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Original Article

Diagnostic Accuracy of Chinese Medicine Diagnosis Scale of Phlegm and Blood Stasis Syndrome in Coronary Heart Disease: A Study Protocol*

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ABSTRACT **Background** Phlegm and blood stasis syndrome (PBSS) is one of the main syndromes in coronary heart disease (CHD). Syndromes of Chinese medicine (CM) are lack of quantitative and easy-implementation diagnosis standards. To quantify and standardize the diagnosis of PBSS, scales are usually applied. **Objective**: To evaluate the diagnostic accuracy of CM diagnosis scale of PBSS in CHD. **Methods**: Six hundred patients with stable angina pectoris of CHD, 300 in case group and 300 in control group, will be recruited from 5 hospitals across China. Diagnosis from 2 experts will be considered as the "gold standard". The study design consists of 2 phases: pilot test is used to evaluate the reliability and validity, and diagnostic test is used to assess the diagnostic accuracy of the scale, including sensitivity, specificity, likelihood ratio and area under the receiver operator characteristic (ROC) curve. **Discussion**: This study will evaluate the diagnostic accuracy of CM diagnosis scale of PBSS in CHD. The consensus of 2 experts may not be ideal as a "gold standard", and itself still requires further study. (No. ChiCTR-OOC-15006599).

KEYWORDS diagnostic accuracy, phlegm and blood stasis, diagnosis scale, syndrome differentiation, coronary heart disease, study protocol

Coronary heart disease (CHD) is one of the leading cause of death in the world.[1,2] For treatments of CHD, Chinese medicine (CM) is considered to be effective, such as *Radix Salviae Miltiorrhizae*.[3] Nowdays CM is gaining popularity for its efficient prevention and treatment of diseases. But many people remain skeptical and even critical of CM because of a number of its shortcomings, one of which is lack of objective diagnosis standards.[4] CM syndromes are in a state of dynamic change in the genesis, development and prognosis of diseases. At different time points and stages of the disease, the syndromes may evolve, transform and even accompany with other syndromes. It is not easy to differentiate a CM syndrome, and diagnosis standards of CM syndromes are also hard to establish. How to improve the accuracy of syndrome differentiation of CM, also evaluate and verify the effectiveness of syndrome differentiation properly has been the hotspot issue in the academic field.

The past decades of CHD syndrome-related research mainly focused on blood stasis syndrome (BSS).[5] In fact, there are 7 basic syndromes of CHD patients including qi-deficiency, yin-deficiency, yang-deficiency (including yang qi vacuity desertion), qi stagnation, blood stasis, cold congelation, and turbid phlegm syndrome (including phlegm heat).[6] Shi, et al[7] have identified the CM core syndromes of CHD patients by complex network. They found that the core deficiency syndrome was qi deficiency, and the core excessive syndrome was phlegm-blood stasis.

The diagnostic process of CM consists of inspection, listening and smelling, inquiry and palpation. To standardize the diagnosis, hyperspectral medical tongue images for tongue diagnosis,[8] tactile sensor system for pulse diagnosis,[9] latent tree models,[4] and scales and questionnaires[10] are developed. Noninvasive

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and familiar methods such as questionnaires are more acceptable.[11] Questionnaires are usually used to collect data for cross-sectional study or descriptive survey,[12] and for those who are not able to fill in the questionnaire, interviews are conducted.[13] Questionnaires can also be developed to diagnose CM syndromes. For instance, Okitsu, et al[10] developed a questionnaire for the diagnosis of qi stagnation. To quantify and standardize the diagnosis of CM syndromes, scales are usually applied.

When a new test is developed, its accuracy must be determined by comparing its diagnostic predictions to the true condition of the patient, and the evaluation result would be reported as sensitivity and specificity. Sensitivity is defined as the probability of a positive test given the presence of disease, whereas specificity is the probability of a negative test given the absence of disease. Unfortunately, the presence or absence of disease is difficult to determine.[14]

The objective of this study is to evaluate the diagnostic accuracy of CM Diagnosis Scale of PBSS in CHD based on systematic reviews and expert consensus.[15] The expert consensus is derived from 3 rounds of Delphi and analytic hierarchy process (AHP) in the past 2 years.

METHODS

This is a multicenter prospective study aiming to evaluate the diagnostic accuracy of CM diagnosis scale of PBSS in CHD. The diagnostic test accuracy (DTA) study is designed based on the Standards for Reporting of Diagnostic Accuracy (STARD) checklist for the recommendations of studies of diagnostic accuracy.[16] This protocol was registered in Chinese Clinical Trial Registry in 2015 (No. ChiCTR-OOC-15006599).

Ethics Approval

Ethical approval of this study has been obtained from Medical Ethics Committee of Tianjin University of Traditional Chinese Medicine (No. TJUTCM-EC2015000). The study will be conducted according to the Declaration of Helsinki. The patients will receive oral and written information about the study and provide written informed consent prior to any study-related procedures.

Inclusion and Exclusion Criteria

Diagnostic criteria of Western medicine are referenced to 2016 American College of Cardiology (ACC)/American Heart Association (AHA) guideline focused update on duration of dual anti-platelet therapy in patients with coronary artery disease,[17] and Chinese guideline for diagnosis and treatment of patients with chronic stable angina published in 2007.[18] Diagnostic criteria of CM included are as follows:[1] PBSS: the common symptoms of local lump and pain, numbness or flaccidity and weakness in the body and limbs, chest stuffiness, profuse sputum, blood-streaked phlegm in dark-purple color, a dark-purple tongue or a tongue with ecchymosis and a greasy coating, a wiry and hesitant pulse and so on.[19] Exclusion criteria are as follows: unstable angina of CHD; age < 40 years old, or age> 75 years old.

Patients Recruitment

The study will be conducted in 5 Class Ⅲ Grade Ⅰ hospitals, including the First Affiliated Hospital of Guangzhou University of Chinese Medicine, the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, the Second Affiliated Hospital of Henan University of Traditional Chinese Medicine, and Affiliated Hospital of Hunan Academy of Chinese Medicine.

Study Design

The design model of this study is shown in Figure 1. The study design consists of 2 phases. The reliability and validity of CM diagnosis scale of PBSS in CHD will be evaluated initially in the pilot test (phase 1) and DTA study will be performed in the formal test (phase 2). The diagnostic accuracy of CM diagnosis scale of PBSS in CHD, namely the new diagnostic method, will be analyzed by sensitivity, specificity, likelihood ratio and area under the receiver operator characteristic (ROC) curve. The diagnostic threshold of the scale can be determined by ROC curve. In phase 2 we can also evaluate the reliability and validity of the scale.

In this study, we will use 2 experts' diagnoses as the "gold standard". Two experts will differentiate the syndromes independently. If they both agree that 1 patient has PBSS, then the patient will be categorized to "present"; on the contrary, if they both disagree, the patient will be categorized to "absent". If their opinions are divided, it should be adjudicated by a

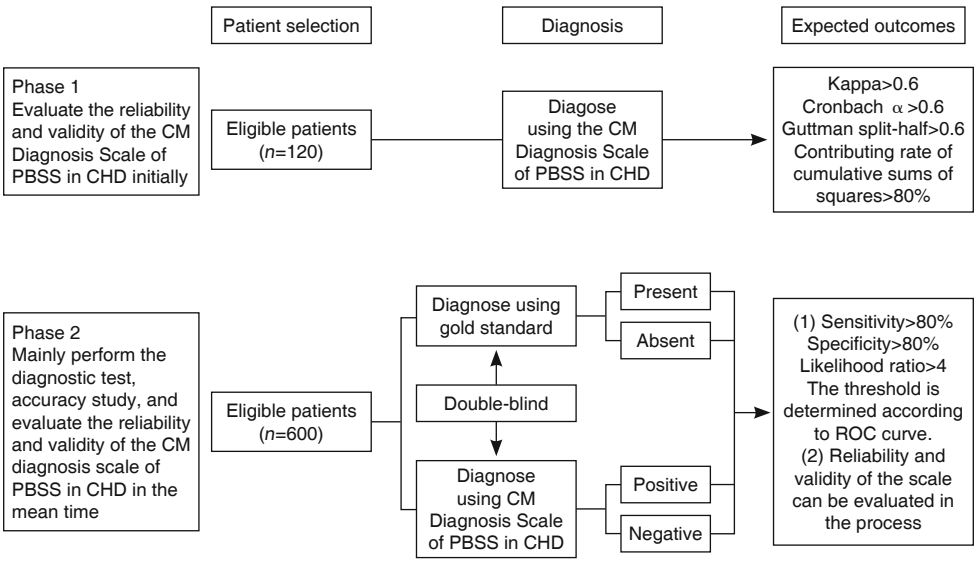

Figure 1. The Study Design Model

third independent diagnosis. The "expert" we define here should meet a certain criteria: (1) specialize in therapy of CM or integrative Chinese and Western medicines on cardiovascular medicine; (2) have senior professional title; and (3) engage in everyday work of clinical diagnosis and treatment over 20 years. Besides, we will use qualitative interview method to extract experts' knowledge.

Estimate of Sample Size

We expect both the sensitivity and specificity are not less than 0.8, so we used the formulase below to estimate the sample size:

$$n_1=\left(\frac{57.3\,Z_\alpha}{\sin^{-1}[\triangle/\sqrt{S_n(1-S_n)}]}\right)^2 \quad n_2=\left(\frac{57.3\,Z_\alpha}{\sin^{-1}[\triangle/\sqrt{S_p(1-S_p)}]}\right)^2$$

n_1 stands for the sample size of the case group, which is a group of patients diagnosed as PBSS by "gold standard". n_2 is the sample size of the control group, which is a group of patients diagnosed as NOT PBSS by "gold standard". △ stands for the allowable error. S_n is the estimate of sensitivity, while S_p is the estimate of specificity. The result shows that 120 patients (60 for case group and 60 for control group) are needed to identify a significant difference based on the precision of the 95% confidence interval (CI) for a proportion. Therefare a total of 600 patients (300 for case group and 300 for control group) will be recruited from 5 centers in this study. Possible dropouts within 10% have been taken into account.

Blinding Method

Blinding method is used when experts of both sides are diagnosing the same eligible patient. To get an independent, blind comparison of test results with a reference "gold standard", the 2 examiners should be blinded to the diagnosis obtained by the independent physician.[20] That is, the physicians who use the new diagnosis method are not aware of the results of the "gold standard", while the physicians who use the "gold standard" method are not aware of the results of the new diagnosis method.[21]

CM Diagnosis Scale of PBSS in CHD

CM Diagnosis Scale is a new method to quantify and standardize the diagnosis of CM syndromes. Based on systematic reviews, and expert consensus that are derived from 3 rounds of Delphi and AHP, combining with works of all research groups of ours, the CM Diagnosis Scale of PBSS in CHD including 14 symptoms is developed. The 14-item scale is shown in Table 1. A symptomatic grading standard is shown in Table 2. The standard is referenced to Guiding Principle of Clinical Research on New Drugs of Chinese Medicine.[22] The items in Table 1 have different weights. The final score will be measured using the percentage system, and it is attached with different scores measured by the weight of the individual items. The diagnostic threshold of the scale will be determined by ROC curve.

Personnel Training

All center members and investigators should attend an unified training work. The training includes the protocol,

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Table 1. CM Diagnosis Scale of PBSS in CHD

Symptoms	Explanation	None	Mild	Moderate	Severe	Score
Chest distress	Suppression or choking sensation in the chest	0	1	2	3	☐
Chest pain	Pain in the center or partial side of the chest	0	1	2	3	☐
Sleepiness	Always want to sleep, day and night, easily aroused and fall asleep later	0	1	2	3	☐
Physical heaviness	Physically heavy and have mobility problems	0	1	2	3	☐
Obesity	Abnormally fat	0	1	2	3	☐
Mouth sticky	Feel sticky and greasy in mouth	0	1	2	3	☐
Cyanotic lips	Lips lost their ruddy gloss and became cyanotic, lilac or dark purple	0	1	2	3	☐
Dim complexion	The face is dark and gloomy	0	1	2	3	☐
Abdominal fullness	Feel full and stuffy in the stomach	0	1	2	3	☐
Anorexia	Loss of appetite	0	1	2	3	☐
Viscous stool	Feel the stool is viscous and hard to clean	0	1	2	3	☐
Tongue body	Dark-purple tongue, petechiae or ecchymosis appear upon the tongue, or sublingual vein cyanosis	0	1	2	3	☐
Tongue fur	Thin or thick greasy coating cover the tongue	0	1	2	3	☐
Pulse condition	The pulse is taut or slippery or uneven	0	1	2	3	☐

Table 2. Symptomatic Grading Standard

Symptoms	Mild	Moderate	Severe
Chest distress	Slightly chest distress	Significant chest distress, sometimes short of breath	Chocking chest distress, and sigh without stop
Chest pain	Slightly chest pain	Significant but tolerable chest pain	Significant chest pain and affect breathing and lead to coughing
Physical heaviness	Feel a little heavy, not enough to restrict the activities	Feel significant heavy relatively, decrease activity	Feel significant heavy, do not want to move
Obesity (BMI)	25 to 28	28 to 32	>32
Sticky mouth	Have a little sticky sensation in mouth, not enough to affect the appetite	Feel sticky and greasy in mouth, with appetite dropping	Feel sticky and greasy in mouth, too uncomfortable to eat anything
Dim complexion	Dark-yellow complexion, less of gloss	Dark-yellow complexion without gloss	Dark complexion without gloss
Abdominal fullness	Feel a little full and stuffy in the stomach, tolerable and not enough to affect the appetite	Feel full and stuffy, alleviate on an empty stomach	Feel unbearable full and stuffy in the stomach all day long
Anorexia	Loss of appetite, but not reduce food intake	Loss of appetite, slightly reduce food intake	Loss of appetite, reduce food intake by more than 1/3
Tongue body	Dark-purple tongue	Petechiae appear upon the tongue	Ecchymosis appears upon the tongue or sublingual vein cyanosis
Tongue fur	Thin greasy coating	Thick greasy coating in the middle or root of the tongue	Thick greasy coating cover the tongue
Pulse condition	Taut pulse	Slippery or uneven pulse	Taut and slippery pulse or taut and uneven pulse

Note: BMI: body mass index

process of clinical investigation, skills for interviewing and data collecting. Clinical data is mainly collected through face-to-face interview and examination by clinicians, and it can be added by the patient's families if necessary.

Evaluation Indices

The Kappa coefficient, sensitivity, specificity and likelihood ratio can be calculated using the corresponding formulae. A ROC curve can be drawn and the threshold of the diagnosis scale according to the area under the ROC curve will be confirmed. Cronbach α coefficient is used to evaluate the reliability of the scale (Cronbach α >0.6 will be ideal), while Guttman Split-half is used to evaluate the split-half reliability of

the scale (Guttman Split-half>0.6 will be ideal). Validity is evaluated by contributing rate of cumulative sums of squares, which should be over 80%.

Quality Control

The bias would diminish the validity of the research and should be effectively controlled. The ways of avoiding bias include: (1) formulating inclusion and exclusion criteria correctly; (2) designing a scientific and perfect survey scale and its detailed instructions; (3) conducting training for each methods, diagnostic criteria and improved the consistency to unified understanding; (4) reducing the interference of psychological factors; (5) reviewing the investigation records and the compliance of the participants regularly; (6) reducing missing rate, and (7) improving the compliance.

To guarantee the quality of clinical research, standard operating procedure (SOP) will be developed, and the evaluation, supervision and inspection on the procedure of clinical investigations should be enhanced.

Statistical Analysis

EpiData Software (version 3.0.2, The EpiData Association, Odense, Denmark) will be employed for data management. The data will be analyzed with SPSS 20.0 software. The result of statistical analysis will be shown as statistics and *P* value, along with diagrams.

DISCUSSION

This study is a prospective, diagnostic accuracy study in a population of 600 patients presenting with stable angina pectoris of CHD. It aims to evaluate the diagnostic accuracy of CM Diagnosis Scale of PBSS in CHD.

Researches of CM syndrome differentiation sometimes should carry out DTA study, in which "gold standard" or diagnostic standard is the crucial link. Some of the diagnostic "gold standard" nowadays have nearly 100% specificity, but unfortunately have low sensitivity,[23] and *vice versa*. The error in the standard test is usually to be blame for bias.[14] Sometimes "gold standard" is hard to attain. To solve this problem, someone proposed a nonparametric maximum likelihood method for estimating and comparing the accuracy of different doctors in detecting a particular symptom without a gold standard when the true symptom status had an ordered multiple class.[24] The "gold standard" of CM syndromes is especially not easy to decide.

Currently, there are several ways to get the "gold standard" of CM syndromes: determined by 2 experts; determined by 2 experts and adjudicated by the third expert if discordant; comparing training samples and verification samples, then use back substitution for retrospective validation, and prospective validation if necessary. The gold standard is determined by training samples that are randomly selected; and determined by nonlinear logistic regression model. However, the first approach, determined by 2 experts, is most recognized and most widely accepted. Therefore we chose this approach to get the gold standard in this study. In general, experts will reach to the same diagnosis result on the same patient. It's rare that 2 experts' opinions are divided, given the experts we chose all have solid theoretical basis and clinical experience, unless on some special cases. For the better optimization of study results, these special cases can be eliminated. Two experts' opinions may not be ideal as a "gold standard", and itself require further study.

Conflict of Interest

The authors declare that they have no conflict of interests.

Author Contributions

Liu XQ participated in study design, and was a major contributor in writing the manuscript. Peng DH and Wang YP participated in the study design and manuscript review. Xie R participated in the study design and data collection. Chen XL majorly contributed in data analysis, study design and manuscript review. Yu CQ participated in clinical research. Li XT provided the conception of the study and draft. All authors read and approved the final manuscript.

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