

Editorial

Formulation and Interpretation of International Diagnostic Guidelines for Blood-Stasis Syndrome

QIU Yu and XU Hao

Blood-stasis syndrome refers to the syndrome caused by poor blood circulation, blood stasis, or blood overflowing outside the vessels and accumulating in the body. The main clinical manifestations are pain, lump, bleeding, dark-purple complexion or cyanosis of lips and tongue, dry and scaly skin, thin and astringent or intermittent pulse. Blood-stasis syndrome is a common basic syndrome in traditional Chinese medicine (TCM), it plays a very important role in many diseases such as cardiovascular and cerebrovascular diseases,^(1,2) tumor,⁽³⁾ diabetes⁽⁴⁾ and inflammation,⁽⁵⁾ immune dysfunction,⁽⁶⁾ tissue hyperplasia⁽⁷⁾ and other related diseases in the occurrence and development process, so the study on blood-stasis syndrome and promoting blood circulation for removing blood stasis has always been the most active research field in TCM and integrated traditional Chinese and Western medicine.

Since the establishment of the first diagnostic standard of blood-stasis syndrome in 1982, it has played an important role in clinical application after many revisions, but at the same time, some problems have been revealed, such as tedious items or judgments, unclear expressions, insufficient diagnostic sensitivity, certain unreasonable items, etc., and there is still a lack of internationally recognized diagnostic standard of blood-stasis syndrome. With the development of globalization of TCM, it is of positive significance to formulate the international guidelines for diagnosis of blood-stasis syndrome, which is recognized by international organizations and meets the needs of modern clinical research, for guiding the diagnosis and treatment of common diseases and major diseases in the world with blood-stasis syndrome as the main syndrome. On December 16, 2021, the international organization standard *International Diagnostic Guidelines for Blood-Stasis Syndrome* (hereinafter referred to as Guide A) proposed and drafted by Academician

CHEN Ke-ji of Xiyuan Hospital of China Academy of Chinese Medical Sciences and National Center for Clinical Medical Research of Cardiovascular Diseases of Traditional Chinese Medicine. Officially issued by the World Federation of Chinese Medicine Societies, this is the first international standard of syndromes issued by the World Federation of Chinese Medicine Societies (hereinafter referred to as the WFCMS) and an important milestone in the international research of blood-stasis syndrome. Guide A has the characteristics of concise diagnosis items, wide coverage, simple judgment criteria, clinically practical and strong operability, which can provide reference for the diagnosis of diseases related to blood-stasis syndrome in the world and is of great significance for further promoting the globalization of TCM. This paper interprets the ideas and highlights of Guide A, and provides reference for understanding, learning and standardizing the application of the Guide.

Guide Formulation Ideas

In 2016, the author's team relies on the National Science and Technology Support Program "Research on Inheritance of Unique Syndrome Differentiation Methods of Famous and Old Chinese Practitioners" of the "Twelfth Five-Year Plan" of the Ministry of Science and Technology, revised the *Practical Diagnostic Criterion for Blood-Stasis Syndrome* (hereinafter referred to as Standard B) by Delphi method on the basis of literature collation, case analysis and qualitative interview, reference of the previous diagnostic criteria of blood-stasis syndrome,

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Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing (100091), China

Correspondence to: Prof. XU Hao, E-mail: xuhaotcm@hotmail.com

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combination of the latest clinical research progress, and the authenticity and reliability of the standard were tested through clinical research, which was published in Chinese and English versions of *Chinese Journal of Integrated Traditional Chinese and Western Medicine* in 2016 by the Professional Committee of Promoting Blood Circulation and Removing Blood Stasis of Chinese Association of Integrated Traditional Chinese and Western Medicine.^(8,9) Guide A is based on Standard B, extensively solicits opinions from experts at home and abroad, and is issued after being examined and approved by the International Standards Department of the WFCMS. The following aspects are fully considered in the specific formulation process.

Keep Pace with the Times based on Reference to Previous Standard

There are mainly 8 diagnostic criteria of blood-stasis syndrome since its establishment (Table 1).

Inherit Experience of Syndrome Differentiation of Famous Old Chinese Medicine Practitioners

Treatment based on syndrome differentiation is one of the basic characteristics of TCM. Famous old Chinese medicine practitioners are the group with the highest clinical level and the deepest academic attainments of Chinese medicine. In the process of

decades of clinical diagnosis and treatment, they have gradually formed their own unique syndrome differentiation methods, which have achieved outstanding clinical curative effect and become the essence of their academic thoughts. Therefore, the unique syndrome differentiation method of famous old TCM practitioners is the core of inheritance. Academician CHEN Ke-ji, a master of Chinese medicine, has formed a unique academic thought and method system of syndrome differentiation and treatment of blood-stasis syndrome after decades of clinical practice, which has important guiding significance for clinical practice. Academician CHEN Ke-ji once presided over the formulation of the first *Trial Standard for Diagnosis of Blood-Stasis Syndrome*, and his research on "Blood-Stasis Syndrome and Promoting Blood Circulation and Removing Blood Stasis" won the first prize of national scientific and technological progress awards in the field of TCM. Under the influence of Academician CHEN Ke-ji's academic thought of promoting blood circulation and removing blood stasis, the modern school of promoting blood circulation and removing blood stasis has matured day by day, and formed the phenomenon of promoting blood circulation and removing blood stasis in clinical practice, which has greatly promoted the whole Chinese medicine industry.

Table 1. Basic Characteristics of Existing Diagnostic Criteria for Blood-Stasis Syndrome

Year	Standard	Author/organization	Formulate methods	Characteristic
1982	Trial diagnostic standard for blood-stasis syndrome ⁽¹⁰⁾	Professional Committee of Promoting Blood Circulation and Removing Blood Stasis of Chinese Society of Integrated Traditional Chinese and Western Medicine	LR, EC	Qualitative
1983	Diagnostic standard for blood-stasis syndrome ⁽¹¹⁾	Terazawa Katsutoshi, et al., Japan	LR, CE	Quantitative
1986	Diagnostic standard for blood-stasis syndrome ⁽¹²⁾	Professional Committee of Promoting Blood Circulation and Removing Blood Stasis of Chinese Society of Integrated Traditional Chinese and Western Medicine	LR, EC	Qualitative
1986	Trial international standard for diagnosis of blood-stasis syndrome ⁽¹³⁾	Ogawa Arata, et al., Japan	LR, EO	Qualitative
1988	Diagnostic standard for blood-stasis syndrome ⁽¹⁴⁾	WANG Jie and CHEN Ke-ji, et al., China	LR, CE	Quantitative
1988	Reference standard for diagnosis of blood-stasis syndrome ⁽¹⁵⁾	International Conference on Blood-Stasis Syndrome Research	LR, EC	Qualitative
2011	Consensus on diagnosis and treatment of blood-stasis syndrome with integrated traditional Chinese and Western medicine ⁽¹⁶⁾	Professional Committee of Promoting Blood Circulation and Removing Blood Stasis of Chinese Society of Integrated Traditional Chinese and Western Medicine	LR, DM, EC	Qualitative
2016	Practical diagnostic criteria for blood-stasis syndrome ^(8,9)	Professional Committee of Promoting Blood Circulation and Removing Blood Stasis of Chinese Society of Integrated Traditional Chinese and Western Medicine	LR, QI, DT	Qualitative + quantitative

Notes: LR: literature review; EC: expert consensus; CE: clinical epidemiology; EO: experts' opinion; DM: Delphi method; QI: qualitative interview; DT: diagnostic test

During the development of Standard B, the research team used the methods of collation of works, individual interview and physical analysis to discuss Academician CHEN Ke-ji's ideas and methods of syndrome differentiation of blood-stasis syndrome, summarize his academic thoughts of syndrome differentiation of blood-stasis syndrome, and provide theoretical basis for revising and perfecting the diagnostic criteria of blood-stasis syndrome. Through the study of literature and works, the preliminary theoretical framework of Academician CHEN Ke-ji's syndrome differentiation of blood-stasis syndrome was formed, which laid the foundation for drawing up the interview outline. Then, the topic analysis method was used to analyze the data of two in-depth interviews with Academician CHEN Ke-ji, the interview data of his inheritors and typical medical cases of blood-stasis syndrome, and three themes were determined, namely, theoretical framework, syndrome differentiation characteristics and syndrome differentiation basis, thus forming the preliminary entry of Standard B, and establishing the first draft of Standard B by Delphi method. In Standard B, Academician CHEN Ke-ji's syndrome differentiation thought of blood-stasis syndrome, which is specific symptoms and signs, is fully reflected, which is also the biggest feature different from previous standards.

TCM syndrome differentiation diagnosis has strong subjectivity and speculation, which is difficult to describe by quantitative research methods. Qualitative research method emphasizes the in-depth understanding and interpretation of phenomena, which is a better method to explore the academic thoughts and diagnosis and treatment experience of TCM. In the process of formulating Standard B, we took the lead in adopting standardized qualitative research methods to explore and summarize Academician CHEN Ke-ji's unique syndrome differentiation method of blood-stasis syndrome. The concept of triangular mutual evidence was also used. The analysis results of individual interview data were cross-referenced with the analysis results of case data and the contents of literature works. At the same time, the research results were revised in combination with Academician CHEN Ke-ji's feedback, so as to improve the authenticity of the research results and provide methodological reference for the future research on the inheritance of TCM syndrome differentiation methods.⁽¹⁷⁾

Pay Attention to Reliability and Authenticity Evaluation of the New Standard

It is necessary to evaluate the reliability and authenticity of a new diagnostic standard before it is applied to clinic, but there is no relevant research on previous standards. Reliability is also called repeatability, that is, the stability of the results obtained by repeated diagnosis of a diagnostic standard under the same conditions. Good reliability is the premise and foundation of evaluating authenticity. To evaluate the reliability, the research team used Kappa consistency test to analyze the consistency of different researchers' results of diagnosing the same patient with standard B.⁽¹⁸⁾ Authenticity refers to the degree of agreement between the diagnosis results and the actual situation by using the diagnostic criteria to be evaluated, and the basic indicators of its evaluation are sensitivity and specificity. Traditional diagnostic test methods need reliable "gold standard" to evaluate the authenticity. Due to the lack of reliable "gold standard" in TCM syndrome diagnosis standard, it is difficult to make a correct evaluation by traditional diagnostic test methods. Researchers at home and abroad have carried out relevant research on Bayesian method, and the results suggest that Bayesian method can be used to effectively estimate the sensitivity and specificity of diagnostic tests without "gold standard".⁽¹⁹⁻²¹⁾ For the first time, this research team used Bayesian method to verify the authenticity of TCM syndrome diagnostic criteria, selected representative diagnostic criteria of blood-stasis syndrome in 1986 and 2011 as reference standards, diagnosed the same batch of patients with standard B and two reference standards, and estimated the authenticity related indicators such as sensitivity and specificity of this standard by Bayesian method. The results showed that the diagnostic coincidence rate of different doctors applying standard B was 91.96%, and the consistency was good; and standard B significantly improved the sensitivity without significantly reducing the specificity.⁽¹⁸⁾

Widely Solicit Opinions from Experts at Home and Abroad

During the development of Standard B, experts from various fields were fully absorbed into the research team, forming a revision group with multi-disciplinary experts working together. In addition, the Standard B validation team includes 37 experts from more than 20 provinces and cities in China,

all of whom are well-known experts in the research field of blood-stasis syndrome and promoting blood circulation and removing blood stasis in China. In order to formulate internationally applicable diagnostic guidelines for blood-stasis syndrome, the research team also extensively solicited opinions from experts at home and abroad, and invited 30 experts from Chinese mainland, Hong Kong (China), Taiwan (China), Macau (China), South Korea, the United States, Britain, Germany, Canada, Australia, Singapore and Malaysia as members of the Working Group of Guide A to further revise and improve on the basis of Standard B.

After the draft guide A was submitted to the International Standards Department of the WFCMS, it solicited opinions from home and abroad, and invited three domestic and three international experts to review it. After examination and approval, the draft Guide A was finalized by the Validation Expert Committee convened by the International Standards Department of the WFCMS, including 10 domestic experts and 3 international experts. The approved draft Guide A was publicized by the WFCMS for one month, and finally approved by the WFCMS Council. The revised Guide A has undergone domestic and international review rounds, validation by a validation committee, an international public consultation and review by the WFCMS Council.

In a word, in the process of formulating Guide A, nearly 100 experts at home and abroad have been consulted. According to the expert opinion, the guide has been revised accordingly, and the unrevised ones have been clearly explained. Strict guide validation process and extensive solicitation of expert opinions at home and abroad ensure the full international representation and applicability of Guide A.

Interpretation of Guide A

The diagnostic criteria of Guide A include 8 main criteria and 8 secondary criteria. If one of the main criteria or two of the secondary criteria are met, blood-stasis syndrome can be diagnosed. Compared with Standard B, some items in the guide are merged and some items are revised.

Main Criteria

In Article 1, the description of "blue, purple-black, varicose or swollen sublingual vein" is added.

Although Article 3 "varicosity or telangiectasia at any sites" includes this part, in view of the importance of sublingual vein manifestation, this part is emphasized in Article 1 of Guide A.

Articles 1 and 2, according to experts' opinions, improve the color description of tongue quality and face, lips, gums, eyes or fingers (toes), and add "dull red" on the basis of "dull purple or cyanosed", which is more in line with clinical practice.

Article 3, "any sites" refers to conjunctiva, fundus, oral mucosa, abdominal wall, lower limbs, digestive tract, etc. After varicose veins or telangiectasia appear in the above parts, blood-stasis syndrome can be diagnosed.

Articles 4, 5 and 6 are the same as Standard B and previous standards, without modification, and the entries are clearly explained. Among them, Article 4, "blood outside the meridians (blood stasis and blood accumulation in organs, tissues, subcutaneous or serous cavity caused by bleeding)" and Article 6, "dark menstrual flow, or slightly dark blood clots", are intuitive manifestations of blood-stasis syndrome. Article 5 "Abdominal tenderness and tightness" is the main manifestation of blood stasis abdomen syndrome. Japanese scholars such as Ogawa Arata and others pay special attention to the significance of blood stasis abdomen syndrome for the diagnosis of blood-stasis syndrome, and put forward blood stasis abdomen syndrome as an essential item for the diagnosis of blood-stasis syndrome in the *Trial International Standard for Diagnosis of Blood-Stasis Syndrome*.⁽¹³⁾

The contents of Articles 7 and 8 are one in Standard B. The imaging of Article 7 mainly includes CT, ultrasound, X-ray, etc., which can intuitively find the existence of vascular stenosis, while "material evidence of thrombosis, infarction or embolism" involves many contents, not only imaging examination, so it is divided into Articles 7 and 8. At the same time, according to the degree of stenosis, stenosis $\geq 50\%$ is the main standard, and stenosis less than 50% is the secondary standard (Article 6 of the secondary standard). Academician CHEN Ke-ji advocated that bringing the examination indicators of modern medicine into the system of CM syndrome differentiation can extend and broaden the diagnostic vision of TCM, and at the same time, it is also the embodiment of the new standard

keeping pace with the times and keeping up with the progress of clinical research.

Article 8 is "material evidence of thrombosis, infarction or embolism". Poor blood flow or blood stasis is a typical manifestation of blood-stasis syndrome. The concepts of thrombosis, infarction and embolism put forward by modern medicine are all poor blood circulation or stopped blood flow, which can be diagnosed as blood-stasis syndrome after the objective evidence is clear. At the same time, according to experts' opinions, "obstruction" is changed to "infarction", which is consistent with modern medical concepts.

Compared with standard B, guide A deletes the entry of "intermittent claudication". According to expert opinion, intermittent claudication can be caused by arterial occlusion of lower limbs, but some patients may also be caused by lumbar spinal stenosis. If the patient's further examination determines that it is a vascular cause, it should also meet the requirement of vascular stenosis $\geq 50\%$, so intermittent claudication should be deleted from the main index.

Secondary Criteria

Secondary criteria for the diagnosis of blood-stasis syndrome is also of great significance, but a certain one is not enough to diagnose blood-stasis syndrome, and more than two common evidence is needed to diagnose blood-stasis syndrome.

Article 1, "fixed pain, stabbing pain, or pain aggravated at night" is a typical pain feature of blood-stasis syndrome. Compared with standard B, "colic" is deleted, mainly because the pain features of colic and blood-stasis syndrome are not completely consistent. So it is deleted in order to reduce ambiguity.

Article 2, according to the opinions of the Examination and Approval Expert Committee of the WFCMS, it is suggested to add "joint swelling and deformity" on the basis of "limb numbness or hemiplegia". After discussion, the research team thinks that it is consistent with the actual clinical diagnosis and treatment, so it is added as a secondary standard, which also better reflects the performance of blood-stasis syndrome in different specialized diseases.

Articles 3, 4 and 5, which are consistent with

previous research standards and Standard B, are classic items of previous standards. The research team has not revised them, and relevant experts have not put forward revision opinions, so they are directly adopted. "Dry and scaly skin" and "pathological lumps" can be clearly diagnosed in clinic. As a typical pulse condition of blood-stasis syndrome, "unsmooth pulse, or intermittent or hardly perceivable pulse" has no obvious ambiguity in clinical application. However, it should be noted in clinic that with the increase of interventional operation through radial artery, the pulse condition of some patients is obviously affected, and can manifest as no pulse, which should be paid attention to clinically.

Article 6 corresponds to Article 7 of the main standard, because the degree of stenosis is slight ($< 50\%$), which is not enough to be directly diagnosed as blood-stasis syndrome. So it is listed as a secondary standard.

Article 7 is also an examination index of modern medicine, but the "concentrated, viscous, coagulated and aggregated state of blood" displayed in the examination contents of hemodynamics, coagulation function, fibrinolysis function and microcirculation involved in this article belongs to microscopic characterization, so it is listed as a secondary standard.

Compared with standard B, the content of Article 8 is more accurate by modifying "induced abortion" to "abortion". TCM believes that long-term illness will lead to blood stasis, so the content of "prolonged course (≥ 10 years)" is added.

Compared with Standard B, Guideline A omits "dysmenorrhea" and "mania or forgetfulness". According to the expert opinion, dysmenorrhea is also a kind of pain, which belongs to the content of Article 1 of the secondary standard. There are many reasons for mental mania or forgetfulness. For example, Chinese medicine thinks that the main pathogenesis of mania is phlegm and fire disturbing God, so two contents are deleted.

Summary

Blood-stasis syndrome has been highly valued by medical world at home and abroad since 1980s. On the basis of previous diagnostic criteria of blood-stasis syndrome, *International Diagnostic Guidelines*

for *Diagnosis of Blood-Stasis Syndrome* fully absorbed Academician CHEN Ke-ji's decades of experience in syndrome differentiation of blood-stasis syndrome, the latest research progress and the opinions of experts at home and abroad, and evaluated its reliability and authenticity by rigorous and scientific methods. This standard has the characteristics of concise items, wide coverage, simple judgment standard, conforming to clinical practice and strong operability, which is worthy of further popularization and application.

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