RESEARCH ARTICLE

Utilizing data mining techniques to analyze traditional Chinese medicine patterns in patients with acute cardiorenal syndrome

Deshuang Yang[1,2] | Jiangquan Liao[1] | Shiyi Tao[2] | Ziyi Sun[2] | Li Huang[1] | Xiang Xiao[1] | Fang Wang[1] | Mingjing Shao[1]

[1]China-Japan Friendship Hospital, Beijing, China

[2]Beijing University of Chinese Medicine, Beijing, China

Correspondence
Mingjing Shao and Fang Wang.
Email: shaomingjing0707@163.com and wangfangwangxingyi@126.com

Abstract

Objective: This study intends to investigate the medication patterns of traditional Chinese medicine (TCM) for the treatment of acute cardiorenal syndrome (ACRS) through clinical data mining.

Methods: A retrospective study was conducted at China-Japan Friendship Hospital, encompassing hospitalized patients with ACSR admitted from June 1, 2013, to June 30, 2022. Patient treatment records, including TCM prescriptions, were gathered to establish a comprehensive prescription database. The prescriptions underwent analysis using the ancient and modern medical case cloud platform, incorporating the frequency, properties and flavors and channel tropism of each herbs, and clustering patterns, combination relationships, and complex network analysis of the whole.

Results: A total of 330 prescriptions from eligible hospitalized patients were included, which totally involves 324 kinds of different herbs. The therapeutic effects primarily emphasized descending qi and eliminating turbidity, promoting diuresis and reducing swelling, drying dampness and dispelling phlegm, and promoting the ascension of Yang Qi. The properties were largely warm, netural, slightly cool and cold, with warm being predominant. The flavors were chiefly sweet, spicy, and bitter, with sweetness being the most common. The major channel tropism were the lung and spleen meridians, followed by the stomach, liver, heart, and kidney meridians. Combination analysis identified 30 pairs of combinations, with higher associations found in combinations such as Jiegeng, Huangqi, Chaihu, Baizhu, Zhimu, and Dangshen. Cluster analysis categorized high-frequency herbs into 4 groups: Gualou–Fabanxia–Chuanxiong–Chishao, Fuling–Baizhu–Zhigancao–Chenpi, Maidong–Guizhi–Huangqi–Chaihu–Shengma–Zhimu–Shanzhuyu, and Huangqi–Dangshen–Jiegeng–Chaihu–Shengma–Zhimu–Shanzhuyu. Complex network analysis revealed core prescriptions for treating ACRS, including 17 herbs.

Conclusions: In the treatment of ACRS, TCM herbs with the properties of warm and neturality, and the flavors of sweet and spicy are commonly utilized. The prescribed herbal formulas have the effect of descending qi and eliminating turbidity, tonifying qi, activating blood and resolving stasis, resolving phlegm and promoting water.

INTRODUCTION

Acute cardiorenal syndrome (ACRS) is a prevalent form of cardiorenal syndrome distinguished by acute kidney injury (AKI) triggered by acute heart disease [1]. ACRS is associated with high mortality and disability rate, with its primary clinical manifestations, including acute cardiac function decline, resistance to diuretic, and AKI [2, 3]. Acute heart diseases mainly encompass acute decompensated heart failure, acute coronary syndrome (ACS) and cardiogenic shock [1]. Acute myocardial infarction (AMI) within the spectrum of ACS signifies the primary demographic at risk for developing ACRS [4]. At present, the pathogenesis of ACRS is predominantly attributed to hemodynamic alterations, heightened neuroendocrine activation, oxidative stress, and an immune inflammatory response. The pathogenesis, diagnostic markers and therapeutic drugs for ACRS are still under investigation. Identifying early predictive markers for ACRS and deploying timely interventions to mitigate its progression are crucial aspects of managing this condition.

In traditional Chinese medicine (TCM), there is no specific disease name for ACRS as found in ancient TCM books and records. According to its clinical manifestations, ACRS can be categorized within TCM as "edema," "asthma," "phlegm and fluid retention," "water-qi disease," and "heart–kidney non-interaction syndrome." According to TCM principles, the location of ACRS is associated with the heart and kidney, and has connections to the spleen and liver. The TCM pathogenesis of ACRS involves the co-presences of deficiency and excess, specifically the deficiency of qi, blood, Yin, and Yang viscera, as well as the accumulation of phlegm and static blood and the invasion of dampness in the heart and kidney. Western medicine relies on the clinical indicators and laboratory examination and thus establish more symptom-targeted regimens, while TCM focus on individual patient differences to alleviate symptoms and delay progression of ACRS. TCM compounds have a synergistic effect on multi-targets and multi-pathways. Exploring and summarizing the medication rules of TCM in the management of ACRS is essential for deepening our understanding for this condition.

At China-Japan Friendship Hospital, the past 8 years witnessed our endeavor to standardize TCM prescriptions for patients with ACRS, with the aim of the establishment of a database for the treatment of ACRS. Utilizing the Ancient and Modern Medical Record Cloud Platform, we conducted frequency analysis, properties, flavors, meridian tropism, clustering, combination, and complex network analysis of prescriptions to explore the rules and concepts of TCM medication in the

treatment of ACRS [5]. This study is pivotal in extracting insights from TCM compounds, capturing the cutting-edge developments in TCM, addressing clinical demands for ACRS and further developing of novel drugs.

LITERATURE RESOURCE

This paper enrolled the data of patients hospitalized in China-Japan Friendship Hospital from June 1, 2013 to June 30, 2022.

DIAGNOSTIC CRITERIA FOR ACUTE CARDIORENAL SYNDROME

(1) The diagnostic parameters for AMI adhere to the 2017 European Society of Cardiology Guidelines [6]. These criteria necessitate evidence of cardiac injury (cardiac troponin levels surpassing the 99th percentile upper reference limit) and clinical symptoms such as of myocardial ischemia (typical symptoms such as chest pain, as well as atypical symptoms such as radiating pain in the neck, jaw, or left arm, shortness of breath, nausea/vomiting, fatigue, palpitations, or syncope).
(2) The diagnostic criteria for AKI as delineated in the 2012 KDIGO Clinical Practice Guidelines [7] include an increase in serum creatinine by $\geq$0.3 mg/dl (26.5 µmol/L) within 48 h, a rise in serum creatinine to $\geq$1.5 times the baseline value over the preceding 7 days, or a persistent urine output of less than 0.5 mL/kg/h for at least 6 consecutive hours.

The diagnosis of ACRS is established when both AMI and AKI occur simultaneously.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

① Participants aged between 30 and 90 years; ② Individuals with a verified diagnosis of AMI and AKI; ③ Availability of complete hospitalization records; ④ Receipt of TCM prescription during their hospital stay.

Exclusion criteria

① Patients scheduled for being discharged within 48 h of admission; ② Those unable to complete the full

course of assessment; ③ Patients who have not disclosed their full medical history and are subsequently found ineligible based on inclusion criteria during the trial; ④ Patients with incomplete records during their hospitalization.

METHODS

Type of study design

This retrospective study aimed to investigate the features and patterns of TCM formulas for patients with ACRS.

Data organization and establishment of database

Following the predefined inclusion and exclusion criteria, a comprehensive review and organization of the enrolled medical cases was undertaken, culminating in the selection of 330 prescriptions that conformed to the stipulated standards. The standardization of included herbs was carried out with reference to authoritative sources, such as *Pharmacopoeia of the People's Republic of China* [8], *Compendium of Materia Medica* [9], *Chinese Medicinal Herbs* [10], *Pharmacology of TCM* [11], etc. For example, uniform changes were implemented, converting "Yuanhu" to "Yanhusuo," "Suanzaorenmian" to "Suanzaoren," "Yejiaoteng" to "Shouwuteng," "Yimi" to "Yiyiren," "Heishunpian" to "Fuzi," "Shanyurou" to "Shanzhuyu," "Chaoshenqu" to "Shenqu," "Shenglonggu" and "Duanlonggu" to "Longgu," "Shengmuli" and "Duanmuli" to "Muli," and so forth for other herbs, ensuring consistency and accuracy in their representation.

An Excel template was procured from the Ancient and Modern Medical Case Cloud Platform. Within this template, the prescriptions and related medical case information meeting the established criteria were cataloged, including basic information of patients, such as age, gender, and TCM prescriptions. Data entry was conducted by two individuals in tandem, with cross-validation for accuracy. Any discrepancies were adjudicated by a third party. Subsequently, a database was established and the data was imported into the Ancient and Modern Medical Case Cloud Platform.

Data statistical analysis

By utilizing the web portal of the Ancient and Modern Medical Case Cloud Platform for analysis, the data mining module was employed to import TCM prescriptions into the "analysis pool." The mined and analyzed content primarily includes: the frequency of herbal usage, efficacy, properties, flavors, meridian tropism analysis, TCM clustering, association, and complex network analysis.

(1) *Frequency analysis*: Frequency statistical methods were employed to analyze the demographic and prescription characteristics of the patients included in this study. The Ancient and Modern Medical Case Cloud Platform was utilized to analyze the gender and age distribution of the patients, offering initial insights into their general characteristics. Frequency statistical analysis was performed on TCM usage, properties, flavors, meridian affiliations, and efficacy, providing preliminary understanding of overall medication patterns.

(2) *Association rule analysis*: Association rule analysis was performed on high-frequency drugs. Appropriate levels of support and confidence were set to conduct multi-tiered association rule analysis, resulting in the identification of combinations of high-frequency drugs.

(3) *Clustering analysis*: TCM clustering analysis was performed to examine the concerted application among high-frequency drugs and extract frequently used drug combinations.

(4) *Complex network analysis*: A network analysis of TCM combinations was conducted, identifying key prescriptions utilized by the China-Japan Friendship Hospital in recent years for treating ACRS.

RESULTS

General patient information

Gender distribution

A total of 330 hospitalized patients were included in the study, consisting of 210 males and 120 females. The proportions of male and female patients were 63.64% and 36.36%, respectively, yielding a male-to-female ratio of approximately 3:1. The distribution of gender is detailed in Table 1.

Age distribution

A statistical analysis was conducted on the ages of the 330 patients included in this study. The age range

TABLE 1 Patient gender distribution.

Gender	Frequency (N)	Percentage (%)
Male	210	63.64
Female	120	36.36

spanned from 31 years, representing the youngest patient, to 99 years, the oldest. The age group between 71 and 80 years had the highest number of patients, totaling 96 cases, accounting for 29.09% of the total. Subsequently, the age groups of 51–60, 61–70, and 81–90 were also prevalent, representing 16.97%, 22.42%, and 22.73% of the total, respectively. The distribution of ages is presented in Table 2.

Frequency analysis results of TCM herbs

In this study, a total of 330 prescriptions were analyzed involving 324 different TCM herbs with a combined medication frequency of 5758. The top 30 most frequently used herbs are as follows: Huangqi (202 times), Jiegeng (141 times), Baizhu (140 times), Zhigancao (137 times), Fuling (136 times), Chaihu (135 times), Dangshen (120 times), Fabanxia (119 times), Maidong (119 times), Guizhi (113 times), Danggui (112 times), Gualou (112 times), Chenpi (106 times), Zhimu (102 times), Taizishen (99 times), Shanzhuyu (97 times), Baishao (92 times), Shengma (90 times), Chishao (86 times), Chuanxiong (85 times), Xiebai (83 times), Danshen (73 times), Sanleng (71 times), Taoren (68 times), Ezhu (68 times), Wuweizi (67 times), Dihuang (66 times), Huangqin (62 times), Houpo (61 times), Zhishi (60 times). Detailed usage frequencies are shown in Figure 1 and Table 3.

Efficacy analysis results of TCM herbs

The analysis of the efficacy of TCM herbs revealed that the prescribed herbal medicines encompass 10 categories of therapeutic effects. Among these, the majority of herbs has the ability of qi regulation and turbidity expulsion, water metabolism promotion and edema reduction, dampness elimination and phlegm transformation, as well as Yang Qi elevation, with respective frequencies of 304, 279, 260, and 225 occurrences. Please refer to Table 4 and Figure 2 for the distribution of these therapeutic effects.

Property analysis results of TCM herbs

The analysis of properties revealed that the prescribed herbal medicines encompass various properties, including warm, neutrality, slightly cold, and cold. The most prevalent property is warm, constituting 30.60% of the total, followed by neutrality at 23.10%. Additionally, there are also properties categorized as slightly cold and cold, accounting for 17.63% and 14.19%, respectively. Please refer to Table 5 and Figures 3 and 4 for the distribution of these properties.

Flavors analysis results of TCM herbs

The flavor analysis indicated that the prescribed herbal medicines encompass 10 different flavors, with sweet emerging as the most dominant, constituting 47.64% of the total. Pungent is the second most common flavor, accounting for 42.51%, followed by bitter at 41.44%. For a detailed distribution of these flavors, please consult Table 6 and Figures 5 and 6.

Meridian analysis results of TCM herbs

The analysis of meridian tropism suggested that the prescribed herbal medicines involve 12 distinct meridians. The most common meridians are the Lung Meridian (2888 times, accounting for 50.16%) and the Spleen Meridian (2601 times, accounting for 45.17%). Subsequently, there are also significant occurrences in the Stomach Meridian (2054 times, 35.67%), Liver Meridian (1813 times, 31.49%), Heart Meridian (1636 times, 28.41%), and Kidney Meridian (1027 times,

TABLE 2 Age distribution.

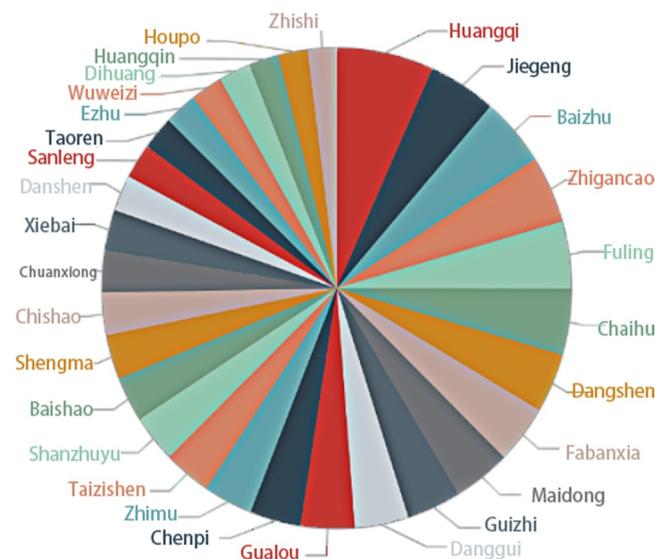| Age range	Frequency (N)	Percentage (%)
30–40	10	3.03
41–50	13	3.94
51–60	56	16.97
61–70	74	22.42
71–80	96	29.09
81–90	75	22.73
91–100	6	1.82

FIGURE 1 Distribution map of herbs.

TABLE 3 Frequency statistics of herbs (top 30 herbs).

Serial number	Herbs	Frequency (N)	Percentage (%)
1	Huangqi	202	61.21
2	Jiegeng	141	42.73
3	Baizhu	140	42.42
4	Zhigancao	137	41.52
5	Fuling	136	41.21
6	Chaihu	135	40.91
7	Danshen	120	36.36
8	Fabanxia	119	36.06
9	Maidong	119	36.06
10	Guizhi	113	34.24
11	Danggui	112	33.94
12	Gualou	112	33.94
13	Chenpi	106	32.12
14	Zhimu	102	30.91
15	Taizishens	99	30.00
16	Shanzhuyu	97	29.39
17	Baishao	92	27.88
18	Shengma	90	27.27
19	Chishao	86	26.06
20	Chuanxiong	85	25.76
21	Xiebai	83	25.15
22	Danshen	73	22.12
23	Sanleng	71	21.52
24	Taoren	68	20.61
25	Ezhu	68	20.61
26	Wuweizi	67	20.30
27	Dihuang	66	20.00
28	Huangqin	62	18.79
29	Houpo	61	18.48
30	Zhishi	60	18.18

TABLE 4 Distribution of efficacies of herbs.

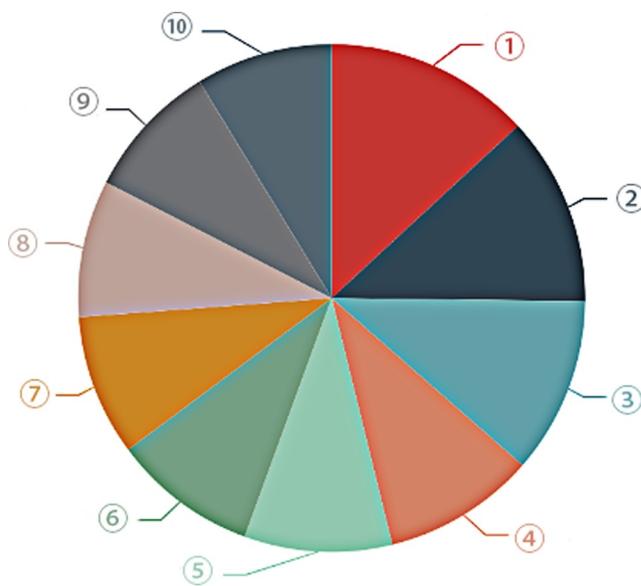| Serial number	Efficacy	Frequency (N)	Percentage (%)
1	Descending qi and eliminating turbidity	304	5.28
2	Promoting diuresis and reducing swelling	279	4.85
3	Draining dampness and expelling phlegm	260	4.52
4	Promoting the ascension of Yang Qi	225	3.91
5	Nourishing the fetus	218	3.79
6	Clearing heat-fire	214	3.72
7	Clearing heat and cooling blood	208	3.61
8	Healing sores and promoting tissue regeneration	202	3.51
9	Supplementing fluids and nourishing the blood	202	3.51
10	Promoting qi flow and alleviating stagnation	202	3.51

FIGURE 2 Distribution map of efficacies of herbs.
① Descending qi and eliminating turbidity. ② Promoting diuresis and reducing swelling. ③ Draining dampness and expelling phlegm. ④ Promoting the ascension of Yang Qi. ⑤ Nourishing the fetus. ⑥ Clearing heat-fire. ⑦ Clearing heat and cooling blood. ⑧ Healing sores and promoting tissue regeneration. ⑨ Supplementing fluids and nourishing the blood. ⑩ Promoting qi flow and alleviating stagnation.

17.84%). A comprehensive overview of the distribution across these meridians refer to Table 7 and Figures 7 and 8.

Association analysis results of TCM herbs

The association analysis method is utilized to examine the intrinsic connections between different herbs in the database and is commonly employed for calculating frequently used drug combinations. In this study, a drug association analysis was conducted on 330 prescriptions, with a confidence level set at ≥0.7 and a support level at ≥0.2. This resulted in the

TABLE 5 Distribution of properties of herbs.

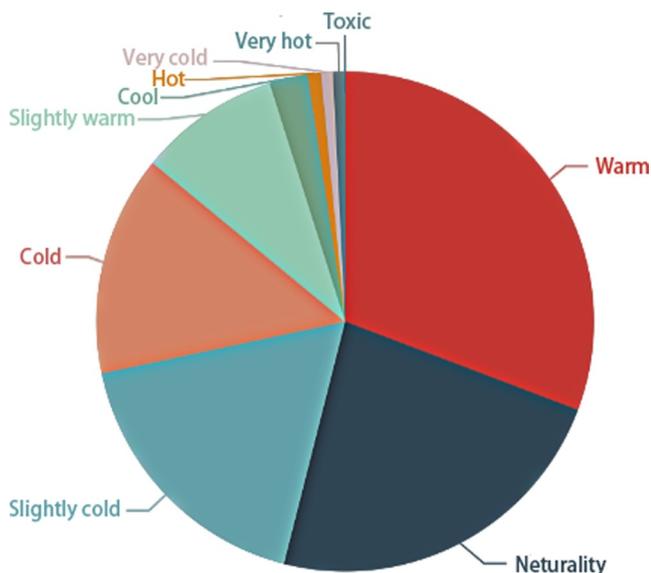| Serial number	Properties	Frequency (N)	Percentage (%)
1	Warm	1762	30.60
2	Neturality	1330	23.10
3	Slightly cold slightly cold	1015	17.63
4	Cold	817	14.19
5	Slightly warm	525	9.12
6	Cool	143	2.48
7	Hot	49	0.85
8	Very cold	44	0.76
9	Very hot	44	0.76
10	Toxic	1	0.02

FIGURE 3 Distribution map of properties of herbs.

identification of 30 pairs of herb combinations, with high associations observed among eight medicinal herbs: Jiegeng, Huangqi, Chaihu, Baizhu, Zhimu, Dangshen, Shanzhuyu, and Shengma. The results of herb association are presented in Table 8 and can be visualized in Figure 9.

Cluster analysis results of TCM herbs

A cluster analysis was performed on the 330 included prescriptions of TCM herbs, classifying the herbs within each prescription based on their potential similar, complementary, or synergistic functions. The top 20 ranked herbs were selected for cluster analysis using the furthest neighbor method with Euclidean distance as the distance metric. A vertical clustering diagram was
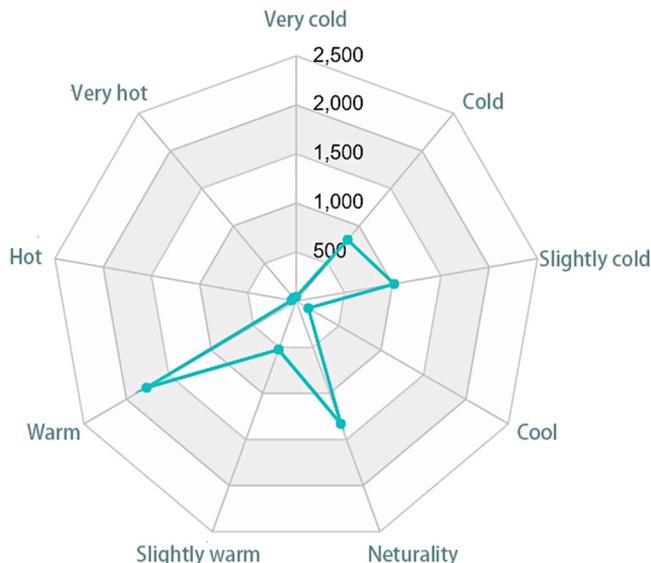

FIGURE 4 Radar chart of properties of herbs.

TABLE 6 Distribution of flavors of herbs.

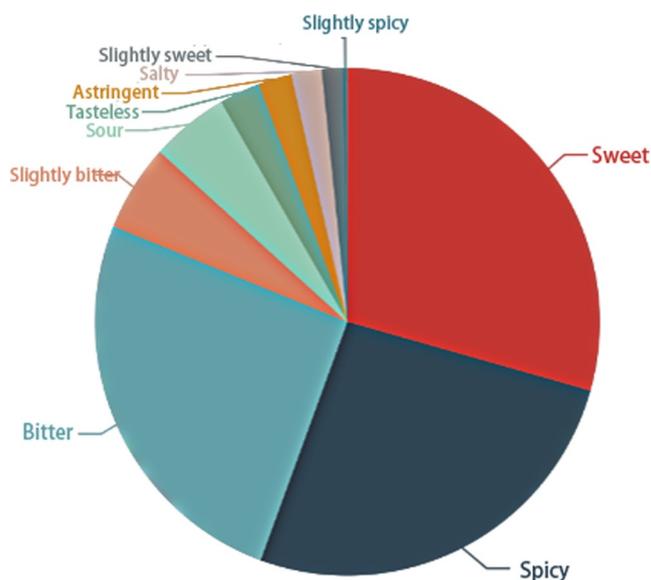| Serial number	Herbflavors	Frequency (N)	Percentage (%)
1	Sweet	2743	47.64
2	Spicy	2448	42.51
3	Bitter	2386	41.44
4	Slightly bitter	517	8.98
5	Sour	466	8.09
6	Tasteless	246	4.27
7	Astringent	198	3.44
8	Salty	182	3.16
9	Slightly sweet	126	2.19
10	Slightly spicy	26	0.45

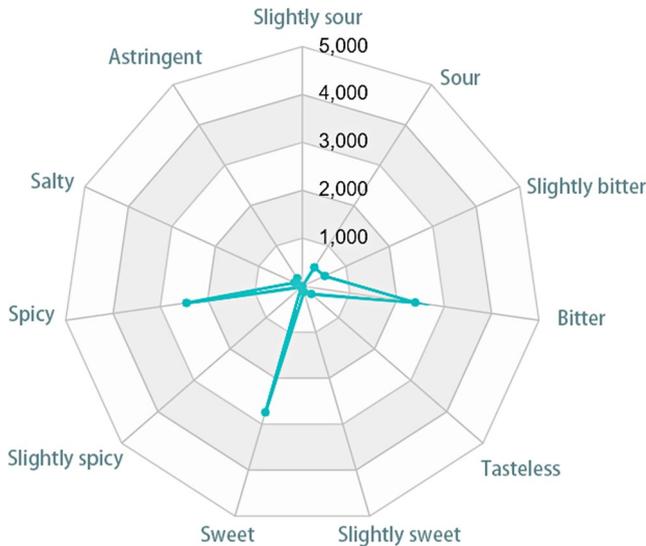**FIGURE 5** Distribution map of flavors of herbs.

FIGURE 6 Radar chart of flavors of herbs.

TABLE 7 Distribution of meridians of herbs.

Serial number	Meridians	Frequency (N)	Percentage (%)
1	Lung	2888	50.16
2	Spleen	2601	45.17
3	Stomach	2054	35.67
4	Liver	1813	31.49
5	Heart	1636	28.41
6	Kidney	1027	17.84
7	Large intestine	678	11.77
8	Bladder	332	5.77
9	Gallbladder	328	5.70
10	Pericardium	142	2.47
11	Small intestine	93	1.62
12	Triple energizer	72	1.25

FIGURE 7 Distribution map of meridian tropism of herbs.

FIGURE 8 Radar chart of meridian tropism of herbs.

constructed, categorizing high-frequency herbs into four groups: Gualou–Fabanxia–Chuanxiong–Chishao, Fuling–Baizhu–Zhigancao–Chenpi, Maidong–Guizhi–Taizishen–Danggui–Baishao, Huangqi–Dangshen–Jugeng–Chaihu–Shengma–Zhimu–Shanyurou. The TCM herbs clustering can be found in Table 9 and Figure 10.

Complex network analysis results of TCM herbs

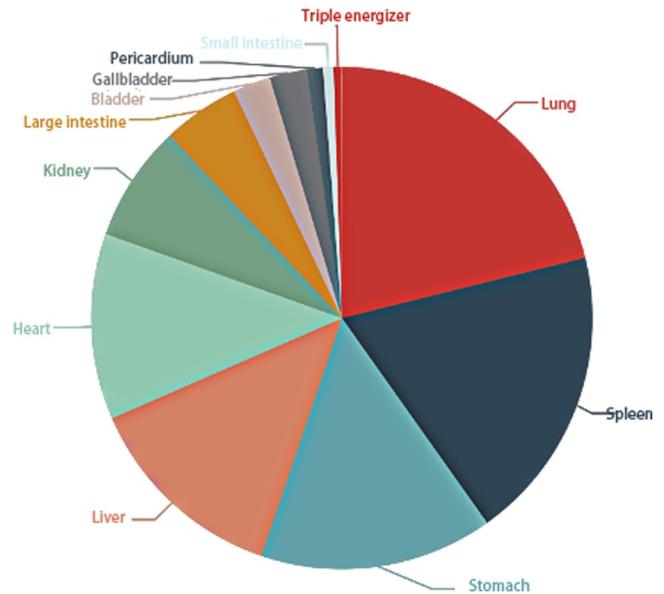A complex network analysis was conducted to examine the relationships between TCM herbs. Edge weights were set at 80, and the core 17-ingredient prescription for treating ACRS was extracted. This analysis yielded a network of interrelationships between Chinese herbal medicines, which was visualized and depicted as a network analysis diagram (see Figure 11). As depicted in the figure, the core herbal prescription consists of 17 Chinese herbal ingredients, including Huangqi, Jugeng, Chaihu, Baizhu, Dangshen, Zhimu, Fuling, Shanzhuyu, Zhigancao, Shengma, Danggui, Guizhi, Maidong, Gualou, Fabanxia, Sanleng, and Ezhu.

TABLE 8 Correlation analysis between herbs.

Serial number	Herbs	Herbs	Support	Confidence	Lift	Co-occurrence
1	Jiegeng	Huangqi	0.35	0.81	1.32	114
2	Chaihu	Huangqi	0.32	0.78	1.27	105
3	Baizhu	Huangqi	0.31	0.72	1.18	101
4	Jiegeng	Chaihu	0.3	0.7	1.71	99
5	Chaihu	Jiegeng	0.3	0.73	1.71	99
6	Zhimu	Huangqi	0.29	0.95	1.55	97
7	Dangshen	Huangqi	0.29	0.81	1.32	97
8	Shanzhuyu	Huangqi	0.28	0.95	1.55	92
9	Shengma	Huangqi	0.28	1.01	1.65	91
10	Danggui	Huangqi	0.27	0.79	1.29	88
11	Guizhi	Huangqi	0.26	0.77	1.26	87
12	Shengma	Jiegeng	0.25	0.92	2.15	83
13	Zhimu	Chaihu	0.25	0.8	1.96	82
14	Shengma	Chaihu	0.25	0.9	2.2	81
15	Zhimu	Jiegeng	0.25	0.79	1.85	81
16	Shanzhuyu	Zhimu	0.24	0.8	2.59	78
17	Shanzhuyu	Chaihu	0.24	0.8	1.96	78
18	Zhimu	Shanzhuyu	0.24	0.76	2.59	78
19	Shanzhuyu	Jiegeng	0.23	0.77	1.8	75
20	Sanleng	Huangqi	0.22	1.04	1.7	74
21	Shengma	Zhimu	0.22	0.8	2.59	72
22	Zhimu	Shengma	0.22	0.71	2.6	72
23	Ezhu	Huangqi	0.22	1.04	1.7	71
24	Shanzhuyu	Shengma	0.21	0.72	2.64	70
25	Shengma	Shanzhuyu	0.21	0.78	2.65	70
26	Xiebai	Gualou	0.2	0.8	2.36	66
27	Sanleng	Shanzhuyu	0.2	0.92	3.13	65
28	Sanleng	Chaihu	0.2	0.92	2.25	65
29	Chuanxion	Chishao	0.2	0.76	2.92	65
30	Chishao	Chuanxion	0.2	0.76	2.95	65

Note: Confidence refers to the probability of Chinese medicine B co-occurring with Chinese medicine A within the same prescription, while support indicates relative frequency of prescriptions in which both Chinese medicine A and Chinese medicine B appear among all prescriptions. To illustrate this with an example related to commonly used drug pairs in this study, let consider the Jiegeng → Huangqi drug pair. The confidence is 0.81, and the support is 0.35. This indicates that when Jiegeng is utilized in a prescription, there exists an 81% probability that Huangqi is also employed, and the likelihood of Jiegeng and Huangqi appearing together in the same prescription is 35%. Lift reflects the correlation between Chinese medicine A and Chinese medicine B in the association rules. A lift value greater than 1 signifies a stronger positive correlation, while a lift value less than 1 suggests a higher negative correlation. A lift value equal to 1 indicates no correlation. Co-occurrence represents the frequency at which Chinese medicine A and Chinese medicine B simultaneously appear together.

DISCUSSION

Analysis of distribution of patient gender and age

This study included a total of 330 patients from the perspective of patient gender. Among them, there were 210 males, accounting for 63.64% of the total, and 120 females, accounting for 36.36% of the total. Overall, the study observed a greater prevalence of male patients compared with female patients, with previous studies that indicates a higher incidence of coronary heart disease (AMI) among males [12]. The age distribution ranged from 31 years as the youngest patient to
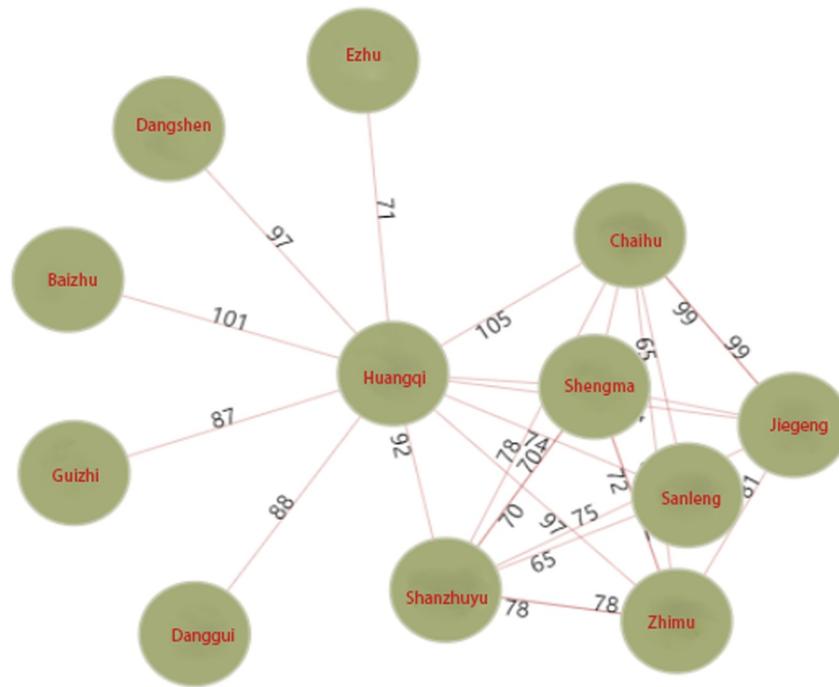
FIGURE 9 Correlation analysis between herbs. With a confidence level set at ≥0.7 and a support level at ≥0.2. The numbers on the lines represent the frequency of co-occurrence.

TABLE 9 High-frequency herbs group from cluster analysis.

Group number	Composition of herbs
1	Gualou, Fabanxia, Chuanxiong, Chishao
2	Fuling, Baizhu, Zhigancao, Chenpi
3	Maidong, Guizhi, Taizishen, Danggui, Baishao
4	Huangqi, Dangshen, Jiegeng, Chaihu, Shengma, Zhimu, Shanyurou

FIGURE 10 Cluster analysis plot of high-frequency herbs.

99 years as the oldest. The breakdown by age groups was as follows: 10 patients aged 30 and 40, 13 patients aged 41 and 50, 56 patients aged 51 and 60, 74 patients aged 61 and 70, 96 patients aged 71 and 80, 75 patients aged 81 and 90, and 6 patients aged 91 and 100. From the results, it can be observed that ACRS can occur at various age stages of life but predominantly affects individuals between the ages of 51 and 90, primarily impacting middle-aged and elderly population.

Analysis of frequency and efficacy of TCM usage

Data mining was employed to quantify the prescriptions for treating ACRS, identifying a total of 324 types of TCM herbs involved, with a medication frequency reaching 5758 instances. Among these, TCM herbs with a usage frequency exceeding 30% included Huangqi, Jiegeng, Baizhu, Zhigancao, Fuling, Chaihu, Dangshen, Fabanxia, Maidong, Guizhi, Danggui, Gualou, Chenpi, Zhimu, and Taizishen.

Further analysis of the efficacy of these prescribed TCM herbs has elucidated their main functions, which included moving qi for reducing qi stagnation, promoting urination for eliminating edema, draining dampness and resolving phlegm, uplifting Yang Qi, relieving desertion, clearing heat-fire and cooling blood, healing wounds, nourishing Yin and blood, and resolving static
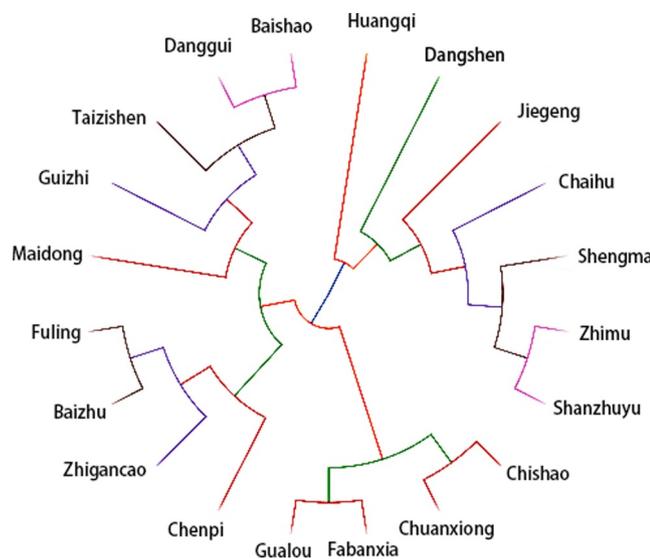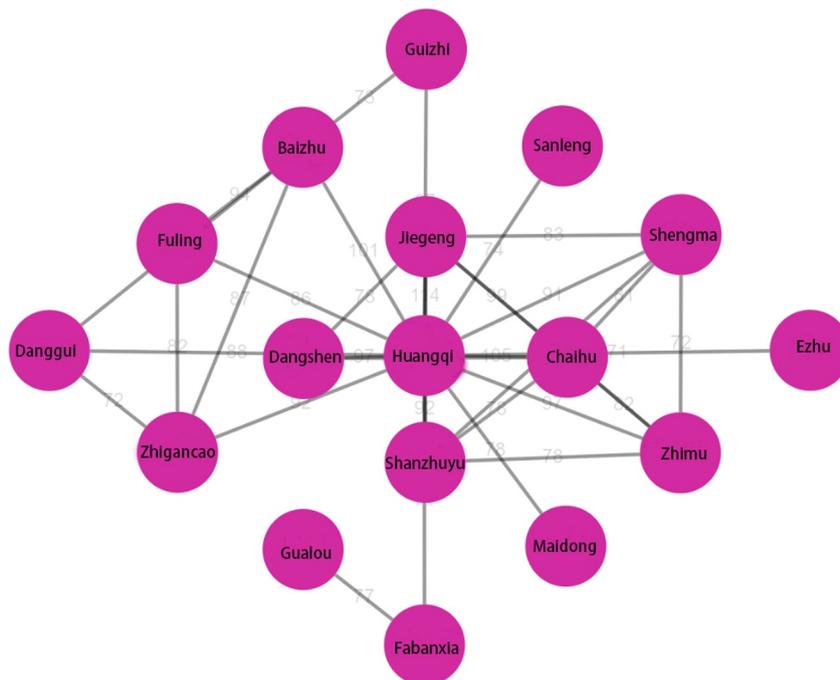
FIGURE 11 Complex network analysis diagram. Edge weights were set at 80, and the core 17-ingredient prescription for treating acute cardiorenal syndrome was extracted.

blood. These efficacy properties corresponded to the frequency of herbal usage in the prescriptions.

Based on the frequency of utilization and efficacy of TCM herbs, it was found that a majority of patients exhibited patterns of yang deficiency not ascending, phlegm obstruction, blood stasis, and internal retention of fluids. Additionally, they presented with certain signs of deficiency heat. The underlying pathological root of the disease is characterized by a combination of deficiency and excess. In contrast, most patients with AMI showed signs of deficiency with an invasion of external pathogenic factors. Their onset was sudden and marked by symptoms such as dyspnea and even coma, indicative of yang deficiency not ascending. The acute onset of the disease was characterized by patterns of excess, including the patterns related to phlegm, stasis, and obstruction. Additionally, some patients exhibited signs of deficient yang with upper manifestation, such as fever and profuse sweating. Following AMI, patients frequently experienced AKI, leading to abnormalities in fluid metabolism. Furthermore, several presented with oliguria, indicating the retention of fluids.

Analysis of nature, flavor, and meridian tropism of TCM herbs

By analyzing the properties of TCM herbs, a deeper understanding of the prescriptions can be gained from the perspective of medicinal properties, providing guidance for clinical diagnosis and treatment [13]. In this study, an analysis was conducted on the four natures (cold, cool, warm, and hot) of the 330 herbs. The findings revealed that warming and neutrality were the predominant medicinal properties in these prescriptions, followed by slightly cold and cold. In the case of patients suffering from ACRS, the pathogenesis is characterized by a coexistence of deficiency and excess, disharmony between yin and yang, deficiency of healthy qi, and the invasion of pathogenic factors. This can result in the occlusion of cardiac vessels and abnormal body fluids metabolism. In some cases, symptoms resembles "Guan Ge" a TCM term referring to the sensation of throat obstruction and the co-occurrence of dysuria and frequent vomiting. The treatment of ACRS has recently integrated the variety of warm-natured herbs at the China-Japan Friendship Hospital. This approach achieves several objectives: firstly, it raises sinking Yang Qi; secondly, it supplements deficiency of healthy qi, promoting pulse restoration and reinforcing the body's defense mechanisms; thirdly, it assists in promoting blood circulation, resolving blood stasis, and eliminating phlegm. These interventions contribute to smooth circulation of qi and the restoration of normal fluid metabolism, addressing symptoms commonly observed in ACRS patients such as deficient yang rising and virtual heat, as well as abnormalities in fluid metabolism. The accumulation of harmful substances in the body can lead to damage, therefore the use of cold-natured herbs serves a dual purpose: targeting virtual heat symptoms and alleviating discomfort caused by excess heat, while also aiding in clearance of harmful substances from the body. The incorporation of both warm and cold-natured

herbs in the prescriptions reflects the complex pathogenesis of ACRS, promoting a balanced regulation of warmth and coldness throughout the entire prescription.

An exploration of the therapeutic effects of TCM five flavors—sour, bitter, sweet, spicy, and salty—allows for a comprehensive description of their diverse therapeutic attributes. Spicy-flavored herbs are recognized for their ability to enhance qi circulation and dispel cold. Bitter-flavored herbs possess the capacity to clear heat and dampness. Sweet-flavored herbs are often used for tonifying, alleviating urgency, and pain relief. Sour-flavored herbs exhibit astringent and consolidating properties while promoting the generation and circulation of body fluids. Salty-flavored herbs are frequently employed to disperse masses [14]. The utilization of herbs with distinct flavors is intended to rectify internal imbalances and is implemented in the clinical treatment of different diseases. In this section of the study, a statistical analysis was conducted on the flavors of herbs in prescriptions for patients with ACRS. The predominant flavors identified in these prescriptions were sweet, spicy, and bitter. Patients with ACRS exhibit a combination of deficiency and excess, characterized by clinical manifestations such as dyspnea, angina pectoris, oliguria, and diaphoresis. Therefore, sweet-flavored herbs are employed to alleviate chest pain and tonify the patient's healthy qi, while spicy-flavored herbs are used to disperse qi and blood and warm the body, draining dampness. In cases of disrupted fluid metabolism, spicy-flavored herbs are often employed to promote the smooth circulation of qi in the body. Additionally, bitter-flavored herbs have the effect of drying dampness and transforming phlegm. The combined use of spicy and sweet flavors falls within the yang category, while bitterness is categorized as cold. The combination of spicy and sweet flavors can neutralize the cold nature of bitterness, preventing it from depleting the patient's righteous qi. This adheres to the compatibility principle in TCM known as "removing the extreme while preserving the substance."

In the analysis of TCM meridian and organ attribution, herbs are often categorized based on their affinities with meridians and organs. These herbs can exert their effects by directly influencing on meridians or organs, leading to the cluster of similar herbs targeting at specific organ-related treatments [15]. In this section of the study, a statistical analysis was conducted on the meridian attribution of TCM herbs utilized in 330 prescriptions. The findings revealed that the predominant use of these herbs is attributed to the lung meridian, followed by the spleen, stomach, liver, heart and kidney meridians. Based on these meridian attributions, it was determined that dysfunction of the lung and spleen is identified as the main cause of ACRS, resulting in qi deficiency and qi descent. The lung and spleen show signs of deficiency: the lung is compromised in its ability to disseminate and descend while the spleen is impaired in its transforming and transporting functions, resulting in insufficient nutrient metabolism. This serves as the primary pathological mechanism of the disease. Clinical treatment often involves the use of herbs such as Huangqi and Baizhu to tonify the lung and spleen. The deficiency heat of lung and stomach meridians, may manifest symptoms in spontaneous sweating, indicating the potential use of Huangqin for clearing heat. When there is an imbalance in the liver meridian, it disrupts overall regulation of qi throughout the body, leading to imbalances in ascending and descending functions. Therefore, clear yang fails to ascend, leading to malnutrition of clear orifices and loss of consciousness. Herbs such as Chaihu and Shengma can be used to regulate the liver meridian and assist in tonifying lung and spleen qi while promoting the lift of Yang. The association with the heart and kidney meridians signifies a dual treatment approach targeting both organs to restore normal physiological function within the body.

Analysis of TCM associations

Association analysis, also referred to as association mining, entails the exploration of frequent patterns, associations, correlations, or causal structures within item sets or object sets in transactional data, relational data, or other information carriers [16]. TCM association analysis was conducted using the Ancient and Modern Medical Case Cloud Platform to discover relationships between different herbs. Through an examination of TCM usage frequency, effects, properties, flavors, and meridian attributions, it becomes apparent that numerous herbs used in prescriptions exhibit both cold and hot properties as well as a combination of tonifying and purging effects. In the further analysis of relationship, this study established criteria with a confidence level ≥0.7, support level ≥0.2, and lift value ≥1.18. The results revealed strong intrinsic connections among eight herbs: Jiegeng, Huangqi, Chaihu, Baizhu, Zhimu, Dangshen, Shanzhuyu, and Shengma. These herbs are frequently used in the form of combination pairs, such as Jiegeng with Huangqi, Chaihu with Huangqi, Baizhu with Huangqi, Jiegeng with Chaihu, Zhimu with Huangqi, Dangshen with Huangqi, Shanzhuyu with Huangqi, and Shengma with Huangqi to achieve effects such as tonifying and uplifting the middle qi, nourishing blood, and consolidating tissues.

Cluster analysis of TCM herbs

Cluster analysis can assist in the identification of herbal categories within prescriptions, the analysis of the medication patterns in TCM for treating ACRS, and the

provision of insights into the essential components of prescriptions. In this section of the study, we employed the longest distance method with Euclidean distance as the distance metric. High-frequency herbs were categorized into four groups:

Group one: Gualou, Banxia, Chuanxiong, and Chishao. These four herbs are incorporated into the Gualou Xiebai Banxia decoction, supplemented with Chuanxiong and Chishao decoction, to achieve the effects of resolving phlegm, promoting blood circulation, and eliminating stasis. This approach exemplifies the utilization of blood-activating and stasis-resolving methods in treatment of ACRS.

Group two: Fuling, Baizhu, Zhigancao, and Chenpi. This category mainly represents the treatment approach of the Si Junzi decoction, which is known for its effects in tonifying qi and strengthening the spleen. These herbs are commonly utilized to treat symptoms such as sallow complexion, fatigue, poor appetite, low voice, pale tongue with white coating, and weak pulse, all of which align with the spleen deficiency pattern observed in ACRS. Studies have shown that Si Junzi decoction can improve post-AMI cardiac function, reduce C reactive protein (CRP) levels, and decrease the occurrence of restenosis [17, 18].

Group three: Maidong, Guizhi, Taizishen, Danggui, and Baishao. This category encompasses multiple formula strategies, such as Guizhi decoction, Siwu decoction, Si Junzi decoction, and Maidong decoction. These herbs possess the dual effects of tonifying qi and nourishing Yin, warming Yang, and promoting blood circulation.

Group four: Huangqi, Dangshen, Jiegeng, Chaihu, Shengma, Zhimu, and Shanyurou. These herbs have the effects of tonifying qi, raising the fallen qi, promoting blood circulation, activating collaterals, promoting diuresis, and resolving depression. This category represents the final treatment approach for ACRS and reflects different TCM treatment strategies for ACRS, providing a comprehensive view of how TCM herbs are grouped and utilized in practice.

Comparison analysis between core prescriptions and "Shengjie Tongyu decoction"

Through a complex network analysis of TCM prescriptions on the Ancient and Modern Medical Cases Cloud platform, 17 coreherbs against ACRS were identified when the edge weight set at 80. These key herbs include Huqngqi, Jiegeng, Chaihu, Baizhu, Dangshen, Zhimu, Fuling, Shanzhuyu, Zhigancao, Shengma, Danggui, Guizhi, Maidong, Gualou, Fabanxia, Sanleng, and Ezhu. Upon examination of these 17 herbs, it is evident that they address both deficiency and excess patterns. Huangqi, Danggui, and Dangshen tonify qi and nourish blood, while Huangqi, Jiegeng, Shengma, and Chaihu are known for their ability to raise and lift Yang Qi. Additionally, Fuling and Baizhu are utilized to tonify qi andinvigorate spleen. Zhimu clears deficient heat, Maidong nourishes Yin and moistens dryness, Shanzhuyu and Zhigancao tonify deficiency; Guizhi, Gualou, and Fabanxia warm and resolve cold-phlegm; and Sanleng and Ezhu disperse blood, promote qi circulation, eliminate water, and activate blood and resolve stasis. The whole prescription possesses the functions of tonifying qi and lifting Yang, activate blood and resolve stasis, eliminating water.

Through the analysis of the frequency, efficacy, properties, flavors, meridian tropism, combination, clustering characteristics, and complex networks of medicines, we have elucidated the TCM treatment patterns for ACRS. We have identified the core prescription against ACRS. Upon comparison, it is evident that the "Shengjie Tongyu decoction" shares similarities in terms of herbal properties, flavors, meridian classification, and efficacy with the core prescription. Some of herbs are used together in both formulas, such as Huangqi, Shanzhuyu, Dangshen, Zhimu, Sanleng, Ezhu, Shengma, Chaihu, and Jiegeng. However, compared to the core prescription, the "Shengjie Tongyu decoction" includes an extra herb known as Yimucao. Yimucao is renowned for its ability to promote blood circulation for regulating menstruation, induce diuresis for removing edema, and clear heat and remove toxicity. It is considered a superior herb for nourishing the liver's Yin-blood aspect and possesses mild qualities, facilitating blood flow within the meridians, reducing swelling, promoting urination, and regulating bowel movements. *Treatise on Cold Damage* believes that formula preparation should take factors, such as magnitude, timing, pace, urgency, uniqueness, oddness, and complexity into consideration. In contrast to the core prescription, the "Shengjie Tongyu decoction," with its focus on invigorating qi, promoting blood circulation, eliminating dampness, features a more streamlined combination of herbs, which aligns more closely with TCM formulation principles.

Professor Shi Zaixiang, in accordance with the therapeutic principles of "treating fallen by raising and treating pathogenic accumulation with dissipation" as outlined in the *Su Wen: Zhizhenyao Dalunpian: Discussion on the Most Important and Abstruse Theory* has developed the "Shengjie Tongyu decoction" for the treatment of heart and kidney diseases. Through extensive clinical investigation, rigorous validation, and repeated experimentation, this formula was created based on the therapeutic method of raising, resolving, and promoting blood circulation.

The original formulation of the "Shengjie Tongyu decoction" comprises a combination of herbs, including Huangqi, Shanzhuyu, Dangshen, Yimucao, Zhimu,

Sanleng, Ezhu, Shengma, Chaihu, and Jiegeng. Within this decoction, Huangqi assumes a primary role by not only tonifying qi but also uplifting the middle qi. Dangshen supplements spleen qi to nourish postnatal qi and blood for biochemical processes. Shanyurou serves to both consolidate and astringe kidney qi and replenish the innate essence of the kidneys. When these three herbs combined together, they elevate and replenish the deficient middle qi. Moreover, the rest of herbs such as Sanleng, Ezhu, and Yimucao aid in dispelling congealed blood, promoting circulation, and facilitating diuresis. Together with Chaihu and Shengma which can both raise and disperse qi, and the cooling nature of Zhimu that neutralizes the warming nature of Huangqi. These herbs work in concert to guide the decoction upwards into the chest region. The synergistic effects of these herbs not only serve to supplement qi, raise sunken energy, and promotes blood circulation but also help alleviate water stagnation and resolve emotional stagnation. This formulation is designed to invigorate middle qi, uplift sunken qi, boost chest yang, and ensure the smooth flow of qi and blood. It aligns with the pathological mechanisms observed in ACRS, characterized by deficiencies in qi, blood, Yin, and Yang as well as phlegm, fluid retention, and blood stasis.

Clinical studies have found that the "Shengjie Tongyu decoction" significantly improves clinical symptoms in patients with unstable angina pectoris, improve their quality of life, reduces serum levels of CRP, IL-6, TNF-α, enhances lipid metabolism, and exhibits anti-oxidative properties. Additionally, it mitigates vascular endothelial injury and exerts antiplatelet activation effects [19–21]. Furthermore, the modified "Shengjie Tongyu decoction" significantly alleviates clinical symptoms in patients with chronic heart failure, improve the quality of life, effectively enhances the 6-min walking distance, increases left ventricular ejection fraction, enhances cardiac function, and boosts exercise tolerance [22]. In addition, animal studies have shown that the "Shengjie Tongyu decoction" has the potential to reduce myocardial infarct size during myocardial ischemia/reperfusion (I/R), lower the occurrence of malignant arrhythmias during the ischemic period, decrease serum levels of creatine kinase, malondialdehyde, and superoxide dismutase, increase left ventricular end-systolic pressure, and left ventricular end-diastolic pressure [13, 14]. Furthermore, it exhibits inhibitory on monocrotaline-induced pulmonary arterial hypertension and right ventricular remodeling in rats, leading to significant reduction in right ventricular hypertrophy index, mean pulmonary artery pressure, and pulmonary artery wall thickness percentage [23]. Further investigation is warranted to elucidate the pharmacological effects and mechanisms action of the "Shengjie Tongyu decoction" in treating ACRS.

CONCLUSION

This study gathered TCM prescriptions against ACRS and conducted a medication pattern analysis using the Ancient and Modern Medical Case Cloud Platform. Ultimately, a core formula for treating this condition was derived. The analysis revealed that the "Shengjie Tongyu decoction" exhibited comparable therapeutic efficacy to the core formula. "Shengjie Tongyu decoction" achieves this effect with a more streamlined ingredients composition and better adheres to the formulation principles of TCM. Additionally, this formula is frequently used in clinical treatments for conditions such as AMI, kidney injury, and chronic heart failure, supported by substantial research studies.

LIMITATIONS

Although the clinical data of TCM treatment of ACRS can be mined, but it does not meet the requirements of advance TCM research. Therefore, further exploration is needed to elucidate the pharmacological effects and mechanisms of the "Shengjie Tongyu decoction" in the treatment of ACRS.

LIST OF TCM CHINESE HERBAL MEDICINE NAMES CONFORMING TO INTERNATIONAL REPORTS

Huangqi (*Astragalus mongholicus Bunge*), Jiegeng (*Platycodon grandiflorus (Jacq.) A.DC.*), Baizhu (*Atractylodes macrocephala Koidz.*), Zhigancao (*Glycyrrhiza glabra L.*), Fuling (*Smilax glabra Roxb.*), Chaihu (*Elephantopus scaber L.*), Dangshen (*Salvia miltiorrhiza Bunge*), Fabanxia (*Pinellia ternata (Thunb.) Makino*), Maidong (*Ophiopogon japonicus (Thunb.) Ker Gawl.*), Guizhi (*Neolitsea cassia (L.) Kosterm.*), Danggui (*Levisticum officinale W.D.J.Koch*), Gualou (*Trichosanthes kirilowii Maxim.*), Chuanxiong (*Conioselinum anthriscoides* '*Chuanxiong*'), Chishao (*Paeonia lactiflora Pall.*), Chenpi (*Citrus reticulata Blanco*), Shengma (*Actaea cimicifuga L.*), Zhimu (*Anemarrhena asphodeloides Bunge*), Shanzhuyu (*Cornus officinalis Siebold & Zucc.*), Sanleng (*Cyperus rotundus L.*), Ezhu (*Curcuma aromatica Salisb.*), Taizishen (*Pseudostellaria heterophylla (Miq.) Pax*), Baishao (*Paeonia lactiflora Pall.*), Xiebai (*Allium chinense G.Don*), Danshen (*Salvia miltiorrhiza Bunge*), Taoren (*Juglans regia L.*), Wuweizi (*Schisandra chinensis (Turcz.) Baill.*), Dihuang (*Rehmannia glutinosa (Gaertn.) DC.*), Huangqin (*Scutellaria baicalensis Georgi*), Houpo (*Magnolia officinalis Rehder & E.H.Wilson*), Zhishi (*Citrus × aurantium f. aurantium*), Yimucao (*Leonurus japonicus Houtt.*), Yanhusuo (*Corydalis yanhusuo (Y.H.Chou & Chun C. Hsu) W.T.Wang ex Z.Y.Su & C.Y.Wu*), Suanzaoren

(*Ziziphus jujuba Mill.*), Shouwuteng (*Reynoutria multi-flora (Thunb.) Moldenke*), Yiyiren (*Coix lacryma-jobi L.*), *Fuzi* (*Cyperus rotundus L.*), Shenqu (*Hibiscus sabdariffa L.*), Longgu (*Euphorbia antiquorum L.*), and Muli (*Lantana camara L.*).

AUTHOR CONTRIBUTIONS

Deshuang Yang: Methodology; resources; validation; visualization; writing—original draft; writing—review and editing. **Jiangquan Liao**: Conceptualization; data curation; formal analysis; investigation; resources; writing—review and editing. **Shiyi Tao**: Data curation; validation. **Ziyi Sun**: Data curation; visualization. **Li Huang**: Supervision; validation. **Xiang Xiao**: Formal analysis. **Fang Wang**: Project administration; supervision; validation. **Mingjing Shao**: Project administration; resources; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data supporting the conclusions of this paper have been provided by the authors.

ETHICS STATEMENT

The study has been approved by the Clinical Medical Ethics Committee of China-Japan Friendship Hospital (No. 2022-KY-102).

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