

# Distribution Law and Dynamic Evolution of *Zheng* in TCM

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## ABSTRACT

**Background:** symptoms of coronary heart disease (CHD) patients could be categorized into several subtypes from the perspective of traditional Chinese medicine (TCM), which are named *Zhenges*. TCM practitioners just use *Zhenges* to prescribe herbal medicine and select acupuncture methods. **Purpose:** the purpose of this research was to explore the distribution law and evolvement regulation in the patients with CHD in terms of *Zheng*. **Methods:** We conducted this research from literature, cross-sectional and observation study. The literature search was conducted in China National Knowledge Infrastructure (CNKI) in accordance with the diagnosis of CHD, and each single *Zheng* was identified and extracted from the CHD cases in the included literature. Then 1069 CHD patients from 5 hospitals in China were enrolled and symptoms and signs of each patients were observed and factor analysis was used to see the distribution law of *Zhenges* in CHD patients. 112 patients undergoing PCI were enrolled to explore the *Zheng* evolution rules. **Results:** According to literatures of 5099 CHD patients, the top 6 *Zhenges* of 5099 CHD patients respectively were blood stasis, *qi* deficiency, *yin* deficiency, phlegm turbidity, yang deficiency and

*qi* stagnation. Factor analysis of 1069 CHD patients showed that the top six *Zheng*s of 1069 CHD patients were *qi* deficiency and blood stasis, *qi* deficiency and phlegm turbidity, deficiency of *qi* and *yin*, *qi* stagnation and blood stasis, yang deficiency in both heart and kidney and deficiency in both heart and spleen. After the operation of PCI, *Zheng*s of excess patterns manifested the trend of decrease followed by increase, while *Zheng*s of deficiency patterns showed the increasing trend. Conclusions: *Zheng*s of CHD patients may be intricate and the distribution law could be uncovered by real world cross-sectional study. *Zheng*s evolve before and after PCI and *Zheng*s of individuals are in dynamic evolution.

## INTRODUCTION

Traditional Chinese Medicine (**TCM**) has experienced a long history and advanced its own theory. In the framework of TCM theory, individuals are born different because of different genes inherited from both parents, and with the environment influence, the phenotypes are various from person to person, thus the symptoms and signs may have slight difference among patients even with the same disease. And TCM practitioners always prescribe the herbal medicine and acupuncture formula based on these slight difference and TCM summarizes and names these slight difference as *Zheng*. TCM takes *Zheng* as its basic feature.

According to the 2014 statistical work by the World Health Organization, cardiovascular diseases are the most lethal non-communicable diseases. And the death toll from cardiovascular diseases in China is rapidly rising [1]. The high morbidity and mortality of Coronary Heart Disease (**CHD**) is a substantial threat to human health. Despite the current standard treatments of CHD, which encompass medications, percutaneous coronary intervention (**PCI**) and coronary artery bypass graft surgery (**CABG**), the effectiveness remains unsatisfactory within some patients [2-3]. Whereas, TCM could improve the effectiveness by prescribing relevant herbal medicine and acupuncture based on different *Zheng*s of individuals with CHD. For example, CHD is mainly manifested as chest pain, but this sort of symptom could be categorized into several subtypes from the perspective of TCM. Specifically, stabbing chest pain is considered as *Blood Stasis* which is one type of *Zheng*s, while cold chest pain is identified as *Yang Deficiency* which is another type of *Zheng*s. And TCM doctors just use these different *Zheng*s based on subtypes of symptoms to practice TCM medical services. In this way, every single patient with CHD could be divided into *Zheng* groups, which means each patient will be given different TCM formula according to his or her own situation, so that the best appropriate therapeutic schedule could be produced by TCM practitioners.

It is also imperative that *Zheng*s of individuals are not static but in dynamic evolution. For instance, *Zheng*s of one patient could be different before and after PCI or CABG. That is, *Zheng*s will evolve accompanied by the development of disease and treatment. Therefore, the TCM formula have to be adjusted by TCM doctors on account of the evolvement of *Zheng*s. Then, it is reasonable to report that the treatment of TCM is individualized and dynamic.

We could imagine how easy and clear the process of TCM prescribing could be when the distribution of *Zheng*s in patients with CHD and related involvement regulation are figured out. However, neither the distribution nor the regulation was worked out and both of them were difficult to uncover. So the purpose of this research was to explore the distribution law and involvement regulation in the patients with CHD in terms of *Zheng*. We conducted it from literature research, cross-sectional study and observation study.

## MATERIALS AND METHODS

### Diagnostic Criteria

#### Diagnostic criteria in disease

Nomenclature and Diagnostic Criteria for Ischemic Heart Disease (WHO), “Guidelines for the diagnosis and treatment of chronic stable angina”(2002) joint agreed by ACC/AHA, “Diagnosis of unstable angina and recommendations for treatment” (2000) published by Chinese Society of Cardiology.

#### Diagnostic criteria in *Zheng*s

Guideline on national coronary heart disease (1980) published by Chinese Interactive Medicine Association, Revised Criteria(1990), “Clinical guideline for the treatment of pectoral stuffiness and pains with Traditional Chinese Medicine”(1994) published by Ministry of Public Health, “Guidelines for Clinical Research on Traditional Chinese Medicine” syndrome classification of angina (2002) revised by State Drug Administration.

### Literature Research Based on 5099 Angina Pectoris in CHD

#### Search strategies and selection criteria

Because the researches in terms of this field were conducted in China in the period of 1995 to 2006, the literature search was conducted in China National Knowledge Infrastructure (CNKI) covering the period from inception to April 2006.

**Inclusion criteria:** In accordance with the diagnosis of CHD.

**Exclusion criteria:** Acute myocardial infarction, repeated literature and reviews, and literature lacks of clear classification of Chinese medicine and data support.

#### Method of *Zheng* classification

Based on the criteria of single *Zheng* classification proposed by Academician Wang Yong-yan [4], identified and extracted each single *Zheng* of the CHD cases in the included literature. Criteria of single *Zheng* classification: ① Six-exogenous pathogens: wind, cold, summer-heat, dampness, dryness, fire. ② Five internal excesses: internal wind, internal cold, internal dampness, internal dryness, internal fire. ③ Six *qi* relative factors: *qi* deficiency, *qi* stagnation, *qi* depression, reversed

flow of *qi*, depletion of *qi*, *qi* collapse. ④ Five blood relative factors: deficiency of blood, blood stasis, blood desertion, blood dryness, hemorrhagic. ⑤ Four *Yin*-yang relative factors: deficiency of *yin*, deficiency of yang, excess of *yin*, excess of yang. ⑥ Three other factors: poison, phlegm, water.

The *Zheng*s could be diagnosed according to the table 1.

**Table 1:** Diagnostic Criteria of *Zheng*s in CHD patients.

Type of <i>Zheng</i> s	Primary Symptoms	Secondary Symptoms	Tongue and Pulse
<i>Qi</i> Deficiency	Spontaneous sweating, lack of strength, exacerbation when fatigue	Vertigo, palpitation	Enlarged and teeth-marked tongue, weak pulse
<i>Yin</i> Deficiency	Dull pain, night sweat, vexing heat in the five centers (chest, palms and soles)	Thirst, dry eyes, insomnia	Red tongue and lack of tongue coating, thread and fast pulse
<i>Yang</i> Deficiency	Chest oppression and fear to cold	Edema, nocturia	Fat and white tongue, deep and thread pulse
Blood Deficiency	Dizziness, fatigue, pale facial complexion	profuse dreaming, palpitation	White tongue and thread pulse
Heat	Burning pain, thirst, red facial complexion	Insomnia, vexation, yellow urine	Red tongue and yellow tongue coating, fast pulse
Cold	Cold pain, fear to cold	Edema, pale facial complexion	Purple tongue, deep and slow pulse
Blood Stasis	Sticky pain, dim facial complexion, dim lips	Numbness, dry, scaly skin	purple, dusky tongue, knotted or intermittent pulse (irregularly intermittent)
<i>Qi</i> Stagnation	Distending pain, discomfort in the chest and rib-side, irritability	chest or abdominal mass, sighing, belching	Dusky red tongue, wiry pulse
Dampness	stuffy pain, chest oppression, sticky and greasy sensation in the mouth	Fat, dizziness, fatigue	Thick tongue coating, slippery pulse
Turbid Phlegm	stuffy pain, heaviness of the head, abdominal mass	loose stool, yellow sweat	Thick tongue coating, soggy pulse

Type of *Zheng*s can be diagnosed when both two primary symptoms and one secondary symptom appear or the relevant tongue and pulse arise.

## Statistical analysis

The original data was inputted by double-person recording method, with EXCEL to establish a database. Through the descriptive statistics program, calculated the frequency and percentage of each *Zheng* among the population in the literature with SSPS11.5.

## Cross-sectional Study of 1069 Patients with Angina pectoris

### Design and eligibility

This study was designed as a cross-sectional study. The target enrollment was 1069 patients from 5 hospitals in China. The enrollment criteria consisted of ① CHD type: Stable angina pectoris, early onset angina pectoris, worsening angina pectoris, resting angina, variant angina pectoris, post-infarction angina pectoris and non-ST-elevation myocardial infarction; ② Consistent with CHD diagnosis of angina; ③ By coronary angiography confirmed as 1 or more coronary artery diameter stenosis is  $\geq 70\%$ , or coronary left main diameter stenosis  $\geq 50\%$ ; coronary angiography showed 1 or more coronary artery main branch diameter stenosis is  $\geq 50\%$ , but  $\leq 70\%$ , there should

be coronary artery spasm or acute Q wave myocardial infarction history under angiography; ④ With patient's agreement; ⑤ No limited to the age, gender or ethnicity. And patients were excluded if ① ST segment elevation acute myocardial infarction; ② Confirmed as other heart diseases, severe neurosis, menopausal syndrome, cervical spondylosis, hyperthyroidism, biliary heart disease, or stethalgia caused by stomach and esophageal reflux; ③ Combined congestive heart failure (cardiac function III, IV grade), severe arrhythmia (such as persistent rapid atrial fibrillation, atrial flutter, ventricular tachycardia), cerebral infarction (acute), severe pulmonary insufficiency and other acute diseases; ④ Serious primary disease combined with liver, kidney, hematopoietic system.

## Research methods

Case Record Form was designed based on previous literature research. The symptoms and signs of 24-hours patients, the medical history (including history of present illness, past medical history, family history, etc.), auscultation, laboratory tests (including routine tests, liver and kidney function, blood lipids, blood glucose) and ECG information were observed. After preliminary information collection, the comprehensive information would be analyzed by Four Examination Methods within the framework of TCM. TCM Four Examination Methods included observation, smelling, asking and pulsing, in order to detect the TCM-specific symptoms and signs, such as intolerance of cold or heat, sweating situation, appetite, sleep quality, tongue manifestation and pulse manifestation.

## Statistical analysis

Employed factor analysis to find the common factors among the included patients based on the clinical information and identified the symptoms and signs in each factors, then recognized which *Zheng* each factor belonged to. In this way, every patient could be divided into these factors and related *Zhenges*. Then, used descriptive statistics program to count the number and percentage of each *Zheng* in the included patients.

## Zheng Evolution rules in 112 Patients with unstable Angina pectoris during PCI

### Design and eligibility

The target enrollment was 112 patients at An Zhen Hospital affiliated to Capital Medical University in China. Inclusion criteria: ① Patients who are over 35 years old. ② Coronary intervention was successfully performed, percutaneous coronary balloon angioplasty and coronary artery stent implantation included. ③ With patients' agreement. Exclusion criteria: ① PCI failure caused by various reasons. ② Serious primary disease combined with liver, kidney, hematopoietic system. ③ Patients with mental disorders, dysautonomia or dysnoesia.

## Research methods

The clinical epidemiological method was adopted in the study and the symptoms and signs including the manifestations of tongue and pulse of 143 patients after PCI were recorded. According to the diagnosis criteria and the pathological syndrome types of UAP, conducted *Zheng* differentiation from pre-PCI to 1 week, 4 weeks, and 12 weeks after PCI for further variable cluster analysis.

## Statistical analysis

Analyzed the data with descriptive statistic method by SPSS13.0, counting material adopt  $\chi^2$  inspection and *Fisher* exact test.

# RESULTS

## Distribution Law of *Zheng*s of CHD from literature study

According to literatures of 5099 CHD patients, there were ten *Zheng*s including *blood stasis* (2426 cases), *qi deficiency* (1782 cases), *yin deficiency* (1246 cases), *phlegm turbidity* (1125 cases), *yang deficiency* (688 cases), *qi stagnation* (622 cases), *cold coagulation* (315 cases), *blood deficiency* (126 cases), *endogenous fire* (80 cases) and *endogenous wetness-evil* (58 cases) which could be covered over 95% in CHD, which was shown in figure 1.

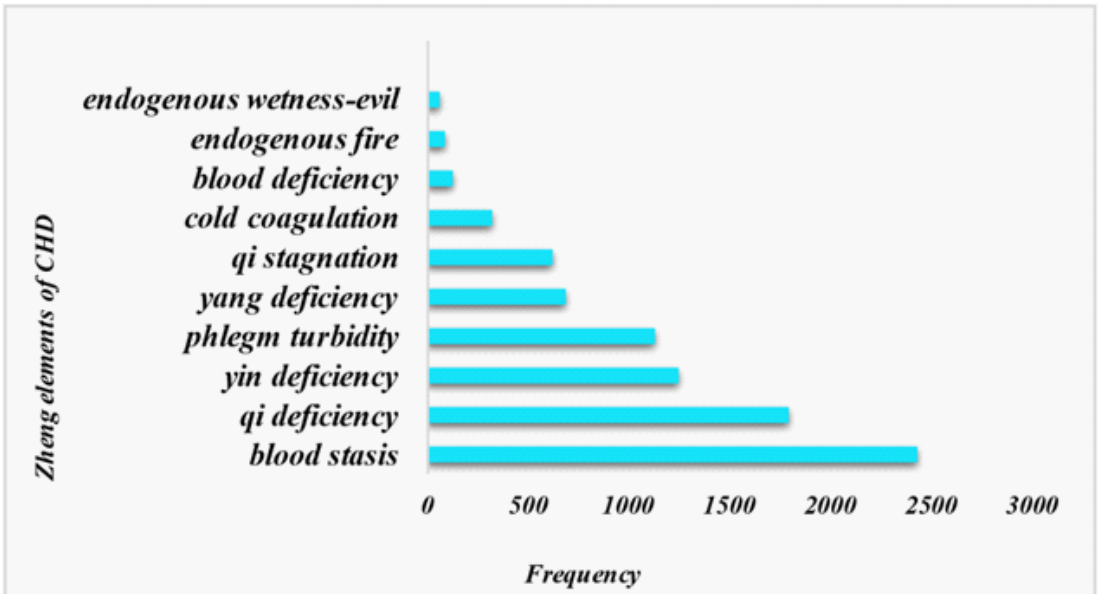


Figure 1: Distribution Law of *Zheng*s of CHD in 5099 CHD patients.

## Distribution Law of *Zheng*s of CHD from cross-sectional study

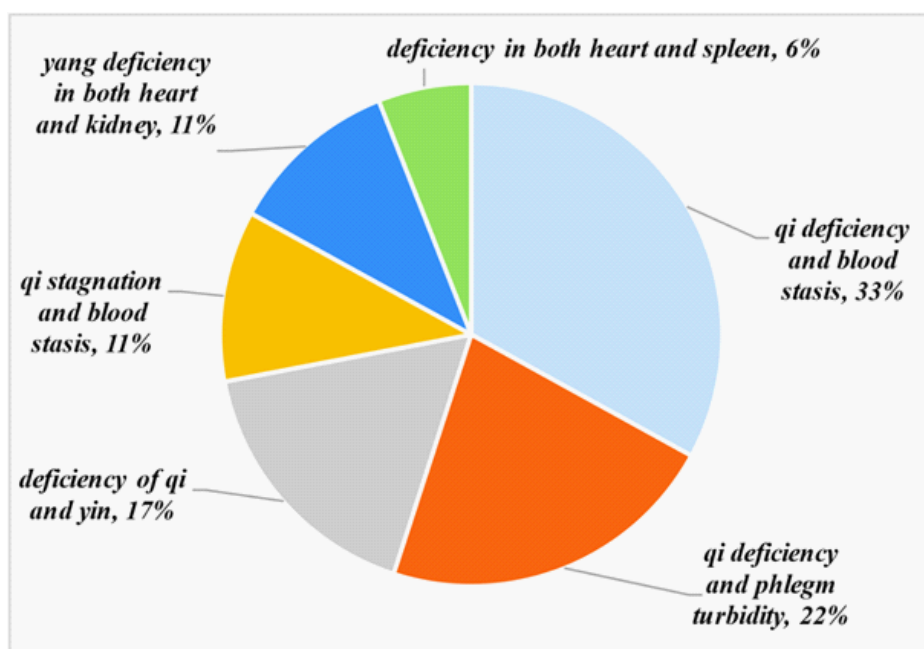
Factor analysis of 1069 CHD patients showed that 6 common factors were extracted as most clinically relevant, whose variable contribution reached 70.48%. Given the eigenvalue value =1.6,

with the maximum variance rotation deep method to obtain six common factors, which represent 6 different syndromes respectively of the 6 factors corresponding to each symptom, according to the principle that the coefficient of the largest factor and the specific symptom, the number of variables contained in the 6 common factors can be derived, and these six factors could be considered as six kinds of *Zheng*s, which was shown in table 2.

**Table 2:** Common factors of the 6 syndromes.

Types	Symptoms	Zhengs
f1	Chest tightness, depression, frequently deep sigh, low voice, heaviness, edema of lower extremity, dark palatal mucosa, dripping urine, abdominal distension bitter taste	Qi stagnation and blood stasis
f2	Night sweating, dryness in the eyes, irritability, dysphoria with feverish sensation in chest palms and soles, red tongue, lassitude, spontaneous perspiration, dry mouth, dizziness, forgetfulness, aversion to cold	Deficiency of Qi and Yin
f3	Lip a pale, abdominal tenderness, abdominal distension, palatal dark, dark purple tongue, dizziness, fatigue, spontaneous perspiration, night sweating, cough, forgetfulness	Qi deficiency and blood stasis
f4	Clear urine, cold abdominal and waist, pale, ecchymosis, diarrhea in the early morning, lip a pale, dripping urine, aversion to cold, emaciation, hemiplegia, defecation weakness, nocturia, heavy limbs, soreness and weakness of waist and knees	Yang deficiency in both heart and kidney
f5	Shortness of breath, lassitude, spontaneous sweating, chest tightness, heart palpitations, cough, white sputum, body fat, soreness and weakness of waist and knees, limb numbness, dark eye color, flushing, mouth sticky, aversion to cold	Qi deficiency and phlegm turbidity
f6	Gastric fullness, belching, bloating, anorexia, nausea and vomiting, pale complexion, depression, insomnia, loose stool, sticky mouth, bitter taste, frequently deep sigh, pale, abdominal distension	Deficiency in both heart and spleen

These six kinds of *Zheng*s included *qi* deficiency and *blood* stasis (352 cases), *qi* deficiency and phlegm turbidity (234 cases), deficiency of *qi* and *yin* (185 cases), *qi* stagnation and blood stasis (118 cases), yang deficiency in both heart and kidney (113 cases), deficiency in both heart and spleen (67 cases), which was illustrated in figure 2.



**Figure 2:** Distribution Law of *Zheng*s of CHD in 1069 CHD patients.

## Zheng evolution rules of PCI patients

Comparing the *Zhenges* at different time points, the results showed that the *Zheng* evolution rules of PCI patients could be evolved. Four stages were to be observed the evolution of *Zhenges*. At pre-PCI stage, *qi* deficiency and *blood* stasis (39 cases), phlegm turbidity and blood stasis (26 cases), *qi* stagnation and blood stasis (15 cases), deficiency of *qi* and *yin* (12 cases), *yang* deficiency and *cold* coagulation (14 cases), and *yin* deficiency in both heart and kidney (6 cases) were identified. At first week, *qi* deficiency and *blood* stasis (37 cases), phlegm turbidity and blood stasis (23 cases), *qi* stagnation and blood stasis (13 cases), deficiency of *qi* and *yin* (15 cases), *yang* deficiency and *cold* coagulation (9 cases), *yin* deficiency in both heart and kidney (7 cases) were recognized. At fourth week, *qi* deficiency and blood stasis (36 cases), phlegm turbidity and blood stasis (7 cases), *qi* stagnation and blood stasis (10 cases), deficiency of *qi* and *yin* (21 cases), *yang* deficiency and cold coagulation (6 cases), *yin* deficiency in both heart and kidney (15 cases) were observed. At twelfth week, *qi* deficiency and *blood* stasis (33 cases), phlegm turbidity and blood stasis (22 cases), *qi* stagnation and blood stasis (7 cases), deficiency of *qi* and *yin* (3 cases), *yang* deficiency and *cold* coagulation (16 cases), *yin* deficiency in both heart and kidney (6 cases) were detected. In this way, the evolution rules of *Zhenges* could be demonstrated in figure 3.

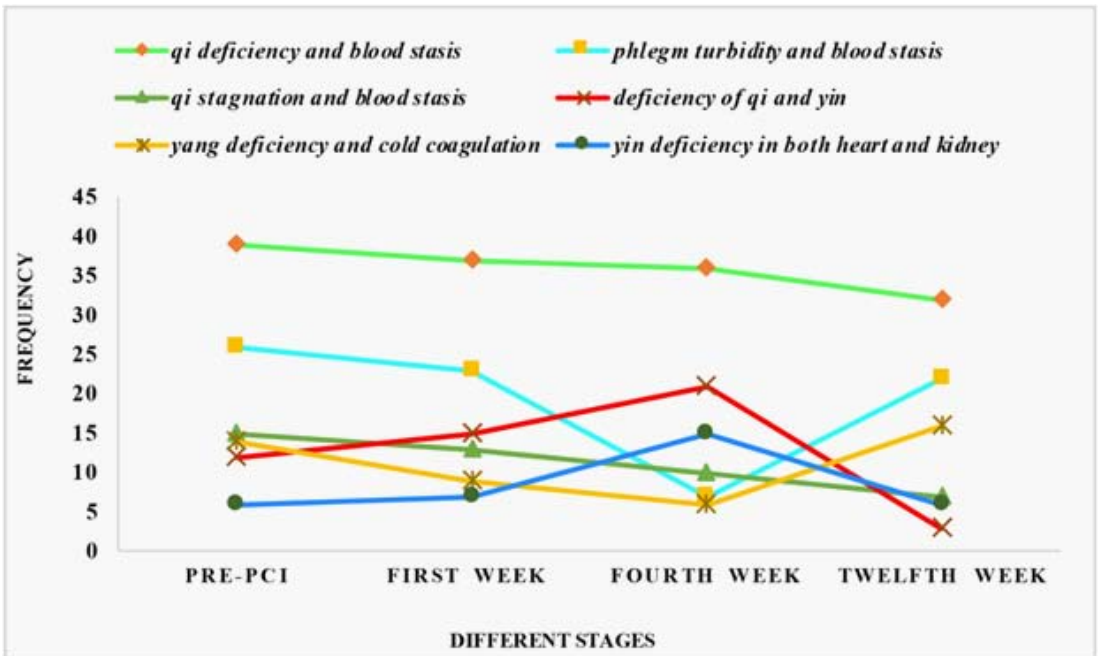


Figure 3: Distribution Law of *Zheng* of PCI patients.



## CONCLUSIONS AND DISCUSSIONS

From the results of literature study, the top 6 *Zheng*s of 5099 CHD patients respectively were blood stasis, *qi* deficiency, *yin* deficiency, phlegm turbidity, *yang* deficiency and *qi* stagnation. The percentage of blood stasis among 5099 patients was 47.58%, which indicated that nearly half of the CHD patients may suffer from the *Zheng* of blood stasis. And the TCM practitioners might refer to this conclusion when prescribing a formula for the CHD patients. Furthermore, further study may focus on the relationship between blood stasis and the pathogenesis, pathology of CHD from the perspective of genomics, transcriptomics, proteomics, metabonomics, within the framework of holistic view.

From the results of factor analysis from cross-sectional study, the top six *Zheng*s of 1069 CHD patients were *qi* deficiency and blood stasis, *qi* deficiency and phlegm turbidity, deficiency of *qi* and *yin*, *qi* stagnation and blood stasis, *yang* deficiency in both heart and kidney and deficiency in both heart and spleen. It is not difficult to find that in the former literature study, we identified and extracted the simple single *Zheng* of each patients, so the results showed the distribution law of single *Zheng*, but in this real world cross-sectional study, we just recognized the original *Zheng* of each patients, so the results showed distribution law of complicated combination of *Zheng*s. It implied that the *Zheng*s of CHD patients may be intricate, which was reasonable because the pathological process of individuals was not that simple itself. However, the distribution law could be explored by this method in spite of its complexity. Therefore, we recommend that more research on the field of *Zheng* distribution law based on the real world study should be conducted, so that more distribution laws of other diseases may be uncovered, which will be more useful for both the TCM doctors and the relevant patients and could be referred to when the associated medical policies are under consideration and worked out.

From the results of evolution rules of PCI patients, it could be implied that with the time passing by after the operation of PCI, *Zheng*s of excess patterns manifested the trend of decrease followed by increase, while *Zheng*s of deficiency patterns showed the increasing trend. This result verified the hypothesis that *Zheng*s evolve before and after PCI and *Zheng*s of individuals are in dynamic evolution. This result also gave a hint about the visible influence of PCI operation on patients from the perspective of TCM. As it stands, although the operation may improve the blood-supply of coronary artery, the process of operation may make patient weak and cause the advance of *Zheng*s of deficiency, which might offer insight into both TCM therapeutic approach after PCI and TCM prevention before PCI. And this kind of potential treatment and prevention is where TCM really shines. So, study on how best prevent the side effects before PCI and treat the *Zheng*s after PCI in light of TCM methods may be the next academic priority in the field of TCM, where we believe it will benefit much more CHD patients.

# ACKNOWLEDGEMENT

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