China Stroke Registry for Patients With Traditional Chinese Medicine (CASES-TCM): Rationale and Design of a Prospective, Multicenter, Observational Study

Luda Feng1,2†, Lingbo Kong1,2†, Xinglu Dong1,2†, Xinxing Lai2,3, Dandan Zhang2, Beida Ren2, Shen Liu2, Xiaolong Xie1,2, Chuanpeng Li1,2, Yuebo Song1,2, Yawei Du1, Kegang Cao5,3*, Chi Zhang2,3* and Ying Gao1,2,4* On Behalf of the CASES-TCM Protocol Steering Group

1Department of Neurology, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, 2Institute for Brain Disorders, Beijing University of Chinese Medicine, Beijing, China, 3Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China, 4Chinese Medicine Key Research Room of Brain Disorders Syndrome and Treatment of the National Administration of Traditional Chinese Medicine, Beijing, China

*Correspondence: Kegang Cao kgdoctor@sina.com
Chi Zhang saga618@126.com
Ying Gao gaoying973@163.com
†These authors have contributed equally to this work

ORCID:
Luda Feng orcid.org/0000-0002-7259-4421
Lingbo Kong orcid.org/0000-0001-5451-4355
Xinglu Dong orcid.org/0000-0003-3071-295X
Kegang Cao orcid.org/0000-0002-6285-2562
Chi Zhang orcid.org/0000-0001-5427-2966
Ying Gao orcid.org/0000-0001-6972-3846

Specialty section:
This article was submitted to Ethnopharmacology, a section of the journal Frontiers in Pharmacology

Received: 19 July 2021
Accepted: 23 August 2021
Published: 31 August 2021

Citation:
Feng L, Kong L, Dong X, Lai X, Zhang D, Ren B, Liu S, Xie X, Li C, Song Y, Du Y, Cao K, Zhang C and Gao Y (2021) China Stroke Registry for Patients With Traditional Chinese Medicine (CASES-TCM): Rationale and Design of a Prospective, Multicenter, Observational Study. Front. Pharmacol. 12:743883. doi: 10.3389/fphar.2021.743883

Background: Given the complexity of stroke treatment and the current widespread use of traditional Chinese medicine (TCM) in the absence of robust, large, long-term effectiveness and safety studies, and the lack of nationwide epidemiology and clinical characteristics of patients with stroke receiving TCM treatment, the acquisition of data from longitudinal cohorts is essential. We intend to generate the major clinical characteristics of patients with stroke who receive TCM treatment and to investigate the effectiveness and safety of TCM in the Chinese population.

Methods: The China Stroke Registry for Patients with Traditional Chinese Medicine (CASES-TCM) study is a prospective, multicenter, observational disease registry aiming to register 20,000 hospitalized patients. Eligible adult patients with clearly diagnosed acute ischemic stroke or intracerebral hemorrhage within 7 days of symptom onset will be consecutively registered from 126 participating sites across China. Baseline data will be recorded, and all patients will be regularly followed up at 3, 6, 12, and 24 months after stroke onset. Collected data will be entered into a web-based system with high-level data security. The primary outcomes include the distribution of scores on the modified Rankin Scale at the 3-months follow-up, and recurrent stroke events within the 12-months follow-up.

Conclusion: To our knowledge, the CASES-TCM study is the first and largest nationwide registry to document comprehensive data on TCM treatment in patients with acute stroke.

Abbreviations: AIS, acute ischemic stroke; ANOVA, analysis of variance; BI, Barthel Index; CASES-TCM, China Stroke Registry for Patients with Traditional Chinese Medicine; CNSR, China National Stroke Registry; DSSEIS, Diagnostic Scale of Syndrome Elements in Ischemic Stroke; EDC, electronic data capture; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; PRO-Stoke, Patient-Reported Outcome Scale for Stroke; SAP, statistical analysis plan; SMASH-U, Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined; SOP, standard operating procedures; TCM, traditional Chinese medicine; TOAST, Trial of Org 10172 in Acute Stroke Treatment.
INTRODUCTION

Stroke is the second leading cause of death globally, and it ranks first in China, in which the annual stroke mortality rate is approximately 114.8/100,000, which is five times that of American and European countries (Wang et al., 2017; GBD 2019 Diseases and Injuries Collaborators, 2020; Zhou et al., 2019). Stroke poses a heavy health and economic burden, which is expected to increase further as a result of population aging (Rajisic et al., 2019). The distribution of stroke burden varies among different regions in China (Wang et al., 2017). Ischemic stroke and intracerebral hemorrhage (ICH) are the two most common subtypes of stroke with a total proportion of roughly 90% (Wang et al., 2011).

The current status of stroke treatment remains unoptimistic, although substantial progress has been achieved. Reperfusion therapy has been recommended as the first-line treatment of acute ischemic stroke (AIS) for improving long-term functional outcome, but it only benefits a limited number of patients given the narrow time-window, imaging dependence, high technical requirements, advanced catheter systems, and requirement for extensive economic resources (Powers et al., 2015; Powers et al., 2019). Although antiplatelet, lipid-lowering, and antihypertensive therapy carry remarkable effects for the secondary prevention of stroke (Wang et al., 2016a), more than half of the Chinese population bear aspirin or clopidogrel resistance (Wang et al., 2016b; Yi et al., 2016), and poor long-term medication compliance merits attention (Wei et al., 2010; Chen et al., 2014). As for ICH, there are no specific treatment options for patients who are ineligible for surgery (Hemphill et al., 2015). Consequently, traditional Chinese medicine (TCM) therapy, as an important, and alternative treatment options for patients who are ineligible for surgery (Group of the China Quality Evaluation of Stroke Care and Treatment, 2010; Wei et al., 2011). Additionally, deemed as a part of TCM, acupuncture for stroke treatment has been used in China for over 1,000 years and is increasingly practiced in some western countries (Wu et al., 2006; Zhang et al., 2015).

The findings of this study will be valuable to improve our knowledge about TCM treatment for patients with stroke and its subsequent outcomes in the actual clinical setting, consequently facilitating and standardizing the optimization of individualized interventions with TCM for stroke prevention and treatment in China.

**Study registration:** This study was registered with Clinicaltrials.gov (URL: https://clinicaltrials.gov/, Unique identifier: NCT04921397).

**Keywords:** stroke registry, acute ischemic stroke, acute intracerebral hemorrhage, traditional Chinese medicine, real-world setting, Chinese population

**METHODS AND DESIGN**

**Study Design**

The CASES-TCM study (registered with ClinicalTrials.gov, Unique identifier: NCT04921397) is a prospective, multicenter,
observational disease registry, attempting to depict major clinical characteristics of stroke in patients treated with TCM and to explore any difference in the comparison with other non-TCM user cohorts and the effectiveness and safety of TCM. An overview of this study flowchart is shown in Figure 1. The registry protocol was approved by the institutional review board of the leading center, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China (No. 2021DZMEC-024-02), and will be approved by the local institutional review boards of all participating sites.

**Patient Population**

Adult patients (≥18 years) admitted to Chinese hospitals with AIS or ICH diagnosed according to the corresponding guidelines, respectively, are eligible for inclusion in the CASES-TCM study (Hemphill et al., 2015; Powers et al., 2019). Only patients within 7 days of symptom onset will be included. Patients who have difficulties with follow-up completion will be excluded. Written informed consent including participation, data collection, and publication will be obtained from all patients or their legally authorized representatives in this study. Patient participation will be entirely voluntary, and patient’s data will be strictly protected. There is no specific risk of participation in this study. Instead, patients will receive regular medical guidance from doctors during the follow-up period. Patient registry is expected to begin in September 2021.

**Specific Treatment**

Different kinds of TCM treatment for patients with stroke will be included because we will focus on whether doctors use TCM based on individual syndrome differentiation, which is etiology in view of TCM theory. We will record TCM application settings including prehospital stage (at home or ambulance), in-hospital stage (emergency department or neurology ward), and hospital discharge (community or at home), and TCM formulations including Chinese patent medicine (injection or oral agents), and TCM compounds. The initiation time of TCM administration for patients with stroke and adherence to TCM treatment will also be recorded. As for other routine treatments, doctors will treat patients with stroke according to the corresponding Chinese guidelines (Chinese Society of Neurology, 2018; Chinese Society of Neurology, 2019). The common management methods include basic control of risk factors, intravenous thrombolysis, mechanical thrombectomy, antiplatelets, anticoagulants, and neuroprotective agents. Additionally, doctors will determine the treatment strategies based on their clinical experience and the patients’ condition when no guideline-recommended therapies are applicable.

**Main Variables**

We established the minimum dataset that includes the main variables using a stepwise approach. To ensure the balance between feasibility and scientificity, we pooled the variables from our previous studies (ChiCTR1800016363, NCT02728180, ChiCTR-OPC-16008451, ChiCTR1900026422) on stroke survey and treatment, which were funded by the Stroke Prevention Project Committee National Health and Family Planning Commission, and the Ministry of Science and Technology of the People’s Republic of China. Taking into account the TCM treatment features, patient burden, potential loss to follow-up, and comparability to variables of other representative large-scale registry studies, we adjusted the variables and finally determined the minimum dataset via expert consensus. The expert panel consisted of clinicians, researchers, healthcare nurses, and experts from other disease registries. Table 1 lists the main variables that will be collected during the study.

**Data Collection and Monitoring**

During patient admission, trained research personnel who are appointed at each participating site will collect baseline data regarding prehospital care and treatment, pre-stroke symptom, and the pre-stroke modified Rankin Scale (mRS) score and will perform assessments using the Glasgow Coma Scale (GCS), National Institute of Health Stroke Scale (NIHSS), Barthel Index (BI), Mini-Mental State Examination (MMSE), and
Diagnosis Scale of Syndrome Elements in Ischemic Stroke (DSSEIS). The patients’ demographics, medical history, family history, physical examination, auxiliary examination, risk factor assessment, and clinical diagnosis will be extracted from medical records. Research personnel will perform GCS, NIHSS, mRS, BI, MMSE, DSSEIS, and Patient-Reported Outcome Scale for Stroke (PRO-Stroke) assessment through a face-to-face interview during patient discharge. The etiologic classification of stroke, stroke-related complications, and new cerebrovascular events will be extracted. The etiologic classification of AIS will be determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria while ICH according to the Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined (SMASH-U) criteria (Adams et al., 1993; Meretoja et al., 2012). In addition to conventional therapies, research personnel will record the type of TCM treatment that is defined according to the World Health Organization (World Health Organization, 2011), details involving Chinese patent medicine, TCM compounds, hospital preparation of TCM, acupuncture, and moxibustion during hospitalization. Data collection and reporting will be conducted using an electronic data capture (EDC) system (http://www.1-dao.net:13579/) with a unique ID. Research personnel can also launch this EDC system on smartphones, and they will complete data collection when they are on daily ward rounds. All laboratory test and auxiliary examination results will be collected. The EDC system can remind research personnel of patients’ follow-up, and it can also automatically check for completeness, coding, value range, and logical error of uploaded data, and then provide feedback to research personnel. Any uploaded data correction, as well as electronic audit trail with electronic signature and date, will be recorded on the system. This registry system is housed on a secure server at the Institute for Brain Disorders, Beijing University of Chinese Medicine. An independent contract research organization will perform online data monitoring during the whole study.

**Follow-Up Procedures**

All patients will be identified and followed up using individual identity cards that are unique to every Chinese citizen, enabling unambiguous linkages. Research personnel will regularly perform face-to-face or telephone follow-up at 3, 6, 12, and 24 months after stroke onset. Information, including death, functional status,
activity of daily living, cardiovascular or cerebrovascular events, cognitive function, and adherence to secondary prevention recommendation and TCM treatments, will be obtained. Death will be confirmed via a death certificate from the local civil registry or from the attended hospital. New cardiovascular or cerebrovascular events leading to rehospitalization will be confirmed by the discharge diagnosis. Suspected recurrent cardiovascular or cerebrovascular events will be determined by the endpoint judgment committee if without hospitalization (Wang et al., 2019).

**Study Outcomes**

In the CASES-TCM study, the distribution of scores on the mRS at the 3-months follow-up, and any recurrent stroke events including ischemic and hemorrhagic stroke (ICH and subarachnoid hemorrhage) within the 12-months follow-up...
will be set as the primary outcomes. Secondary outcomes, which will be assessed at different follow-up visits, include the following: exposure and adherence to TCM treatment, improvement of neurological deficits, patients’ subjective feelings, death, functional outcome, activity of daily living, cognitive function, composite of new clinical vascular events, and incidence of adverse events. The complete outcomes of the CASES-TCM study are illustrated in Table 2.

**Study Sites and Data Source**

The steering committee of the CASES-TCM study will screen hospitals nationwide from each region in the north, east, west, south, and center of mainland China to represent the population. Participating sites in our study are required to admit over 100 cases of patients with stroke per year, have experienced multicenter studies, and be equipped with magnetic resonance imaging or computed tomography machines. A total of 126 participating sites with qualified research capability and proven commitment to the study will be ultimately selected. Figure 2 illustrates the geographical distribution of the selected participating sites.

**Quality Control and Management**

Prior to study initiation, the steering committee will create training videos regarding the study protocol and standard operating procedures (SOPs) in terms of consecutive patient screening and recruitment, obtaining informed consent, and data collection. Research personnel will be required to complete the training videos and obtain a study permit once they pass the examination. The endpoint judgment committee will be responsible for developing SOPs concerning the proper use of scales, outcome assessment, and reporting procedures. An independent data safety and monitoring board will conduct data monitoring to ensure adherence to study documentation, reporting procedures, and the study protocol.

**Study Sample Size**

Generally speaking, the sample size of the registry study should be sufficiently large enough to represent the general population. Based on the annual number of 20 cases of hospitalization per month due to acute stroke in every participating site (a total of 126 sites), we aim to register 20,000 patients in the CASES-TCM study. Enrolment of up to 20,000 patients is anticipated at the end of the first year.

**Statistical Analysis**

A statistical analysis plan (SAP) has been developed prior to the initiation of the CASES-TCM registry. All collected observational data will be analyzed descriptively using established statistical methods. The mean, median, standard median, or interquartile ranges will be used to summarized continuous data, while counts or percentages for categorical data. Between-group comparisons will be conducted using parametric tests [one-way analysis of variance (ANOVA) or Student’s t-test] or non-parametric tests (chi-square test, Fisher’s exact test, Kruskal–Wallis one-way ANOVA on ranks, or Mann–Whitney U test), as appropriate. As for time-to-event analysis, patients will be censored at their last follow-up assessment when experiencing a clinical event, at the end of study, or at the time of withdrawal from the study. Cumulative clinical events will be reported as Kaplan–Meier estimates. Cox proportional hazards regression methods will be used for hazard ratio calculation at 95% confidence intervals, and the treatment effect will be assessed using the log-rank test. During the analysis, confounding factors will be considered, and multivariable regressions will be conducted with adjustments for potential covariates and the propensity score. If not specified otherwise in the SAP, missing data will not be imputed. Subjects with incomplete data will be included in the analysis and for each variable; the number of subjects with missing data will be reported. Interim analyses comprising descriptive summaries of collected data will be conducted every 6 months. All statistical tests will be two-sided and statistical significance will be set at p < 0.05. Statistical analyses will be performed using SAS software version 9.4 (SAS Institute, Inc.).

**DISCUSSION**

Due to the emphasis on the effectiveness, benefits, and disadvantages of various treatment methods, well-designed large-scale registries for patients with stroke that are linked with long-term clinical outcomes should be a priority for clinicians and researchers (Kim et al., 2014). We describe the rationale and design of a prospective, multicenter, registry-based observational study, which will investigate the clinical features, stroke management with TCM, and outcomes of patients with acute stroke in Chinese real-world settings. Given that current guideline-recommended evidence-based treatments for AIS and ICH are limited, there remains a need for an effective and safe therapy for improving the prognosis of patients with stroke. TCM treatments are commonly used for stroke in China but the evidence is insufficient (Wu et al., 2007; Wu et al., 2019). Therefore, the practical effects and disadvantages of TCM in patients with stroke need to be confirmed via a large longitudinal data collection. This study will provide information on potential beneficiary from TCM, proper time to initiate TCM, and appropriate duration of TCM treatment for patients with stroke, on the basis of updated guideline-recommended routine treatment. Besides, this registry-based observational study could reveal the treatment patterns, such as effectiveness of specific treatment, switching therapies during follow-up, and concomitant medications in a real-world setting, which are unlikely to be obtained in conventional clinical trials (Sherman et al., 2016).

Proper TCM use is based on its unique theory system including holism and syndrome differentiation. The core concept of TCM syndrome differentiation lies in personalized treatment (Yuan, 2021). Complex and diversified information are needed to guide personalized treatment to maximize the patient benefits. We will not only examine the natural history of stroke but also focus more on the effects of TCM treatment for stroke based on the TCM theory system in the present study. Table 3 lists the comparison of our study with the other two stroke registries with available TCM information, including study objectives, target population, study scale, area coverage, and disease subtypes (Hao et al., 2011; Wang et al., 2011; Qin et al., 2021).

Similar to other registry studies, the presence of selection bias of participating sites in the CASES-TCM study is unavoidable
although the sample population covers most areas of China (Ohman et al., 2006; Wang et al., 2011). However, the multicenter participation and regular follow-up of consecutively enrolled hospitalized patients in this large-scale clinical-based study guarantee the cross-sectional and longitudinal data. We could explore both the geographical and temporal characteristics of patients with stroke in China to improve the representation of collected data in terms of a disease registry. Further, we will conduct strict quality control with respect to participating site screening, research personnel training, and timely data audit to ensure the accuracy and completeness of collected data. Moreover, some studies with specific hypotheses such as comparative effectiveness research, pragmatic randomized clinical trial, or nested case-control study can also be embedded within this registry study, thereby generating secondary hypotheses for further validation in clinical trials (Lei et al., 2020).

To the best of our knowledge, the CASES-TCM study is the first and largest, comprehensive, prospective, registry-based, observational study to report TCM application for stroke in China, which investigates the major clinical characteristics of stroke in patients treated with TCM and to explore any difference in the comparison with other non-TCM user cohorts and the effectiveness and safety of TCM.

| Study objectives | CSR, To analyze basic data and outcomes in Chengdu Stroke Registry | CNSR, To evaluate the quality of care for stroke patients in China | CASES-TCM, To depict major clinical characteristics of stroke in patients treated with TCM and to explore any difference in the comparison with other non-TCM user cohorts and the effectiveness and safety of TCM. |

| Study region | West China | Across China | Across China |
| Number of sites | 1 | 132 | 126 |
| Number of patients | 3,123 | 21,902 | Anticipated 20,000 |
| Onset to admission | ≤30 days | ≤14 days | ≤ 7 days |
| Disease subtypes | AIS, TIA, ICH, SAH | AIS, TIA, ICH, SAH | AIS, ICH |
| Follow-up | 12 months | 24 months | 24 months |
| TCM information | ✓ Only report TCM treatment as an exposure | ✓ Only report TCM treatment as an exposure Qin et al. (2021) | ✓ Pre-hospital TCM treatment (specific medicine; application setting) |
| | ✓ Inadequately describe important aspects of TCM use | ✓ Inadequately describe important aspects of TCM use | ✓ In-hospital TCM treatment (Chinese patent medicine; TCM compounds; acupuncture; others): including administration time and dose |
| | ✓ Inadequately describe important aspects of TCM use | ✓ Inadequately describe important aspects of TCM use | ✓ Adherence to TCM treatment |

CSR, Chengdu Stroke Registry; CNSR, China National Stroke Registry; CASES-TCM, China Stroke Registry for Patients with Traditional Chinese Medicine; TCM, traditional Chinese medicine; AIS, acute ischemic stroke; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage.

The studies involving human participants were reviewed and approved by The institutional review board of the Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China (No. 2021DZMEC-024-02).

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The institutional review board of the Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China (No. 2021DZMEC-024-02).

AUTHOR CONTRIBUTIONS

Study conception: YG. Study design: YG, CZ, KC, LK, XD, XL, YD, and LF. Data collection and data security: KC, XD, DZ, BR, SL, LF, XX, and CL. Drafting the manuscript: LF. Making supplementary files: LF and YS. Editing and reviewing of the manuscript: YG, CZ, and KC.
**ACKNOWLEDGMENTS**

The authors acknowledge contributions from the CASES-TCM GROUP members all over China.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.743883/full?supplementary-material
Qin, H., Chen, Y., Liu, G., Turnbull, I., Zhang, R., Li, Z., et al. (2021). Management Characteristics and Prognosis after Stroke in China: Findings from a Large Nationwide Stroke Registry. Stroke Vac. Neuro. 6 (1), 1–9. doi:10.1136/svn-2020-000340

Rajicic, S., Gothe, H., Borba, H. H., Sroczynski, G., Vujicic, J., Toell, T., et al. (2019). Economic burden of Stroke: a Systematic Review on post-stroke Care. Eur. J. Health Econ. 20 (1), 107–134. doi:10.1007/s10198-018-0984-0

Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray, G. W., Gross, T., Hunter, N. L., et al. (2016). Real-World Evidence - what is it and what can it Tell Us? N. Engl. J. Med. 375 (23), 2293–2297. doi:10.1056/NEJMsb1609216

Vincent, J. L. (2010). We Should Abandon Randomized Controlled Trials in the Intensive Care Unit. Crit. Care Med. 38, S534–S538. doi:10.1097/ CCM.0b013e3181f208ac

Wang, Y., Cui, L., Ji, X., Dong, Q., Zeng, J., Wang, Y., et al. (2011). The China National Stroke Registry for Patients with Acute Cerebrovascular Events: Design, Rationale, and Baseline Patient Characteristics. Int. J. Stroke 6 (4), 355–361. doi:10.1111/j.1747-4949.2011.00584.x

Wang, Y., Liu, M., and Pu, C. (2016a). 2014 Chinese Guidelines for Secondary Prevention of Ischemic Stroke and Transient Ischemic Attack. Int. J. Stroke 12 (3), 302–320. doi:10.1111/1747-4949.2017694391

Wang, Y., Zhao, X., Lin, J., Li, H., Johnston, S. C., Lin, Y., et al. (2016b). Association between CYP2C19 Loss-Of-Function Allele Status and Efficacy of Clopidogrel for Risk Reduction Among Patients with Minor Stroke or Transient Ischemic Attack. JAMA 316 (1), 70–78. doi:10.1001/jama.2016.8662

Wang, W., Jiang, B., Sun, H., Ru, X., Sun, D., Wang, L., et al. (2017). Prevalence, Incidence, and Mortality of Stroke in China: Results from a Nationwide Population-Based Survey of 480 678 Adults. Circulation 135 (8), 759–771. doi:10.1161/CIRCULATIONAHA.116.025250

Wang, Y., Jing, J., Meng, X., Pan, Y., Wang, Y., Zhao, X., et al. (2019). The Third China National Stroke Registry (CNSR-III) for Patients with Acute Ischaemic Stroke or Transient Ischaemic Stroke: Design, Rationale and Baseline Patient Characteristics. Stroke Vac. Neuro. 4 (3), 158–164. doi:10.1136/svn-2019-000242

Wei, J. W., Wang, J. G., Huang, Y., Liu, M., Wu, Y., Wong, L. K., et al. (2010). Secondary Prevention of Ischemic Stroke in Urban China. Stroke 41 (5), 967–974. doi:10.1161/STROKEAHA.109.571463

Wei, J. W., Huang, Y., Wang, J. G., Liu, M., Wong, L. K., Huang, Q., et al. (2011). Current Management of Intracerebral Haemorrhage in China: a National, multi-centre, Hospital Register Study. BMJ Neurol. 11, 16. doi:10.1186/1471-2377-11-16

World Health Organization. 2011. Traditional Chinese Medicine Could Make ‘Health for One’ True. Available at: https://www.who.int/intellectualproperty/studies/jia.pdf?ua=1

Wu, H. M., Tang, J. L., Lin, X. P., Lau, J., Leung, P. C., Woo, J., et al. (2006). Acupuncture for Stroke Rehabilitation. Cochrane Database Syst. Rev. D4131, CD004131. doi:10.1002/14651858.CD004131.pub2

Wu, B., Liu, M., Liu, H., Li, W., Tan, S., Zhang, S., et al. (2007). Meta-analysis of Traditional Chinese Patent Medicine for Ischemic Stroke. Stroke 38 (6), 1973–1979. doi:10.1161/STROKEAHA.106.473165

Wu, S., Wu, B., Liu, M., Chen, Z., Wang, W., Anderson, C. S., et al. (2019). Stroke in China: Advances and Challenges in Epidemiology, Prevention, and Management. Lancet Neurol. 18 (4), 394–405. doi:10.1016/S1474-4422(18)30500-3

Xia, W., Zheng, C., Zhu, S., and Tang, Z. (2016). Does the Addition of Specific Acupuncture to Standard Swallowing Training Improve Outcomes in Patients with Dysphagia after Stroke? a Randomized Controlled Trial. Clin. Rehabil. 30 (3), 237–246. doi:10.1177/0269215515578698

Yi, X., Wang, C., Liu, P., Fu, C., Lin, J., and Chen, Y. (2016). Antiplatelet Drug Resistance Is Associated with Early Neurological Deterioration in Acute Minor Ischemic Stroke in the Chinese Population. J. Neurol. 263 (8), 1612–1619. doi:10.1007/s00415-016-8181-5

Yu, Y., Tang, L., Cui, F., Jiao, F., Zhang, D., Ma, J., et al. (2021). Effect of Qizhiyongluo Capsule on Lower Limb Rehabilitation after Stroke: A Randomized Clinical Trial. Pharmacol. Res. 165, 105464. doi:10.1016/j.phrs.2021.105464

Yuan, B. (2021). Towards a Clinical Efficacy Evaluation System Adapted for Personalized Medicine. Pharmgenomics. Pers. Med. 14, 487–496. doi:10.2147/PGPM.S304420

Zeng, L., Tang, G., Wang, I., Zhong, J., Xia, Z., Li, J., et al. (2019). Safety and Efficacy of Herbal Medicine for Acute Intracerebral Hemorrhage (CRRICH): a Multicentre Randomised Controlled Trial. BMJ Open 9 (5), e024932. doi:10.1136/bmjopen-2018-024932

Zhang, Y., Jin, H., Ma, D., Fu, Y., Xie, Y., Li, Z., et al. (2013). Efficacy of Integrated Rehabilitation Techniques of Traditional Chinese Medicine for Ischemic Stroke: A Randomized Controlled Trial. Am. J. Chin. Med. 41 (05), 971–981. doi:10.1142/S0192415X13500651

Zhang, S., Wu, B., Liu, M., Li, N., Zeng, X., Liu, H., et al. (2015). Acupuncture Efficacy on Ischemic Stroke Recovery: Multicenter Randomized Controlled Trial in China. Stroke 46 (5), 1301–1306. doi:10.1161/STROKEAHA.114.007659

Zhou, M., Wang, H., Zeng, X., Yin, P., Zhu, J., Chen, W., et al. (2019). Mortality, Morbidity, and Risk Factors in China and its Provinces, 1990-2017: a Systematic Analysis for the Global Burden of Disease Study 2017. Lancet 394 (10204), 1145–1158. doi:10.1016/S0140-6736(19)30427-1

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer CL declared past co-authorships with one of the authors CZ to the handling editor.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2021 Feng, Kong, Dong, Lai, Zhang, Ren, Liu, Xie, Li, Song, Du, Cao, Zhang and Gao. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.