Original Article

Research on Characteristic Manifestations of *Xiaochaihu* Decoction Based on Association Rules Mining

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Abstract

Objective: The aim of this study is to explore the characteristic manifestations and contraindications of *Xiaochaihu* decoction (XD [It also stands for all the seven herbs in XD]) syndrome and to clarify the principle of using XD. **Methods:** By searching on the Encyclopedia of Traditional Chinese Medicine, 254 cases whose symptoms were relieved by XD and 48 cases who misused XD in ancient time were selected. Moreover, they are divided into two groups. Microsoft Excel 2016 was used as a storage tool. These two groups of cases were all treated with XD because of their similar manifestations, but therapeutic efficacies are reverse. The manifestations mislead doctors should be selected out to clarify the indications of using XD. Thus, the professional data mining software RapidMiner was used as a platform to do the frequent statistic and to create association rules between manifestations and herbs of both groups, respectively. After comparing the results of two groups, we can make a conclusion. **Results:** The characteristics of XD syndrome are alternative chills and fever, hypochondriac pain, and inflammatory swelling and pain (ear or breast). When any of these manifestations occur, XD can be used. Wiry pulse paired with alternative chills and fever, headache, thirst, or hypochondriac pain is also regarded as the indications of using XD. XD should not treat for fever paired with other manifestations, such as headache, delirium, or aversion to cold. In addition, the manifestations with high concurrence frequency do not mean the high correlation. Moreover, only according to the frequency, statistics cannot make correct conclusions. **Conclusions:** (1) XD is more fit for the excess syndrome such as excess fire in the liver or gallbladder meridians. (2) The medical records in which the XD is misused are also worth analyzing. (3) Association rules cannot be substituted with frequency statistics.

Keywords: Association rules mining, characteristic manifestation, *Xiaochaihu* decoction

Introduction

Xiaochaihu decoction (XD) is a famous formula recorded in *Shanghanlun* (*Treatise on Cold-Induced Diseases*), a classic medical book written by Zhang Zhongjing in the East Han Dynasty. At present, this prescription is still extensively used to cure a wide range of diseases by traditional Chinese medical doctors.[1] The text where the XD appears for the first time in the book elaborates its ingredients and the manifestations it aims at.

Febrile disease caused by cold or wind

After 5–6 days, when the patient has alternative chills and fevers, he/she feels a distention and a sensation of oppression in the chest and costal region, reluctant to speak and eat, restless and nauseous, and prescribes XD.

Xiaochaihu decoction

Chaihu (Radix Bupleuri) 8 liang
Huangqin (Radix Scutellariae) 3 liang
Renshen (Radix Ginseng) 3 liang
Banxia (Rhizoma Pinelliae) 0.5 sheng
Gancao (Radix Glycyrrhizae Praeparata) 3 liang
Shengjiang (Rhizoma Zingiberis Recens) 3 liang
Dazao (Fructus Ziziphi Jujubae) 12 pcs.

Stew the above seven drugs in one 12 *sheng* of water till 6 *sheng* are left. Filter the decoction and stew it till 3 *sheng* are left. Take 3 doses a day with 1 *sheng* as a dose.

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Subtractions and additions of the decoction

1. To be restless but not nauseous: Take away *Banxia* and *Renshen*, add one piece of *Gualoushi* (*Fructus Trichosanthis*).
2. With thirst for water: Take away *Banxia*, increase *Renshen* to 4.5 *liang*, and add 4 *liang* of *Gualoushi*.
3. With abdominal pain: Take away *Huangqin*, and add 3 *liang* of *Shaoyao* (*Radix Paeoniae*).
4. With lump below the costal margin: Take away *Dazao*, and add 4 *liang* of *Muli* (*Concha Ostreae*).
5. With palpitation and dysuria: Take away *Huangqin*, and add 4 *liang* of *Fuling* (*Poria*).
6. No thirst of water but with a slight fever: Take away *Renshen*, and add 3 *liang* of *Guizhi* (*Ramulus Cinnamomi*). Cover the patient with a quilt to obtain a light perspiration
7. Accompanied by coughing: Take away *Renshen*, *Dazao* and *Shengjiang*, and add 0.5 *sheng* of *Wuweizi* (*Fructus Schisandrae*) and 2 *liang* of *Ganjiang* (*Rhizoma Zingiberis*).

The text shows that this formula is a cure for a series of symptoms and signs. Meanwhile, there is also a guide to applying XD in the book.

Febrile disease caused by cold or wind with *Xiaochaihu* decoction

When one of the symptoms of the syndrome is observed, a diagnosis of XD syndrome can be established.

The text is significant but succinct; therefore, there are a lot of explanations of it since then. The different opinions center on what exactly the indication of applying this formula is.

Before introducing the viewpoints of different scholars, some concepts should be clarified first. In *Shanghan Lun*, diseases are categorized into six groups according to their seriousness. The six groups are named as *Taiyang* (Initial Yang) Syndrome, *Shaoyang* (Lesser Yang) Syndrome, *Yangming* (Greater Yang) Syndrome, *Taiyin* (Initial Yin) Syndrome, *Shaoyin* (Lesser Yin) Syndrome, and *Jueyin* (Greater Yin) Syndrome. XD is the typical formula of *Shaoyang* Syndrome. The symptoms and signs of the *Shaoyang* Syndrome are invariably bitterness in the mouth, a parched throat, and vertigo, which are called the outline of the *Shaoyang* Syndrome. While the main manifestations of XD are alternative chills and fevers, feeling a distention, and a sensation of oppression in the chest and costal region, reluctant to speak and eat, and restless. In addition, there are also the probable manifestations which are nausea, thirst, abdominal pain, lump below the costal margin, palpitation, dysuria, slight fever, and cough.

Some doctors do not agree with the words "one of the symptoms of the syndrome" of the guideline. They deny that diagnosis can be made with only one symptom. They prefer that the "one" should refer to a series of symptoms. For example, You Zaijing thought the characteristic symptoms are alternative chills and fever and a sensation of distention and oppression in the chest and costal region as the records in his book *Shanghan Guanzhuji* (*A String of Beads from Treatise on Cold-Induced Diseases*).[2] In the book *Shanghan Bianzheng Guangzhu* (*Various Dialectical Comments on the Treatise on Cold-Induced Diseases*),[3] Wang Hu expounded his view that outline of the *Shaoyang* Syndrome accompanied with one of main manifestations of XD is the indication to use XD.

If someone can make a diagnosis according to only one symptom, this symptom is the particular one or anyone of the syndrome? Different scholars have different opinions. Cheng Wuji's opinion can be summarized from his book *Zhujie Shanghanlun* (*Treatise on Cold-Induced Diseases with Notes*).[4] that when patients just have one of the probable manifestations, XD should be used. Ke Qin expressed his opinions in *Shanghan Laisuji* (*Renewal of Treatise on Cold-Induced Diseases*)[5] that the characteristic symptom is one of the outline of the *Shaoyang* Syndrome.

Most scholars came up with their ideas just through analyzing the traditional Chinese medical theory. Everyone thought that his view was most correct. Under these circumstances, more clinical and statistical evidence are needed. Some researchers have tried to explain from these aspects. Wu[6] selected some cases treated with XD from Encyclopedia of Traditional Chinese Medicine (TCM). Alternative chills and fever had the highest rate of occurrence. Zhang *et al*.[7] collected 544 medical cases cured by XD from TCM Journals between 1960 and 2008. With frequency statistics, they found that the basic indications of applying XD are the loss of appetite, bitter taste in the mouth, fullness, and pain in the chest and hypochondria, dizziness, irritability and restlessness, nausea, white tongue fur, and wiry pulse. Tao[8] analyzed 763 cases treated with XD recorded in 407 papers between 1994 and 2008 with the method of frequency statistic. It shows that the high-frequency symptoms are like that recorded in *Shanghanlun*. With association rules, Wang[9] analyzed 380 papers describing the clinical applications of XD from 1970 to 2009. The results show that the confidence percentage with manifestations of wiry pulse, dizziness, nausea, and vomiting as the premise and XD as the conclusion can be 83%.

Their jobs are significant but are still needed to improve. First, all the cases they selected have positive results. Records with negative results are also worth analyzing. Second, one word of symptom in Chinese sometimes contains two or more symptoms. When organizing the data, every symptom should be separated from that kind of words. Third, the tools used to do statistics and data analysis should be introduced. Forth, high frequency does not equal to the high association. Therefore, the data should not be analyzed only by frequency statistics. Finally, when using association rules, the two parameters of support and confidence should be clearly defined. In addition, proper criteria should be used to evaluate the rules.

In this paper, the cases treated with XD with both positive and negative results recorded in medical books before 1949 were collected. Moreover, we tried to mine the characteristic manifestations of XD by operating association rules with RapidMiner.

Methods

Sources of dataset

Encyclopedia of Traditional Chinese Medicine is a large electronic series, which contains 1156 ancient medical books before 1949. It is the great achievement of the National Key Project of electronic publishing. Since the purpose is to find the clinical evidence of applying XD, the cases that treated with XD are needed. Therefore, as the keyword, "Xiaochaihu" was used to obtain the relevant records from the Medical Records Part of the encyclopedia, which mainly contains the books from the Ming Dynasty to the Chinese Republic. According to the following inclusion and exclusion criteria, a total of 254 cases treated with XD or its modified formula were included. The medical records were from 70 medical books, and >30% of records were from *Xu Mingyi Lei'an* (*A supplement to the Classified Medical Records of Distinguished Physicians*), which was pressed in 1770 and included medical records before Qing Dynasty [Table 1]. The terminologies of manifestations used in this article refer to the *WHO International Standard Terminologies on Traditional Medicine in the Western Pacific Region*, which has documented the common technical terms used in traditional medicine. Moreover, based on *Pharmacopoeia of the People's Republic of China*, the ingredients of the selected medicinal formulae were listed. All the 109 symptoms or signs and 122 herbs in the collected cases were organized as the attributes to set up a database.

Inclusion criteria

(1) The cases are cured by XD or its modified formulas; (2) the is detailed describing of manifestations in the case; (3) the modified XD must include *Chaihu* and at least another two herbs of the original XD; (4) the XD are taken orally in these cases.

Exclusion criteria

Cases with the following criteria were excluded: (1) <50% herbs that belong to XD in the formula; (2) XD being used to consolidate the treatment effect after taking other formulae; (3) being invalid or exacerbation of the disease after taking XD.

When searching the Encyclopedia of Traditional Chinese Medicine, we found that there are some failure cases. The patients' conditions were getting worse after taking XD. These cases are significant and valuable. Because when writing a prescription, doctors believed that some of the manifestations of the patient were suitable for XD. However, XD was no effect or even harmful to these patients. Therefore, we cannot use XD just according to these manifestations. By finding the basis, they misused XD, and comparing with the result of the 254 cases cured by XD, we can get more reliable conclusions. Accordingly, 48 cases that misused XD were collected, and 70 symptoms and signs were organized as the attributes to establish another database.

Table 1: The sources of cases

n	Sources of medical records	Absolute count	Fraction
1	*Xu Mingyi Lei'an*	77	0.303
2	*Dunyuan Yi'an*	14	0.055
3	*Gujin Yi'an An*	10	0.039

Inclusion criteria

(1) Being invalid or exacerbation of the disease after taking XD or its modified formulas; (2) There is detailed describing of manifestations in the case; (3) The modified XD must include Chaihu and at least another two herbs of the original XD; (4) The XD are taken orally in these cases.

Exclusion criteria

Cases with the following criteria were excluded: (1) Less than 50% herbs that belong to XD in the formula; (2) XD being used with any other Chinese patent drugs.

Statistical analysis

In this article, Microsoft Excel 2016 was used as a storage tool, and then, the RapidMiner was used as a platform to do the primary statistics and analyze the frequency and the association rules of the manifestations and XD.

Association rules are a data mining methodology that seeks to find frequent connections between attributes in a data set.[10] It is widely used in data analysis for direct marketing, catalog design, and other business decision-making processes. While the amount of clinical data increased rapidly, association rules mining was successfully applied into various kinds of studies both in modern[11,12] and traditional Chinese medical categories.[13,14]

There are two main factors that dictate whether or not frequency patterns get translated into association rules: confidence and support.[10] The confidence is the main parameter used when creating rules. This setting tells the software how often an association must be found in a dataset for it to be considered a rule. Association rules are laid out using premises (sometimes called antecedents) and conclusions (sometimes called consequents). The premise is the first attribute in the association, and the conclusions are all attributes associated with the given premise.[15] The support is an easier measure to calculate. This is simply the number of times that the rule did occur, divided by the number of observations in the dataset.

In RapidMiner, the minimum support can be set in the FP-Growth operator, which is the first modeling operator needed for association rules. This operator calculates the frequent itemsets found in the data.[15] The FP in FP-Growth stands for frequency pattern. Frequency pattern analysis is handy for many kinds of data mining and is a necessary component of association rule mining. Without having frequencies of attribute combinations, we cannot determine whether any of the patterns in the data occur often enough to be considered rules. The min-confidence parameter can be set in the Create Association Rule's operator. Only the combinations that satisfy the minimum thresholds on support and confidence were considered to mine meaningful rules (Cross, 2016, North, 2012).[10]

Before setting these two parameters, we will introduce the evaluating parameters first. There are six parameters to evaluate the association rules, lift, Chi-square (χ^2), cosine, all-confidence, max-confidence, and *Kulczynski* (*Kulc*). Among them, only lift and χ^2 are not null-invariant. That means their values will greatly be influenced by the null-transaction. Sometimes, in one dataset, the other four parameters may show totally different result. In this circumstance, imbalance ratio (IR) should be introduced to give a better explanation. Through comparison, *Kulc* and IR are recommended to be the evaluation index.[16] If *Kulc* is far more than 0.5 and IR is near to zero, the result is better.

$$Kulc(P,C) = \frac{1}{2}\left(conf(P \Rightarrow C) + conf(C \Rightarrow P)\right)$$

$$IR(P,C) = \frac{\left|sup(P) - sup(C)\right|}{sup(P) + sup(C) - sup(P \cup C)}$$

To calculate the two parameters above and to find an effective mode, the min-support of 0.1 and the min-confidence of 0.1 were specified in this study.

In the 254 cases, the association rules were first created between the symptoms and herbs. Moreover, the rules of (symptom ⇒ all 7 herbs of XD) are most attractive. And then, we created the association rules between manifestations to do further analysis. Furthermore, 48 cases which misused XD were organized to create association rules between manifestations. This will explore some manifestations which are similar to that in the 254 cases group. Moreover, these manifestations may mislead the doctors to treat with XD. Moreover, in these 48 cases, most of them used the XD without modifying. That means the failure of treatment was due to the whole formula. Moreover, we do not care about which herbs in XD caused the failure; thus, the association rules between the symptoms and herbs is not necessary in this part. After comparing the manifestations between 254 cases group and 48 cases group, the characteristics of XD will be selected out.

Results

Descriptive statistics of demographic attributes

In the cases that cured by XD, there are 151 males and 103 females. Only 36 cases have age record. Moreover, most of them have the age from 10 to 29. There are 25 males and 23 females in the cases that misused XD. And, only 36 cases have an age record. In other cases, that without age, we can infer that most of them are adults according to the descriptions [Table 2].

Table 2: Ages of patients in the cases

Age	254 cases group		48 cases group	
	Absolute count	Fraction	Absolute count	Fraction
2	0	0	1	0.021
9	1	0.004	0	0
10-19	10	0.039	3	0.063
20-29	11	0.043	4	0.083
30-39	5	0.020	0	0
40-49	6	0.024	3	0.063
50-59	3	0.012	2	0.042
60-69	0	0	1	0.021
Null	218	0.858	34	0.708

Association rules mining of 254 cases cured by *Xiaochaihu* decoction

Associations between manifestations and herbs

The association rules we also concerned are which with the manifestations as premises and the XD or some herbs of it as the conclusions. And, mining the bases for using XD is the main purpose of this analysis. The association rules "manifestations ⇒ herbs" with the largest values of conf (P⇒C) or conf (C⇒P) were selected from the results. Besides, the association rules of manifestations paired with XD (including all seven herbs) were also selected [Table 3].

Since *Chaihu (Radix Bupleuri)* was used in every case, it was not displayed in the conclusions. Most confidence values in Table 3 are >0.8. That means if the manifestations occur, the corresponding herbs will more likely to appear.

Seven manifestations such as inflammatory swelling and pain (ear or breast), headache, fever, hypochondriac pain, alternative chills and fever, rapid pulse, and wiry pulse are associated with XD. Among them, inflammatory swelling and pain (ear or breast) with the support of 0.126 has the highest affinity to XD (0.938). Although alternative chills and fever is the most frequent symptom (0.378), the confidence of that paired with XD is only 0.792.

Moreover, although the data are imbalance, the top nine rules are still attractive. When loss of appetite or inflammatory swelling and pain (ear or breast) occurred, *Gancao*, *Shengjiang*, and *Dazao* must be used. If there is hypochondriac pain, *Huangqin* must be used. *Huangqin* and *Gancao* must appear in the prescriptions to the patients with a headache or thirst. If patients with manifestations of wiry and rapid pulse or abdominal pain, *Gancao* must be used. When alternative chills and fever are simultaneous with wiry pulse, *Huangqin*, *Shengjiang*, and *Dazao* must be prescribed. Moreover, if vomiting, *Shengjiang* must be used to stop it.

Referring to *Kulc* and IR, the association rules of alternative chills and fever paired with XD (Rule 29) or herbs of *Huangqin, Banxia, Shengjiang,* and *Dazao* (Rule 23) are better than others.

Association of manifestations

There are only 11 frequent items among the 109 manifestations attributes [Table 4]. Moreover, there are only two association rules after operating by RapidMiner [Table 5].

According to the *Kulc*, rapid pulse and wiry pulse have a better correlation. Moreover, we can see that the two rules

Table 3: Associations rules between manifestations and herbs

n	Premises	Conclusions	Conf (P⇒C)	Kulc	IR
1	Inflammatory swelling and pain (ear or breast)	*Gancao, Shengjiang, Dazao*	1	0.568	0.864
2	Hypochondriac pain	*Huangqin*	1	0.575	0.849
3	Headache	*Gancao, Huangqin*	1	0.565	0.870
4	Wiry pulse, Rapid pulse	*Gancao*	1	0.567	0.866
5	Thirst	*Gancao, Huangqin*	1	0.571	0.857
6	Alternative chills and fever, wiry pulse	*Huangqin, Shengjiang, Dazao*	1	0.564	0.872
7	Loss of appetite	*Gancao, Shengjiang, Dazao*	1	0.566	0.869
8	Vomiting	*Shengjiang*	1	0.557	0.886
9	Abdominal pain	*Gancao*	1	0.559	0.883
11	Fever	*Gancao*	0.984	0.620	0.738
12	Rapid pulse	*Gancao*	0.982	0.600	0.773
13	Alternative chills and fever	*Shengjiang*	0.979	0.681	0.603
14	Thirst	*Gancao, Huangqin, Shengjiang, Dazao*	0.971	0.557	0.848
15	Wiry pulse	*Shengjiang, Dazao*	0.969	0.615	0.724
16	Inflammatory swelling and pain (ear or breast)	*Gancao, Dazao, Banxia, Renshen*	0.969	0.559	0.842
17	Loss of appetite	*Gancao, Shengjiang, Dazao, Banxia*	0.968	0.550	0.859
18	Alternative chills and fever, wiry pulse	*Huangqin, Shengjiang, Dazao, Banxia*	0.967	0.548	0.862
19	Abdominal pain	*Gancao, Banxia*	0.966	0.543	0.872
20	Vomiting	*Shengjiang, Banxia*	0.964	0.540	0.877
21	Hypochondriac pain	*Huangqin, Shengjiang, Banxia*	0.946	0.550	0.828
22	Inflammatory swelling and pain (ear or breast)	XD	0.938	0.543	0.834
23*	Alternative chills and fever	*Huangqin, Shengjiang, Dazao, Banxia*	0.938	0.671	0.555
24	Headache	*Gancao, Huangqin, Renshen*	0.935	0.535	0.847
25	Rapid pulse	*Gancao, Shengjiang, Dazao, Banxia*	0.891	0.554	0.736
26	Fever	*Gancao, Huangqin, Renshen*	0.875	0.568	0.676
27	Headache	XD	0.839	0.483	0.827
28	Hypochondriac pain	XD	0.811	0.479	0.790
29*	Alternative chills and fever	XD	0.792	0.583	0.480
30	Fever	XD	0.781	0.514	0.640
31	Rapid pulse	XD	0.727	0.462	0.678
32	Wiry pulse	XD	0.585	0.386	0.6

*Better association rules. IR: Imbalance ratio, XD: *Xiaochaihu* decoction, *Kulc: Kulczynski*

are all related to pules. Since only 104 cases have pulse manifestations records, we selected out these samples to explore the association rules. And, the rest of the cases do not have any association rules between manifestations.

The frequent items of the manifestations in the 104 cases are as follows [Table 6]. The top three items with high-support are wiry pulse (0.625), rapid pulse (0.529), and alternative chills and fever (0.423). Both hypochondriac pain (0.933) and white tongue fur (0.813) have high affinity to wiry pulse [Table 7]. However, referring to the evaluating parameters, the top three pairs with better association include fever paired with rapid pulse (0.7), alternative chills and fever paired with wiry pulse (0.682), and rapid pulse paired with wiry pulse (0.6). These results are similar to that of the 254 cases.

Association rules mining of 48 cases misused *Xiaochaihu* decoction

The frequent items of 70 manifestation attributes are as follows [Table 8]. Fever and alternative chills and fever are the most frequent ones (0.458). It is obvious that aversion to cold must be accompanied by fever [Table 9]. However, the data are imbalance according to the Kulc and IR. That means if patients have a fever, there is not always accompanied with aversion to cold. Under evaluating, the association rules including a headache paired with fever (Rule 3) and rapid pulse paired with wiry pulse (Rule 5) are more interesting. Moreover, Rule 6 carries no significance because of its low *Kulc*.

A comparison of the results of 254 cases group and 48 cases group

Some of the frequent items are the same in the two groups [Table 10]. Alternative chills and fever has the biggest support in both groups. Every item is associated with at least one other manifestations or XD except vomiting.

There are also different frequent items in two groups [Table 11].

On comparing Tables 7 and 9, the same association rules in two groups are rapid pulse paired with wiry pulse and rapid pulse paired with fever. Rule 1 is better than Rule 2 in two groups [Table 12].

Table 4: Frequent Items of 254 cases

n	Items	Support
1	Alternative chills and fever	0.378
2	Wiry pulse	0.256
3	Fever	0.252
4	Rapid pulse	0.217
5	Hypochondriac pain	0.146
6	Thirst	0.134
7	Inflammatory swelling and pain (ear or breast)	0.126
8	Headache	0.122
9	Loss of appetite	0.122
10	Abdominal pain	0.114
11	Vomiting	0.11

Table 5: Association rules of frequent items in table 4

n	Premises	Conclusions	Conf (P⇒C)	*Kulc*	IR
1	Wiry pulse	Alternative chills and fever	0.462	0.387	0.236
2	Rapid pulse	Wiry pulse	0.6	0.554	0.114

IR: Imbalance ratio, *Kulc*: *Kulczynski*

Table 6: Frequent items of cases with descriptions of pulse

n	Items	Support
1	Wiry pulse	0.625
2	Rapid pulse	0.529
3	Alternative chills and fever	0.423
4	Fever	0.288
5	Thirst	0.212
6	Headache	0.163
7	White tongue fur	0.154
8	Surging pulse	0.154
9	Hypochondriac pain	0.144
10	Vomiting	0.125
11	Slippery pulse	0.115
12	Deep pulse	0.115
13	Loss of appetite	0.106
14	Wiry pulse, Wiry pulse	0.317

The same items and rules can be regarded as the indications of using XD by doctors, but the differences are needed more attention. They may be the determinants of using XD or not.

Discussion

The imbalance of the results

In method part, we introduced the evaluating parameters, *Kulc* and IR. The results with higher *Kulc* and lower IR are better. However, most rules have low *Kulc* and high IR and show an extreme imbalance. Why did that happen? And whether we should deny the results only according to the two parameters or not.

Kulc is the average of conf (P⇒C) and conf (C⇒P). Therefore, the data with higher confidence will have higher *Kulc*. Since the confidence values are influenced by the support values, the difference between conf (P⇒C) and conf (C⇒P) is obvious sometimes due to the different support values of premises and conclusions. If the support of premise is much higher than that of the conclusion, the conf (P⇒C) will be low and the conf (C⇒P) will be high. Hence, the *Kulc* will also be low. While the meaning of the conf (P⇒C) is that the occurrence frequency of C when *P* occurs. In this article, we want to observe what the manifestation is when XD or other specific manifestations have high occurrence frequency. Therefore, sometimes, we just care about conf (P⇒C), the single oriental of the arrow, and the results with low *Kulc* are not meaningless.

IR is determined by the absolute D-value of sup(P) and sup(C). However, when searching the cases, for example, we just selected the cases treated with XD. Therefore, the herbs belong to XD must have an extremely high rate of occurrence. The support values of them are always >0.8. While the manifestations are diverse, the most frequent symptom is alternative chills and fever, and is only with the support of 0.37. When setting the manifestations as the premises and the herbs as the conclusions, the IR must be high. Under the circumstance, the high IR due to the cases we selected. To this kind of data, IR is just a reference rather than a determinant when evaluating a rule.

The results of association rules

In Table 3, some confidence values are 1. That means when a symptom or sign occur, some herbs must be used. There are some rules like that, such as loss of appetite/inflammatory swelling and pain (ear or breast) ⇒ *Gancao*, *Shengjiang*, *Dazao*; alternative chills and fever, wiry pulse ⇒ *Huangqin*, *Shengjiang*, *Dazao*; headache/thirst ⇒ *Huangqin*, *Gancao*; hypochondriac pain ⇒ *Huangqin*; (wiry and rapid pulse/abdominal pain ⇒ *Gancao*; vomiting ⇒ *Shengjiang*. Here, *Chiahu* has been omitted because it is used in every case.

Gancao (Licorice root) is most frequently prescribed as an important ingredient in many prescriptions of TCM. It is described in *Shanghanlun* that *Gancao* (1) harmonizes all drugs and detoxifies the adverse effects of herbs, (2) works synergistically with other drugs, (3) relieves spasm and pain, and (4) has a detoxifying action.[17] The Chinese term *Gancao* means the "sweet plant." In TCM theory, sweet flavor acts on the spleen and can enhance the function of the digestive system. At present, >400 compounds have been isolated from licorice and demonstrated a variety of pharmacological activities, such as anticancer, anti-inflammatory, antiviral, hepatoprotective, expectorant, and memory enhancing activity.[18] All these above can explain the using of *Gancao* aiming to those manifestations.

Shengjiang (Ginger) has been used to treat many medical conditions such as dyspepsia, flatulence, nausea and abdominal pain. It can stimulate gastric emptying and antral contractions in patients with functional dyspepsia.[19] This can explain that patients with the loss of appetite or vomiting are all treated with

Table 7: Association rules of frequent items in table 6

n	Premises	Conclusions	Conf (P⇒C)	*Kulc*	IR
1	Hypochondriac pain	Wiry pulse	0.933	0.574	0.758
2	White tongue fur	Wiry pulse	0.813	0.506	0.720
3*	Fever	Rapid pulse	0.7	0.541	0.392
4*	Alternative chills and fever	Wiry pulse	0.682	0.572	0.266
5	Thirst	Wiry pulse	0.682	0.456	0.596
6	Headache	Wiry pulse	0.647	0.408	0.677
7*	Rapid pulse	Wiry pulse	0.6	0.554	0.115
8	Thirst	Rapid pulse	0.591	0.414	0.515
9	Fever	Wiry pulse	0.5	0.365	0.438
10	Alternative chills and fever	Rapid pulse	0.432	0.389	0.138
11	Fever	Wiry pulse, rapid pulse	0.4	0.382	0.059
12	Alternative chills and fever	Wiry pulse, rapid pulse	0.273	0.318	0.170

*Better association rules. IR: Imbalance ratio, *Kulc*: *Kulczynski*

Table 8: Frequent items of attributes in 48 cases group

n	Items	Support
1	Alternative chills and fever	0.458
2	Fever	0.458
3	Headache	0.292
4	Rapid pulse	0.208
5	Wiry pulse	0.188
6	Delirium	0.146
7	Aversion to cold	0.125
8	Sweating	0.104
9	Vomiting	0.104

Table 9: Association rules of frequent items in table 8

n	Premises	Conclusions	Conf (P⇒C)	*Kulc*	IR
1	Aversion to cold	Fever	1	0.636	0.727
2	Delirium	Fever	0.857	0.565	0.651
3*	Headache	Fever	0.643	0.526	0.295
4	Rapid pulse	Fever	0.6	0.436	0.462
5*	Rapid pulse	Wiry pulse	0.6	0.633	0.074
6	Headache	Alternative chills and fever	0.357	0.292	0.257

*Better association rules. IR: Imbalance ratio, *Kulc*: *Kulczynski*

Table 10: Support of same frequent items in two groups

n	Items	Support	
		254 cases	48 cases
1	Alternative chills and fever	0.378	0.458
2	Fever	0.252	0.458
3	Headache	0.122	0.292
4	Rapid pulse	0.217	0.208
5	Vomiting	0.11	0.104
6	Wiry pulse	0.256	0.188

Shengjiang. Moreover, some researches also proved that ginger volatile oil has potent anti-inflammatory and can treat pain and chronic inflammation.[20] That is why doctors used *Shengjiang* when patients have inflammatory swelling and pain.

Dazao (the fruits of jujube) is widely used in TCM. It is conventionally used for antifungal, antibacterial, antiulcer, anti-inflammatory, and sedatives. Moreover, it is helpful for chronic constipation and proved to be effective against neonatal jaundice.[21] As the rules showing, *Dazao* is always used with *Shengjiang* as a pair to protect the spleen and stomach qi. However, *Dazao* has a sweet flavor and can sometimes impede the spleen qi. Therefore, patients with nausea or vomiting won't be treated with *Dazao*, *Gancao*, or other herbs that have sweet flavor.

In TCM theory, pathogenic fire flaming is characterized by a headache, a sore throat, thirst, redden eyes, and gum bleeding. *Huangqin* can move heat and dampness, and can also purge fire and remove the toxin from the body. Hence, it is effective to a headache and thirst. *Chaihu* and *Huangqin* are the important couplet medicines and are also the main ingredients of XD. If patients have *Shaoyang* syndrome or XD patterns, XD or at least *Chaihu* and *Huangqin* will most probably be used. Alternative chills and fever are always regarded as the characteristic symptom of *Shaoyang* and XD syndrome in *Shanghanlun*. There is another article in *Shanghanlun* that wiry pulse indicates that the *Shaoyang* is attacked by pathogens. Since the *Shaoyang* channel goes along the hypochondria and ears, hypochondriac pain and deaf will occur when the *Shaoyang* channel is attacked. Therefore, aiming at these symptoms, *Chaihu* and *Huangqin* must be used.

In Table 3, there are some manifestations having high affinity to XD. That means when these manifestations occur, the original formula of XD will be most probably used. This is reflected by the confidence value in the association rules. Some researchers we mentioned before thought that the manifestations with high occurrence frequency must be the indications of using XD. However, the figure below reverses this opinion.

Figure 1 shows that the symptom of alternative chills and fever with the highest support does not have the highest affinity to XD. On the contrary, the symptom of inflammatory swelling and pain with much lower support has the highest confidence. Moreover, if having any manifestations above, at least more than half of the patients will be treated with XD. However whether any of these seven manifestations can be regarded as the indication of using XD or not should still be deliberated.

By comparing the frequent items and association rules between 254 cases group and 48 cases group, we can see more interesting results. For example, the same association rules in two groups are (rapid pulse ⇒ wiry pulse) and (rapid pulse ⇒ fever). That means doctors should not treat with XD only in accordance with these pairs of manifestations.

Furthermore, Figure 2 is based on Table 10 which shows the same frequent items of two groups. Obviously, the occurrence

frequency of fever and headache in 48 cases group is much higher than another group. Meanwhile, fever and headache have a high correlation in 48 cases group. Consequently, we would better not use XD when patients with these two symptoms.

In Figure 2, alternative chills and fever has the highest support in both groups. And it has high affinity to wiry pulse as well as XD in 254 cases group. While in 48 cases group, alternative chills and fever has the same support to fever, most association rules are related to fever. Hence, the alternative chills and fever can be regarded as one of the characteristic symptoms of XD syndrome.

The wiry pulse and rapid pulse have a similar support value in 254 cases group, but most association rules are related to wiry pulse. Therefore, the wiry pulse seems to be one sign of using XD. However, in Figure 1, wiry pulse has the lowest affinity to XD. Thus, wiry pulse must accompany other symptoms together to be the characteristics, such as alternative chills and fever, headache, thirst, or hypochondriac pain, according to Table 7.

Vomiting has a similar and lowest frequency in two groups. Moreover, it also has no association rules with other manifestations or XD under the criterion that min-confidence

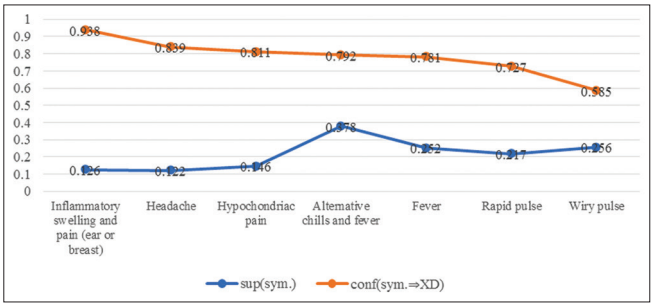

Figure 1: Comparison between support and confidence

Table 11: Support of different frequent items in two groups

n	254 cases group		48 cases group	
	Items	Support	Items	Support
1	Hypochondriac pain	0.146	Delirium	0.146
2	Thirst	0.134	Aversion to cold	0.125
3	Inflammatory swelling and pain (ear or breast)	0.126	Sweating	0.104
4	Loss of appetite	0.122		
5	Abdominal pain	0.114		

are 0.1. Although there is an article in *Shanghanlun* that XD can treat for fever paired with vomiting, we cannot find any evidence from these medical records.

In addition, Table 11 shows the different frequent items in two groups. Among them, hypochondriac pain and inflammatory swelling and pain (ear or breast) in 254 cases group have high affinity to XD. Thus, these two manifestations can be the characteristics of XD syndrome. In addition, in 48 cases group, delirium, and aversion to cold are associated to fever. This shows that fever is not the characteristic of XD syndrome.

Conclusions

1. The characteristics of XD syndrome are alternative chills and fever, hypochondriac pain, and inflammatory swelling and pain (ear or breast). When any of these manifestations occur, XD can be used. Wiry pulse paired with alternate chills and fever, headache, thirst, or hypochondriac pain is also can be regarded as the indications of using XD. However, these manifestations indicate that XD can be used, not must be used. XD should not treat for fever paired with some manifestations, such as headache, delirium, or aversion to cold. It shows that XD is more fit for the excess syndrome such as an excess fire in the liver or gallbladder meridians
2. In this article, we select some ancient cases, in which the manifestations became worse after using XD. These doctors treated with XD just because some manifestations were similar to the XD syndrome. Analyzing these cases can help us distinguish the real characteristics of XD
3. By comparing some support values and confidence values, we proved that high occurrence frequency does not equal to the high association. Hence, the researchers cannot get a conclusion only according to the frequency statistic when exploring the principle of using XD or other formulas.

The defect of this article is that the dataset is not large enough. However, the medical cases in ancient time were analyzed with association rules by RapidMiner are tried for the first time. In the future, more data and multiple methods should be used to deeply research the principle of using XD and other TCM formulas.

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Table 12: Same association rules in two groups

n	Premises	Conclusions	254 cases group			48 cases group		
			Conf (P⇒C)	*Kulc*	IR	Conf (P⇒C)	*Kulc*	IR
1	Rapid pulse	Wiry pulse	0.6	0.554	0.115	0.6	0.633	0.074
2	Rapid pulse	Fever	0.382	0.541	0.392	0.6	0.436	0.462

IR: Imbalance ratio, *Kulc*: *Kulczynski*

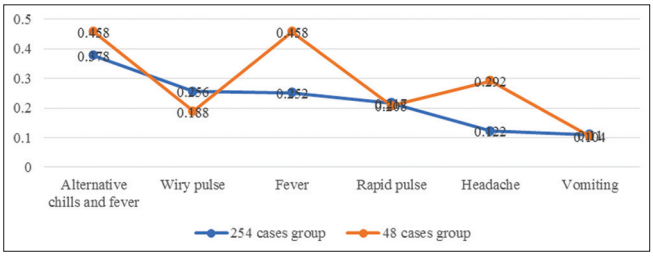

Figure 2: Comparison of support values between two groups

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Conflicts of interest

There are no conflicts of interest.

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