Risk assessment model for endpoints of ischemic stroke: A study protocol for a registry study

Zhang Yin, Liu Yue, Wang Guiqian, Sun Shuailing, Gao Yang, Xie Yanming

Abstract

OBJECTIVE: To evaluate the risk of ischemic stroke endpoints by establishing risk assessment models that combine Traditional Chinese Medicine (TCM) and modern medicine indicators.

METHODS/DESIGN: The proposed study is a registry-based participant survey conducted in seven hospitals nationwide in China. After obtaining informed consent, 3000 patients diagnosed with ischemic stroke will be recruited. One-year follow-ups will be performed on-site in hospitals and by telephone to track endpoint events. Comparative analysis of the prevalence of endpoint events and other TCM or modern medicine features in different groups will be conducted using frequency analysis and χ² tests, and the results will be expressed as composition ratios. Comparative analysis of quantitative scores and related patterns or symptoms will be conducted using a rank-sum test. Correlation analysis of endpoint events and TCM or modern medicine factors will be performed using a multivariate Cox proportional hazard model.

DISCUSSION: Previous reports have described modern medicine indicator-based risk assessment models for ischemic stroke endpoint events, but no such studies have included TCM features. Our new risk assessment model combines TCM and modern medicine indicators and thus has the potential to facilitate early warning, early intervention, and early control of ischemic stroke endpoint events.

© 2018 JTCM. All rights reserved.

Keywords: Stroke; Medicine, Chinese traditional; Secondary prevention; Endpoint determination; Risk assessment; Protocol; Registry study

INTRODUCTION

Stroke is characterized by a high incidence and high rates of mortality, recurrence, and disability. The World Health Organization has declared that the incidence of stroke in China ranks first worldwide, with an annual increase rate of 8.7%. More than 2 million new cases of stroke are diagnosed in China every year, and patients with ischemic stroke account for > 70% of the total number of patients with stroke. Recurrence and other endpoint events of ischemic stroke are the main causes of rehospitalization, long-term disability, and increasing mortality, all of which significantly decrease patients’ survival time and quality of life. According to recent epidemiologic stud-
ies, the global 7-day, 1-month, 3-month, 1-year, 3-year, 5-year, and 10-year recurrence rate of ischemic stroke after the first occurrence is 2%, 2% to 4%, 4% to 6%, 8% to 18%, 20% to 28%, 29% to 34%, and 43% to 50%, respectively. This situation is even more serious in China, which has by far the largest number of patients with ischemic stroke worldwide. Thus, effective treatment and secondary preventions are urgently needed to address the substantial global health burden of ischemic stroke.

The American Stroke Association and American Heart Association issued the latest Recommendation for Stroke and Transient Ischemic Attack Secondary Prevention Guidelines in 2014, providing a systematic summary of the latest advances in studying the risk factors for ischemic stroke endpoint events. Aiming to provide more practical strategies in line with China’s local conditions, the cerebrovascular disease branch of the Chinese Society of Neurology (a specialty society of the Chinese Medical Association) also updated the latest Chinese Guidelines for Secondary Prevention of Ischemic Stroke and Transient Cerebral Ischemic Attack in 2014, emphasizing the importance of monitoring multidimensional risk factors in China.

Several studies have demonstrated that Traditional Chinese Medicine (TCM) can be used to effectively treat ischemic stroke, including eliminating neurological deficits, improving the quality of life, and reducing the incidence of recurrence, death, and deformity. The mechanisms of these effects involve anti-thrombosis, anti-coagulation, defibrillation, reducing inflammatory reactions, and reducing post-stroke neurotoxicity. The modern-day TCM strategy for treatment and prevention of ischemic stroke is based on the time-honored principle of identifying symptom patterns and constitutions to determine the root of ischemic stroke. Several trials have been conducted to evaluate the effectiveness of ischemic stroke treatment based on the identification of TCM symptom patterns and constitutions.

Risk assessment is of vital importance for preventing ischemic stroke endpoint events in the early disease stage. Secondary prevention programs may reduce the rates of recurrence, disability, and mortality of ischemic stroke. Some reports have also evaluated the relationship between TCM symptom patterns or constitutions and ischemic stroke recurrence and other endpoint events, suggesting the feasibility of the above-mentioned TCM features as potential risk factors. However, no large, rigorous observational studies have been conducted to reveal the exact role of TCM indicators in secondary prevention of ischemic stroke. Because of the limitations inherent to the currently widely used modern medicine risk assessment tools for ischemic stroke recurrence and other endpoint events, the herein-proposed study will focus on revealing the role of multidimensional indicators combining TCM and modern medicine features in the risk assessment of ischemic stroke endpoint events. This large-scale study will be performed to facilitate TCM secondary prevention programs for ischemic stroke in China. We will attempt to overcome these shortcomings, allowing us to find compelling evidence and establish new risk assessment models from an integrative medicine perspective.

METHODS

Design

This multicenter registry study will be conducted in seven hospitals nationwide in China and will be led by the Institute of Basic Research in Clinical Medicine (BRCM), China Academy of Chinese Medical Sciences (CACMS). No designed allocation arms will be present in the study protocol. According to the inclusion and exclusion criteria, 3000 eligible participants will be identified by screening patients with ischemic stroke within 12 months after beginning the study. After obtaining informed consent, multidimensional indicators and blood samples of all participants will be collected upon recruitment. Endpoint events and multidimensional indicator dynamics will be tracked during a 1-year follow-up.

Aims

The goal of this registry study is to establish risk assessment models for ischemic stroke endpoint events with good sensitivity and specificity by combining multidimensional TCM and modern medicine indicators. The study will also evaluate the dynamics of TCM and modern medicine clinical features depending upon the course of ischemic stroke.

Outcome measures

The primary outcome measure will be ischemic stroke recurrence events, including cerebral infarction, cerebral hemorrhage, and transient ischemic attack, according to the definition of ischemic stroke recurrence events given by the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) study. Secondary outcome measures will be death and disability events caused by ischemic stroke. Endpoint events of atherosclerotic cardiovascular disease and atherosclerotic peripheral vascular disease will also be included.

Study population

Screening: the study population will comprise patients who meet all inclusion criteria and no exclusion or elimination criteria. Study personnel will continuously screen eligible patients who present to the hospitals until the sample size is reached.

Recruitment: this study will be conducted in seven hospitals nationwide in China: Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine, Beijing Tian Tan Hospital affiliated to Capital Medical
University, Guangdong Provincial Hospital of TCM, Affiliated Hospital of Changchun University of Chinese Medicine, the first Hospital Affiliated to Henan University of TCM, Dongfang Hospital Affiliated to Beijing University of Chinese Medicine, and Taiyuan Municipal Hospital of TCM. Recruitment will begin in December 2016 and is expected to end in December 2018.

Diagnostic criteria: the modern medicine diagnostic criteria for ischemic stroke in this study will be defined with reference to the Acute Ischemic Stroke Diagnosis and Treatment Guideline of China (version 2014), as promulgated by the Chinese Society of Neurology of the Chinese Medical Association. The criteria for a TCM diagnosis of ischemic stroke will be consistent with the Guidelines for Treating Stroke by TCM New Drug (version 2015) issued by the China Food and Drug Administration. The criteria for symptom pattern identification will be established with reference to the Standard of Stroke Syndrome Diagnosis and Therapeutic Effect Assessment (trial version) as formulated in 1996 by the National TCM Acute Cerebral Diseases Research Panel, State Administration of Traditional Chinese Medicine of China. The criteria for a TCM constitution diagnosis will be established with reference to the Standard of Constitution Diagnosis issued by the China Association of Chinese Medicine in 2009.

Inclusion criteria: the inclusion criteria will be as follows. (a) The patient meets the diagnostic criteria for ischemic stroke. (b) The patient has large-artery atherosclerosis or a small-artery occlusion subtype of ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. (c) The patients with the first onset of ischemic stroke that within the first 2 weeks should be account for ≥50% of all included cases. (d) The patient is 38 to 80 years of age. (e) The patient is willing to respond truthfully and in a timely manner to researcher queries after recruitment and is able to cooperate with data and sample collection during follow-ups. (f) The patient is willing to provide written informed consent.

Exclusion criteria: the exclusion criteria will be as follows. (a) The patient meets the diagnostic criteria for transient ischemic attack, hemorrhagic stroke, or mixed stroke. (b) The patient has cardioembolism or other determined or undetermined etiologies of ischemic stroke according to the TOAST classification. (c) The patient is unable to participate in data or sample collection for any reason. Informed consent: study personnel will obtain written informed consent from all participants prior to enrollment. The patients will then be able to provide consent via a signature on a written consent form. An informed consent script will be read aloud to any patients who are illiterate.

Allocation arms: because this is a registry study, there will be no designed allocation arms. All patients enrolled in the study will continue to receive any necessary medical care for ischemic stroke at the discretion of their treating health care providers either in the hospitals or at home.

Research personnel training and deployment
Prior to initiation of the study, a cohort of study team practitioners who are responsible for data and blood sample collection will be trained via a series of structured standard courses. The focused training by BRCM study personnel will cover all study procedures and will be sufficient for the practitioners to gain competence.

Data collection
Study personnel will assess indicators at baseline and again at predetermined intervals. Baseline demographic characteristics, other clinical information, and blood samples will be gathered at the time of enrollment. On-site follow-ups at fixed and non-fixed time points will be carried out in all hospitals. Telephone follow-ups designed to track possible endpoint events will be conducted once a month. Ischemic stroke endpoint events as well as related TCM and modern medicine features will be monitored throughout the follow-up period. The on-site data collection time points and content are outlined in Table 1. The telephone data collection time points and content are outlined in Table 2.

Data management
Data will initially be collected on preprinted standardized data collection forms. These forms will be organized based on unique participant identification numbers and contain no personal identifiers. After collection, the data will be entered into a well-protected database by a specific online electronic data capture system. The online electronic data capture system and operation rules of data entry, auditing, and locking will be constructed by data administrators from the BRCM of CACMS. All data will undergo subsequent re-entry to check for input errors. If any discrepancy is found between the first and second entry, the entry will be reconciled by consulting the original documents. All source documents will be securely stored and accessible only by the study investigators. Confidentiality will be maintained at all levels of data management. The collected data will not be linked to any individual or personal identifiers.

Statistical analysis
Sample size: the sample size for this study will be determined according to the framework of a registry study. Taking a 1-year recurrence rate of 8% or 18% after the first onset of ischemic stroke in accordance with previous studies and a non-response rate of 20%, the estimated sample size would be 525 or 1325, respectively. Because this study is supported by the State Administration of Traditional Chinese Medicine of China, the practical sample size will be 3000 under full consider-
Outcome analysis and reporting: according to formalized procedural protocols, a detailed statistical analysis plan will be created prior to study initiation.

Comparative analysis of the prevalence of endpoint events and other TCM or modern medicine measures in different groups will be performed using frequency analysis and $\chi^2$ tests, and the results will be expressed as composition ratios. Comparative analysis of quantitative scores and related patterns or symptoms will be conducted using the rank-sum test. Two-way analysis of variance with repeated measures in one factor (time) will be performed to compare the features over time. A $P$ value of $<0.05$ will be considered statistically significant for all analyses.

To evaluate the risk of ischemic stroke endpoint events,
a correlation analysis of endpoint events and TCM or modern medicine factors will be performed using a multivariate Cox proportional hazard model. The area under the receiver operating characteristic curve will be used to evaluate the predictive performance of the model. The significance level for introducing and removing variables will be 0.05 and 0.10, respectively. All statistical analyses and plotting in this study will be performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC, USA), R software (version 3.3.1; The R Project for Statistical Computing, Auckland, NZ), and Office Excel (version 2007; Microsoft Inc., Redmond, WA, USA).

**Ethical approval and study status**

This study is designed in accordance with the 2007 Biological Ethics Review Method Involving Humans by the Ministry of Health of the People’s Republic of China and the principle of protecting patient rights and interests. The study will be conducted in accordance with the Declaration of Helsinki (version 8). The protocol has received ethical approval from the BRCM of CAMS Ethical Review Board (approval number: 2016-8). All study personnel have been trained in the standard operating procedure. The study is ready for recruitment.

**DISCUSSION**

The increasing morbidity and high mortality of ischemic stroke have currently emerged as public health threats in China. Given the national high burden of the lower incidence of ischemic stroke endpoint events in China, research of secondary prevention of ischemic stroke is necessary. Considering the current limitations of secondary prevention programs, optimization of early intervention options and early warning tools is required. TCM theories have played a vital role in treating and preventing stroke in both ancient China and the present day. TCM treatment and prevention strategies are based on identification of symptom patterns and constitutions to identify the root of ischemic stroke. This time-honored principle has been proven effective by clinical practice for 3000 years, including in recent trials. After identifying a patient’s symptom patterns and constitution, the TCM practitioner systematically collects detailed information about the presenting signs and symptoms using the classic diagnostic methods of looking, smelling, listening, asking, and palpating. This comprehensive information is then evaluated according to clinical experience based on TCM theory to identify the key pathologic changes during different disease stages and the patient’s current physical condition. Individualized treatment and prevention programs are then applied in accordance with the conclusions drawn from identification of the patient’s symptom patterns and constitution.

Preliminary epidemiologic studies have demonstrated a potential correlation between the diversity and dynamics of TCM features and the risk of stroke progression. Although the TCM symptom patterns and constitutions have been proven to be related to the risk of ischemic stroke recurrence and other endpoint events, previous risk assessment models for ischemic stroke endpoint events have merely focused on modern medicine indicators without combining any TCM features. We have designed the present study to address this current deficit.

A registry study is an observational study without any designed allocation arms in the study protocol. The present registry study aims to model the risk of ischemic stroke endpoint events by combining TCM and modern medicine features. Thus, the study involves continuous monitoring of TCM factors, including symptom patterns, constitution patterns, and related signs and symptoms, from which the distribution and interrelation of TCM and modern medicine potential risk factors can be clarified. We will also test the sensitivity and specificity of these new models based on short-term and long-term follow-up data to further determine whether they are of better efficiency than previously reported conventional modern medicine models.

By developing individualized distinctive ischemic stroke prevention and risk control strategies from an integrative medicine perspective, the present study will facilitate TCM secondary prevention programs for ischemic stroke in China, the notion of which is clinically important. The strengths and weaknesses of our study should be noted. The strengths of the present study include the large number of participants, the relatively diverse population, and the multicenter design, which will allow for application of our results in a diverse range of settings in China. Moreover, we plan to gather multidimensional information on a large number of potential risk factors and confounding factors for which we may adapt or control in the multivariable models. In addition, we will validate the occurrence of ischemic stroke by full-scale imaging examinations in this trial, allowing us to gather additional information such as the timing of the stroke event and precise location of the ischemic stroke. Several limitations of the present study must also be considered. In terms of the study design, selection bias may exist to some extent because the data will be mainly derived from participants in TCM hospitals in China; such cases are likely not representative of the indicators and endpoint events in patients in modern medicine hospitals of China. Another limitation is that considering the research costs, the follow-up time is limited to 1 year in this study. This may prevent us from tracing ischemic stroke endpoint events with high efficiency. Longitudinal studies, including prospective cohort studies with long follow-up times, are needed to provide stronger evidence and further verify and expand the conclusions of this study.
ACKNOWLEDGMENTS

The authors thank Prof. Cai Yefeng from Guangdong Provincial Hospital of TCM, Prof. Zhao Xingquan from Beijing Tian Tan Hospital affiliated to Capital Medical University, Profs. Ma Yinzhi and Shen Xiaoming from The First Hospital affiliated to Henan University of TCM, Prof. Xie Yingzhen from Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine, Prof. Zhao Dexi from the hospital affiliated to Beijing University of Chinese Medicine, and Prof. Yu Haiqing from Taiyuan Municipal Hospital of TCM for their critical review of and constructive suggestions regarding the study protocol. The authors thank Dr. Zhou Aijian from World Federation of Chinese Medicine Societies and Beijing University of Chinese Medicine for his language editing of this manuscript.

REFERENCES


