and Fuling (Poria). Guizhi (Ramulus Cinnamomomi) moves stagnation in meridians and collateral vessels by warming the channels and increasing blood circulation. Chishao (Radix Paeoniae Rubra) can dissipate blood stasis. Fuling (Poria) has a bland flavor and an efficacy of draining dampness. A combination of those three medicines can remove pathologic factors (e.g., stasis and phlegm) and dredge collateral vessels. These three medicines are also important ingredients in the classic formulation Guizhi Fuling Pill.

The third group comprised Chaihu (Radix Bupleuri Chinesis), Zhishi (Fructus Aurantii Immaturus), and Gancao (Radix Glycyrrhizae). According to the cluster analyses, these three medicines are often used in combination. Chaihu (Radix Bupleuri Chinesis) can soothe the liver and raise Qi. Zhishi (Fructus Aurantii Immaturus) can break Qi and remove stagnation. Gancao (Radix Glycyrrhizae) can tonify Qi and relax tension. Using medicines with different effects can move Qi and disperse stagnation to dredge collaterals. Adding Chishao (Radix Paeoniae Rubra) to these three medicines results in the classic formulation Sini Powder.

**Prescription characteristics**

The statistical analyses revealed that most of the prescriptions in our study were based on classic formulations and that on average, each prescription contained 12.17 medicines. Xu prefers classic formulations and believes that they have a simpler recipe and greater effect than non-classic formulations. The classic formulations in the present study were Sini powder, Guizhi Fuling pill, Danggui Shaoyao powder, Yi fi Fuzi Baijiang powder, Da Chaihu decoction, and Mahuang Fuzi Xixin decoction. The most frequently used basic formulations for SPID in our study were Guizhi Fuling pill and Sini powder, each of which accounted for about one-third of the formulations. The statistical results of the prescriptions were consistent with the data for the medicinal combinations described above.

**Characteristics of core formulations**

The medicines used in core formulations were divided into three types according to efficacy: blood-activating medicines, Qi-regulating medicines, and tonics. Most medicines used in core formulations can activate blood and resolve stasis. An important medicine in our study

**Figure 6 Cluster analyses diagram**

This diagram showed the combination progress of the top 17 medicines in cluster analysis. Synthesizing the result of cluster analysis and the theory of Chinese medicine, we classified medicines into four categories: (a) Fuling (Poria), Guizhi (Ramulus Cinnamomomi), Taoren (Semem Persicae), Muli (Concha Ostreae), Weilingsian (Radix et Rhizoma Clematidis Chinensis), and Chuanyxuan (Radix Diplacis Asperidos), which could be regarded as modified Guizhi Fuling Pill and had the efficacy of activating blood and draining dampness to dredge the collaterals; (b) Baizhu (Rhizoma Atractylodis Macrocephala) and Danggui (Radix Angelicae Sinensis), the combination of which could replenish Qi and blood; (c) Chaihu (Radix Bupleuri Chinesis), Zhishi (Fructus Aurantii Immaturus), and Gancao (Radix Glycyrrhizae), which were the ingredients of Sini Powder and had the efficacy of regulating Qi to dredge the collaterals; (d) Sanqi (Radix Notoginseng), Huangqi (Radix Astragali Mongolici), Chishao (Radix Paeoniae Rubra), Ezhu (Rhizoma Curcumae Phaeocaulis), Danshen (Radix Salviae Miltiorrhizae), and Shuizhi (Hirudo), which consisted of many blood-activating medicines and one Qi-reinforcing medicinal, having the efficacy of reinforcing Qi to promote blood circulation.

**Figure 7 Complex network analyses**

The size of the dot of each medicine represents the nodal degree (or importance of the medicine). The line between the dots represents the relationship between medicines used simultaneously.
was Chishao (Radix Paeoniae Rubra), which can cool and activate blood and disperse stasis to relieve pain. Sanqi (Radix Notoginseng) can also dissipate stasis and relieve pain, but it can also strengthen Qi to some degree. Danshen (Radix Salviae Miltiorrhizae) can promote blood circulation and nourish blood, which can also improve hemorheology,\(^7\) improve the microcirculation,\(^8\) and inhibit fibrosis.\(^9\) Ezhu (Rhizoma Curcumae Phaeocaulis) has strong efficacy in breaking the stagnation of Qi and dispelling blood stasis. Shuizhi (Hirudo) can break the stagnation of blood in TCM theory. According to the research of modern pharmacology, it has the efficacy of antifibrosis\(^9\) and anticoagulation with bioactive molecules like hirudin, factor Xa inhibitor, anticoagulant peptides, and other substances.\(^9\) Guizhi (Ramus Cinnamomi) can warm blood vessels and meridians to activate blood and cure the pain of cold and blood stasis; it also has anti-inflammatory,\(^26,27\) anti-platelet aggregation, and antithrombotic activities.\(^28\) Chaihu (Radix Bupleuri Chinensis) can soothe the liver to relieve depression, clear heat, and disperse nodules. Zhishi (Fructus Aurantii Immaturus) dissipated accumulation and soothes the liver to break Qi stagnation in the abdomen, through which the liver meridian passes. Huangqi (Radix Astragali Mongolici) can strengthen Qi, which is beneficial for circulating blood.\(^29\) Therefore, Huangqi (Radix Astragali Mongolici) is often used in conjunction with medicines that can activate blood to increase the dissipation of stasis, dredge collateral vessels, and reduce the disadvantages of Qi consumption. Fuling (Poria) fortifies the spleen and drains dampness so that Yang can be inspired without the obstacle of dampness, which is beneficial for elimination of the pathologic factors of Yin (e.g., blood stasis and phlegm). Gancao (Radix Glycyrrhizae) can reconcile various medicines and improve the taste of decoctions with its sweet flavor.

The core medicines mentioned above were divided into four groups according to the relationships among the medicines used in combination as shown by the cluster analyses. Group 1 comprised Guizhi (Ramulus Cinnamomi), Chishao (Radix Paeoniae Rubra), Fuling (Poria), and Danshen (Salviae Miltiorrhizae Radix Et Rhizoma), which is similar to the recipe of the classic formulation Guizhi Fuling pill and has efficacy in dissolving blood stasis and dredging meridians and collaterals. Group 2 comprised Chaihu (Radix Bupleuri Chinensis), Chishao (Radix Paeoniae Rubra), Zhishi (Aurantii Fructus Immaturus), and Gancao (Radix Glycyrrhizae), which is the recipe of the classic formulation Sini Powder and has the function of breaking stagnation and regulating Qi to dredge collaterals. Group 3 comprised Sanqi (Radix Notoginseng), Ezhu (Rhizoma Curcumae Phaeocaulis), and Shuizhi (Hirudo). These medicines can activate blood and remove stasis, and some of these medicines have such robust effects that they can be used for treatment of severe blood stasis. Group 4 comprised Huangqi (Radix Astragali Mongolici), a tonic that can supplement the consumption of Qi and improve blood circulation.

### Treatment of CPP caused by SPID

Xu proposes that chronic PID, as a complex and refractory disease, not only shown as a single heat syndrome, but has some manifestations of deficiency-cold syndrome, as many patients complain about debility, fatigue and aversion of cold. When treating CPP, Xu emphasizes choosing appropriate medicines and formulations according to syndrome differentiation rather than using heat-clearing and detoxifying medicines directly. Additionally, as the deficiency-cold syndrome is common, warm medicines are frequently used. From a TCM perspective, Xu hypothesized that the pathogenesis of SPID involves blood stasis and stagnation. These blockages in meridians can obstruct the circulation of Qi and blood to cause chronic pain. This hypothesis refers to the main pathologic changes observed in SPID in Western Medicine (hyperplasia of fibrous tissue and formation of scars and adhesions). Hence, the main treatment goal is to resolve the blood stasis and stagnation in the meridians and collateral vessels of the abdomen and pelvic cavity.

In recent years, studies on blood rheology have shown that the blood circulation of patients with SPID (or animal models of SPID) is relatively viscous.\(^30,31\) Tissue adhesion can also be seen in the pelvic cavity of patients with SPID using laparoscopic methods. Such findings also demonstrate the validity of Xu’s hypothesis. Because of the characteristics of blood stasis and stagnation, the main therapeutic principle of CPP secondary to SPID is activating blood to resolve stasis, dredging

### Table 6 Cluster analysis of the 17 most frequently used medicinals

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of medicinals</th>
<th>Medicinals</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>6</td>
<td>Fuling (Poria), Guizhi (Ramulus Cinnamomi), Taoren (Semen Persicae), Multi (Concha Ostreae), Wellingxian (Radix et Rhizoma Clematidis Chinensis), Chuanxuduan (Radix Diplaci Aperoidis)</td>
</tr>
<tr>
<td>C2</td>
<td>2</td>
<td>Baizhu (Rhizoma Atractylodis Macrocephalae), Danggu (Radix Angelicae Sinensis)</td>
</tr>
<tr>
<td>C3</td>
<td>3</td>
<td>Chaihu (Radix Bupleuri Chinensis), Zhishi (Fructus Aurantii Immaturus), Gancao (Radix Glycyrrhizae)</td>
</tr>
<tr>
<td>C4</td>
<td>6</td>
<td>Sanqi (Radix Notoginseng), Huangqi (Radix Astragali Mongolici), Chishao (Radix Paeoniae Rubra), Ezhu (Rhizoma Curcumae Phaeocaulis), Danshen (Radix Salviae Miltiorrhizae), Shuizhi (Hirudo)</td>
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the meridians and collateral vessels, and dissipating stagnation and adhesions. Therapy can be achieved with the blood-activating medicines like Chishao (Radix Paeoniae Rubra), Sanqi (Radix Notoginseng), Ezhu (Rhizoma Curcumae Phaeocaulis), Guizhi (Ramulus Cinnamomi), Weilingxian (Radix et Rhizoma Clematidis Chinensis), Danshen (Radix Salviae Miltiorrhizae), and Taoren (Semen Persicae), most of which have bitter or pungent flavors. The medicines that can activate blood and regulate Qi can also consume Qi, and many patients feel fatigued after treatment. Patients also tend to feel weak and tired after a long duration of SPID before treatment is initiated. Therefore, Xu attaches great importance to the use of Qi-tonifying medicines [particularly Huangqi (Radix Astragali Mongolici)] combined with stasis-resolving medicines. The combination of Chishao (Radix Paeoniae Rubra), Huangqi (Radix Astragali Mongolici), and Sanqi (Radix Notoginseng) (one of the most frequently used medicinal combinations according to the correlation analyses) may strengthen Qi and expel blood stasis together, which is a concrete embodiment of the principle of strengthening healthy Qi and eliminating pathologic Qi.

In conclusion, according to the TCM practice of Xu at China-Japan Friendship Hospital, treatment of CPP caused by SPID should focus on dissolving stasis and obstructions using medicines that can activate blood, resolve stasis, regulate Qi, and dissipate adhesions. Qi-benefiting medicines are usually added to reinforce healthy Qi and help dissolve stasis. His prescriptions are often Guizhi Fuling pill and Sini powder. More blood-activating, stasis-resolving, or tonifying medicines can be used according to the accompanying symptoms or symptom patterns identified.

REFERENCES
12 Zhou J. Analysis of data mining results of Prof. Xu Runsan’s three old Chinese medicines in treating the sequelae of pelvic inflammatory diseases. Beijing University of Chinese Medicine, 2011: 19-36.


