

## Current Situation and Re-understanding of Syndrome and Formula Syndrome in Chinese Medicine

Jie Wang<sup>1</sup>, Pengqian Wang<sup>2</sup> and Xingjiang Xiong<sup>1\*</sup>

<sup>1</sup>Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China

<sup>2</sup>Department of Endocrinology, Traditional Chinese Medicine Hospital of Mentougou District, Beijing 102300, China

### Abstract

The relationship between disease, syndrome and formula is thought to be one of the most significant problems in Traditional Chinese Medicine (TCM) clinical and basic practice. Syndrome is not only the core of TCM basic theory and syndrome differentiation, but also the bridge linking disease and formula, the essence of which is a classification according to subjective symptom and objective sign collected by physician through inspection, auscultation-olfaction, interrogation and palpation. In China, further researches on the standardization and clarifying essence of syndromes were carried out in recent decades. The research work mainly consists of diagnostic criteria, distribution, evolutionary laws, and biological basis of syndrome. However, it is found out that syndrome is relatively generous, vague, uncertain and abstractive, which has brought great difficulties to the clinical and scientific research of syndrome standardization. Based on clinical practice for years, we learned the TCM literature of past dynasties systematically and excavated the TCM basic theory thoroughly. Consequently, we found that formula syndrome, reserved in TCM classics, is a special theory system in diagnosis and treatment, which is another bridge linking disease and formula in TCM. Syndrome and formula syndrome are closely related but completely different, which are the core of two characteristic inheritance veins respectively in TCM. Further researches on formula syndrome mainly includes: a) study on diagnostic criteria of formula syndrome; b) study on distribution rules of formula syndrome of certain disease; c) study on the change rules of herb syndrome on the basis of formula syndrome; d) study on combined prescription rules; e) study on dynamic evolution laws of formula syndrome. Carrying out the researches of formula syndrome of certain disease is beneficial to grasp the characteristics of formula syndrome and treatment rules of disease.

### Introduction

The relationship between disease, syndrome and formula is thought to be one of the most significant problems in TCM clinical and basic practice presently. Generally speaking, syndrome is not only the core of TCM basic theory and syndrome differentiation, but also the bridge linking disease and formula, and the base of definite diagnosis and proper treatment [1]. However, it was pointed out recently that, there were different factions in TCM history. Syndrome differentiation was not the unique inheritance, and the establishment of its qualitative character and central position in TCM was just in the late 1950s [2-5]. Based on clinical practice for years, we learned the TCM literature of past dynasties systematically and excavated the TCM basic theory thoroughly. Consequently, we found that formula syndrome, reserved in TCM classics, is a special theory system in diagnosis and treatment. For quite a long time, syndrome theory, originated from the *Canon of Internal Medicine* and the *Classic on Medical Problems*, was believed to be the academic focus in TCM. Conversely, formula syndrome theory, originated from *Auxiliary Verse on Drugs, Methods for Zangfu Organs* and *Treatise on Febrile Diseases*, had been paid little attention, even ignored [6]. The aim of this article is not only to review achievements and consensus of syndrome studies, but also to explore the limitation of syndrome studies, clarify the connotation differences between syndrome and formula syndrome, and explore the further researches on formula syndrome.

### The Essence of Syndrome and its Research Progress

#### Essence of syndrome

In Traditional Chinese Medicine (TCM) theory, syndrome, which is also called a zheng or pattern, is the basic unit and a key concept. TCM syndrome is the abstraction of a major disharmonious pathogenesis, which is identified from a comprehensive analysis of clinical information from four main diagnostic TCM methods: observation, listening, questioning, and pulse analyses [7,8]. Different

from biomedical disease diagnosis, syndrome is a classification in clinical practice from an alternate viewpoint/dimension according to subjective symptom and objective sign collected by physician through inspection, auscultation-olfaction, interrogation and palpation [9]. Disease is based on microscopic thinking, while syndrome is based on macroscopic thinking [10]. According to specific law of symptomatic combination, there are several classifications in Chinese medicine, such as yin-yang classification method, six exogenous pathogenic factors classification method, Zang Fu classification method, meridian classification method, defensive-qi-nutrient-blood classification method and triple warmer classification method [11,12].

According to yin-yang classification method, Yang syndrome or hot syndrome of rheumatoid arthritis (RA) is mainly manifested as thin yellow fur of tongue, red tongue, thirst, irritancy, fever in joint, deep-colored and turbid urine and fever, while yin syndrome or cold syndrome is manifested as aversion to cold, cold limbs, pale tongue and cold in joint. Logistic regression analysis, decision tree analysis and neural network are used to analyse the correlation between symptoms and clinical curative effect. The results showed that different curative effects were acquired in patients with different symptoms combination, who were treated with the same therapeutic scheme. A

**\*Corresponding author:** Xingjiang Xiong, Department of Cardiology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beixiangge 5#, Xicheng District, Beijing 100053, China, Tel: +86 1088001817; Fax: +86 1088001229; E-mail: [5administration@163.com](mailto:5administration@163.com)

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better therapeutic effect could be getting in some specific symptoms combination, which may be similar to syndrome classification in traditional Chinese medicine. It has important significance for deepening the understanding of disease and improving the clinical efficacy [13-16].

### Research progress of syndrome

In China, further researches on clarifying essence of syndromes were carried out recently. The research mainly consists of diagnostic criteria, distribution, evolutionary laws, and biological basis of syndrome.

The study of syndrome diagnostic criteria is the precondition in carrying out researches on the distribution principle, the evolution laws, and the biological basis of syndrome. The concept of syndrome is fuzzy, broad and sweeping, and there are still problems remaining in classification of syndrome. Therefore, inconsistency of syndrome diagnosis appeared frequently. That is why syndrome diagnostic criteria were considered as the base of modernization and scientification of TCM, and it is absolutely necessary to study syndrome diagnostic criteria [17]. The research of syndrome diagnostic criteria began from the 1980s. Currently, studies on diagnosis standardization of blood stasis syndrome conducted by academician Chen Keji was the relatively mature research. Under the guidance of Prof. Chen, we have been engaged in the research since 1989 [18]. Recently, based on 2004 patients with blood stasis syndrome collected in 4 centers, 75 items were selected from 110 items in item pool of quantitative diagnosis about blood stasis syndrome by the way of epidemiological investigation. Secondly, the selected items were analyzed by six methods such as expert investigation method, correlation coefficient method, discrete tendency, principal component analysis, regression analysis and discriminatory analysis. Then, 19 items in accordance with any 4 methods in all the above methods were selected again as the quantization table of blood stasis syndrome, including vertigo, angina pectoris, dysmenorrhea, etc. The reliability and construction validity were quite high, which means that it was a better means of survey and in well agreement with TCM clinical diagnosis [19].

A certain progress has also been made in the distribution regularity and evolution laws of TCM syndromes. The distribution regularity of syndromes is the static description of pathological features such as the cause, location, nature and trend of disease. For instance, a previous study on syndrome differentiation of 900 patients' posthepatic cirrhosis mainly showed 5 syndrome patterns: liver-kidney yin deficiency, internal accumulation of dampness-heat, internal accumulation of blood stasis-heat, liver depression and spleen deficiency, and spleen-kidney qi deficiency [20]. The evolution laws of syndromes are the dynamical description of syndrome varied from the illness. The characteristic of the evolution of syndrome was summarized as "dynamic time and space" by academician Wang Yongyan, which was the most significant and critical characteristic of syndrome [21,22]. Therefore, understanding the characteristic is beneficial to reveal the essence of syndrome and improve the efficacy of disease. For example, TCM syndrome variation regularity in acute stage of ischemia stroke was investigated based on clinical dynamic state information of ischemia stroke from 72 h to 14 days. And it was found out that wind, fire and phlegm syndromes were the most frequent syndromes in acute stage of ischemia stroke. The wind syndrome and fire-phlegm syndrome were increasing as the course was extending in acute stage of ischemia stroke. The wind-phlegm syndrome was decreasing in the first three days, the wind-fire syndrome peaked on the third day, and the phlegm syndrome was decreasing on the fifth day. The wind-fire-phlegm was the most frequent and undulate syndrome on the fifth day.

The wind-phlegm-stagnation syndrome was increasing for the first three days [23].

Researchers also found that TCM syndrome had biological basis based on the study of kidney deficiency syndrome, syndrome of posthepatic cirrhosis, and the cold and hot syndrome of rheumatoid arthritis [24]. Taking viral hepatitis B for example, it is pointed out that the research of biological basis of syndrome should include: a) studies on gene polymorphism of different syndromes; b) researches of systems biology based on the characteristic spectrum of genomics, proteomics, and metabolomics in different syndromes; c) studies on metabolic network of syndrome; d) identification and classification of syndrome and the association studies between syndrome and laboratory indexes such as virology index, pathological indexes, biochemical indexes and immune indexes; e) analysis on the relationships between different syndromes and omics science including genomics, proteomics, transcriptomics and metabolomics [25-27]. Some scholars have investigated the difference of gene expression profiles in cold and heat syndromes of rheumatoid arthritis by using genechip analytical techniques and systems biology analysis. And several differences in the regulation of pathways were found between cold and heat syndromes. More importantly, 7 potential biomarkers which could be able to distinguish between cold and heat syndromes were identified. Studies have shown that there were biological basis for classification of cold and heat syndrome pattern in Chinese medicine in rheumatoid arthritis patients at the mRNA and metabolites level [28-30]. In addition, biochemical characteristics of common syndrome of posthepatic cirrhosis were analyzed. It showed that internal accumulation of dampness-heat syndrome was characterized by obvious hepatic inflammation, poor synthesis function and more ascites. Liver-kidney yin deficiency syndrome was characterized by low-level hepatic inflammation, poor synthesis function and more ascites. Internal accumulation of blood stasis-heat syndrome was characterized by low-level hepatic inflammation, poorer synthesis function, ascites and splenomegaly. The results also show that different syndrome patterns have different pathological features and biological basis [31].

### Re-understanding the Characteristics of Syndrome

Although great achievements have been made in syndrome research, there still exist some limitations. Firstly, syndrome is the product of speculation in TCM, which belongs to the category of imagery thinking. It depends on the doctor's learning, medical experience, academic origins and other factors. Therefore, the judgment made by doctors on cause, location, nature, trend of disease are individual and variable, and there will be a strange phenomenon that 10 TCM doctors may give 10 different diagnosis when facing the same patient. So, syndrome is relatively generous, vague, uncertain and abstractive. And we couldn't exaggerate the flexibility of the syndrome in TCM. In other words, syndrome is not necessarily consistent with the essential features of disease, which brought great difficulties to the clinical and scientific research of syndrome standardization.

Secondly, although it is considered that the same syndrome should be given the identical treatment in theory, we found that it is not entirely true in clinical practice. The same syndrome could also be treated with different methods. In another word, the clinical manifestations of the same syndrome in different diseases are not exactly the same, and the treatments also laid particular emphasis on respectively. So, one syndrome could also be treated by many different prescriptions in TCM theory. Thus, it could be concluded that accurate diagnosis of syndrome cannot be able to guide clinical diagnosis and prescription accurately. And there is a lack of necessary link between syndrome and

prescription possibly. This is not integral to study syndrome theory without prescription [32]. And it was found out that formula syndrome theory maybe probably a shortcut to solve this problem by excavating the classical theory in TCM.

## Formula Syndrome: A Neglected Concept Linking Disease and Formula

What is formula syndrome? Formula syndrome is the objective indication of formula, which is the bridge between disease and formula in TCM [33]. Differing from syndrome differentiation and treatment, the theory of formula syndrome is a unique model described in the classics of TCM for treatment. The core of the theory is formula corresponding to its objective indications. The theory is derived from *Treatise on Febrile Diseases*, the remarkable characteristic of which is that the formulae and their indications are documented clearly. For instance, the indications of *Banxia Xie Xin Tang* (Decoction of *Pinellia Ternate* for Purging Heart) are nausea, vomiting, diarrhea and epigastric distension, while not intermittent heat and cold syndrome.

Pathogenesis-based clinical medication is the core idea of syndrome differentiation. However, formula syndrome-based clinical medication is not exactly the same. The most significant difference between them is whether attention is paid to the objective evidences of formula utilization or not. Therefore, objectively visible symptoms and signs are the basis of diagnosis in formula syndrome, which is not liable to the doctor's learning, medical experience, academic origins and other factors. That is to say, the same diagnostic conclusion of formula syndrome could be given by 10 different TCM doctors when facing with the same patient. Yoshimasu Todo, a famous TCM doctor of classic formula school in Japan, once ever said, "When facing the same disease and syndrome, the diagnostic conclusions given by the teacher and students must be identical." So, formula syndrome is relatively objective, definitive, certain and specific. In other words, formula syndrome is much closer to the essential features of the disease. By means of mathematical formulas, the diagnosis and treatment model of formula syndrome can be expressed as "disease=formula syndrome+herb syndrome", which is not exactly the same as the model of syndrome differentiation expressed as "disease=syndrome+herb".

It is noteworthy that there were certain historical origin and realistic reasons in the desalination of clinical medication based on formula syndrome. The formula syndrome theory was replaced by syndrome differentiation gradually after *Treatise on Febrile Diseases*. *Qian Jin Yao Fang* (Essential Prescriptions Worth Thousand Golden) and *Qian Jin Yi Fang* (Supplement to Essential Prescriptions Worth Thousand Golden), written by the "King of Medicine" *Sun Simiao* in Tang Dynasty, were important marks of concourse of medical classics school with classical prescription school, which were also the beginning of the confusion of formula syndrome with syndrome. It had regained attention by *Xu Lingtai* and *Ke Qin* until the Qing Dynasty. After the establishment of Republic China, more interest had been laid by excellent doctors in TCM, such as *Ye Juquan*, *Hu Xishu* and *Huang Huang*. It is of great significance for realizing standardization of TCM, improving the level of the clinical effect and deepening the mood of syndrome differentiation. Advocating the research of formula syndrome theory is beneficial to get rid of the theoretical speculation, concretize the theory of syndrome differentiation, and grasp the essence and core of various methods of syndrome differentiation.

## Further Researches on Formula Syndrome

### Study on diagnostic criteria of formula syndrome

Formula syndrome is composed of relatively objective symptoms and signs regularly. The thinking characteristics of formula syndrome is more similar to physical image thinking rather than image thinking, therefore, study on diagnostic criteria of formula syndrome is much easier to implement. According to the connotation of formula syndrome, the diagnostic criteria contains three aspects such as symptoms and signs, disease and constitution, among which the disease and constitution are the further extension of symptoms and signs. To be specific, it mainly derives from TCM classics, clinical experiences, herb-syndromes and so on.

However, as the indications of the formula recorded in TCM classics are very simple, especially in *Treatise on Febrile Diseases*, interpretation of the classical provisions is particularly critical in the study on formula syndrome. In order to grasp the indications of formula syndrome comprehensively, it is of great necessity to combine contents recorded in TCM classics with the cognition of pathological mechanism, diagnosis, treatment and prognosis in modern medicine. And considering advances in modern pharmacology researches is another important method to comprehensively analyze the application indications of the formula.

For instance, it is recorded in *Synopsis of Golden Chamber* that, the indications of *Fuling Xingren Gancao Tang* (Decoction of *Poriacocos*, *Almond*, and *Glycyrrhiza*) and *Ju Zhi Jiang Tang* (Decoction of *Orange peel*, *Ginger*, and *Citrus aurantium*) contains thoracic obstruction, chest distress and shortness of breath. The current teaching materials pointed out that the pathogenesis of *Fuling Xingren Gancao Tang* (Decoction of *Poriacocos*, *Almond*, and *Glycyrrhiza*) lies in attack of lung by the retention of excessive fluid, and its indications also includes cough, vomiting of fluid, dysuria and white smooth fur on tongue besides the above mentioned symptoms. However, as we know that the disease of thoracic obstruction in TCM is similar to coronary heart disease (CHD) in modern medicine, the symptoms and signs described above may be just CHD combining pulmonary infection with the guidance of combination of disease and syndrome. In this case, there is seldom yellow phlegm due to the not severe pulmonary inflammation. In our clinical practice, *Fuling Xingren Gancao Tang* (Decoction of *Poriacocos*, *Almond*, and *Glycyrrhiza*) combined with other prescriptions are often used to treat cardiovascular system diseases such as CHD and heart failure combining acute and chronic bronchitis or chronic obstructive pulmonary disease. Good therapeutic effects could be achieved once the formula is suitable for the disease.

### Study on distribution rules of formula syndrome of disease

Previous studies on syndrome mainly focused on probing the distribution of TCM syndrome types of certain disease through large-scale epidemiological survey. However, researches on distribution rules of formula syndrome especially emphasize on investigating the common formula syndrome of certain disease through sufficient literature investigations and clinical verification researches on the basis of the diagnostic criteria of formula syndrome. Some scholars suggested [34] that making repeated clinical trials aiming at finding the specific indications was the way of improving clinical efficacy of TCM. The above research methods are similar to approaches used in studies on diagnostic rules of formula syndrome.

Studies on diagnostic criteria of formula syndrome mainly embodies the mode of "governing disease under formula", the



main line of which is formula syndrome. Nevertheless, studies on distribution rules of formula syndrome of disease embodies the other mode of “governing formula under disease”, the main line of which is disease. And the two modes are mutually complementary. The second mode was very common in ancient prescription works such as *Qian Jin Yao Fang* (Essential Prescriptions Worth Thousand Golden), *Tai Ping Hui Min He Ji Ju Fang* (Formularies of the Bureau of People’s Welfare Pharmacies) and *Sheng Ji Zong Lu* (Complete Record of Holy Benevolence). The writing style and manner of these works were quite similar, in which diseases were followed by formulae and the formulae syndrome clearly, and etiology and pathogenesis were rarely recorded. It was just the notable feature of classical prescription school, which is different from medical classics school.

However, the distribution rules of formula syndrome recorded in ancient Chinese medical literature were expressed in the guidance of TCM disease names. It is inevitably of certain limitations under the new situation of changes of diseases spectrum currently. Therefore, it maybe a feasible approach to carry out the researches with the guidance of modern medical disease names, which will create a new situation in modern researches on formula syndrome.

### Study on the change rules of herb syndrome on the basis of formula syndrome

In clinical practice, the disease has its own course. As a result, formula syndrome of diseases and its evolutionary law are of its own characteristics. According to the principle of herb syndrome in the theory of formulae corresponding to syndromes, there are certain rules to follow in the changes of herb syndrome on the basis of formula syndrome. That is to say, a certain formula syndrome has fixed compatibility with one or more specific herb syndrome. The deep reasons may be associated with the changes of pathological mechanism of the disease. For instance, *Si Ni San* (Powder for Treating Cold Limbs) syndrome is always accompanied with *Dan Pi* (*Cortex Moutan*) syndrome and *Shan Zhi Zi* (*Gardenia*) syndrome in chronic atrophic gastritis, while accompanied with *Sheng Di Huang* (*Radix Rehmanniae*) syndrome in constipations. Equally, *Xiao Chaihu Tang* (Minor Bupleurum Decoction) syndrome is always accompanied with *Shi Shi Gao* (*Gypsum Fibrosum*) syndrome, *Yi Yi Ren* (*Semen Coicis*) syndrome and *Jie Geng* (*Radix Platycodi*) syndrome in cough with thermalization tendency of Shaoyang syndrome as a result of Shaoyang transferring to Yangming or Yangming transferring to Shaoyang, while accompanied with *Gan Jiang* (*Rizoma Zingiberis*) syndrome and *Wu Wei Zi* (*Fructus Schisandrae*) syndrome in cold conversion tendency of Shaoyang syndrome.

### Study on combined prescription rules

As we know some diseases could be treated by a single prescription directly, while some are treated by two or more prescriptions combined together. According to the principle of combined prescription in the theory of formulae corresponding to syndromes, a certain formula syndrome always has fixed compatibility with one or more other formula syndrome, which may be determined by the pathological mechanisms of the disease. Taking exogenous disease as an example, *Xiao Chaihu Tang* (Minor Bupleurum Decoction) syndrome is regularly accompanied with *Guizhi Tang* (Cassia Twig Decoction) syndrome in disease with Taiyang and Shaoyang meridians involved. In the treatment of angina pectoris, stagnation of yang in the chest by turbid phlegm syndrome could be treated by the *Gualou Xiebai Banxia Tang* (Decoction of *Trichosanthes kirilowii* maxim, *Allium macrostemon bunge*, and *Pinellia ternata*) combined with *Gualou*

*Xiebai Baijiu Tang* (Decoction of *Trichosanthes kirilowii* maxim, *Allium macrostemon bunge*, and white wine) and *Zhishi Xiebai Guizhi Tang* (Decoction of *Citrus aurantium*, *Allium macrostemon bunge*, and *Cassia* Twig). *Banxia Baishu Tianma Tang* (Decoction of *Pinellia ternata*, *Atractylodes macrocephala*, and *Gastrodia elata*) accompanied with *Zexie Tang* (Decoction of American water Plantain) are widespread used in treating hypertension with fluid retention syndrome. Moreover, *Banxia Xie Xin Tang* (Decoction of *Pinellia Ternate* for Purging Heart) is often combined with *Shengjiang Xie Xin Tang* (Decoction of *Ginger* for Purging Heart), *Gancao Xie Xin Tang* (Decoction of *Glycyrrhiza* for Purging Heart), *Fuzi Xie Xin Tang* (Decoction of *Aconite root* for Purging Heart) and *Dahuang Huanglian Xie Xin Tang* (Decoction of *Chinese rhubarb* and *Coptis Chinensis Franch* for Purging Heart) in treating digestive diseases with combination of cold and heat syndrome.

### Study on dynamic evolution laws of formula syndrome

The dynamic evolution law of formula syndrome is the description of the changing process of formula syndrome in the course of the disease. The research is meaningful in understanding the essence of the disease and giving the right prescription. For example, in exogenous diseases, if the exterior syndrome of Taiyang disease is not cured by *Mahuang Tang* (Ephedra Decoction) in time, it will transform into *Ma Xing Gan Shi Tang* (Decoction of *Herba Ephedra*, *Semen Armeniacae Amarum*, *Radix Glycyrrhizae*, and *Gypsum Fibrosum*) syndrome, the pathogenesis of which is external cold and internal heat. It is holding by Zhang Xichun, a famous TCM doctor in the Republic of China Period, that, *Xiao Qing Long Tang* (Minor Green Dragon Decoction) syndrome can transform into *Cong Long Tang* syndrome with appropriate treatment. If the patient with *Guizhi Jia Houpu Xingzi Tang* (Decoction of Cinnamon Twig with *Magnolia* and *Apricot Kernel*) syndrome suffer wind-cold, he might be suitable for the treatment by *Xiao Qing Long Jia Shigao Tang* (Minor Green Dragon plus *Gypsum* Decoction) or *Ma Xing Gan Shi Tang* (Decoction of *Herba Ephedra*, *Semen Armeniacae Amarum*, *Radix Glycyrrhizae*, and *Gypsum Fibrosum*). Based on the above, we found that the dynamic evolution laws of formula syndrome are closely related to key herb syndrome.

### Summary

Currently, certain consensus and achievements have been achieved in the research of standardization and clarifying essence of syndromes. Nevertheless, the clinical guidance value will be even greater if the study is carried out combined with formula syndrome rather than syndrome alone. Syndrome and formula syndrome are closely related but completely different, which are the core of two characteristic inheritance veins respectively in TCM, namely syndrome differentiation and formula corresponding to syndrome. Previous theoretical and literature research showed that: a) the formula syndrome theory is the core of Zhang zhongjing’s theory and the significant characteristics in TCM; b) clinical efficacy depends on the corresponding degree of formula and their indications; c) formula syndrome is not contradictory to syndrome differentiation. Carrying out the research of formula syndrome of disease is beneficial to grasp the characteristics of formula syndrome and treatment rules of disease.

### Conflict of Interests

All authors manifest that there is no conflict of interests.

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