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Clinical features, management and outcomes of severe ischaemic stroke in tertiary hospitals in China: protocol for a prospective multi-centre registry-based observational study

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ABSTRACT

Introduction

Severe ischaemic stroke is a devastating condition with high mortality and morbidity; however, there is insufficient evidence on its management. Lack of effective interventions is partly due to our limited knowledge on mechanisms that underpin the malignant evolution of stroke in some patients. The aim of this study is to investigate causes, risk factors, clinical course, management and outcomes of severe ischaemic stroke in a real-world setting in tertiary hospitals in China.

Methods and analysis

This is a prospective, multi-centre, registry-based observational study. We will recruit 2500 patients with acute ischaemic stroke from nine tertiary hospitals in western China. Patients with acute ischaemic stroke admitted to the Department of Neurology within 30 days of stroke onset will be included. Patients will be visited within 24 hours after admission, on day 3, day 7 and at discharge, to collect data on their clinical state, blood biomarkers, and brain imaging. All patients will be followed up by a structured telephone interview at 3 months and 1 year after stroke onset to collect their functional outcomes. In-hospital outcomes will include symptomatic haemorrhagic transformation and brain oedema by day 7 of admission, and survival status (death or survival) by discharge; follow-up outcomes will include survival status and functional outcome (assessed by modified Rankin scale, mRS) at 3 months and 1 year. The current study will improve our knowledge about the development of severe

ischaemic stroke at acute phase and factors influencing its outcomes, which will eventually facilitate optimisation of individualised interventions for its prevention and treatment.

Ethics and dissemination

Ethics approval is obtained from The Biomedical Research Ethics Committee of West China Hospital, Sichuan University (Reference No. 2017(130)). We will present our findings at the national and international conferences and peer-reviewed journals in stroke and neurology.

Trial registration: ClinicalTrials.gov NCT03222024

KEYWORDS

Ischaemic stroke, severe, malignant, risk factors, management, prognosis

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a large multi-centre registry-based prospective cohort study to systematically investigate clinical features, management and outcomes of patients with severe ischaemic stroke in tertiary hospitals in China.
- We chose tertiary hospitals because most patients with severe ischaemic stroke in China are cared in these hospitals, which would reflect a real-world practice pattern.
- Another strength is that we used a comprehensive definition of severe stroke, incorporating initial neurological function and clinical worsening during hospitalisation, to better cover patients requiring intensive management in acute phase.
- We provided intensive in-hospital assessments and long-term follow-up to understand natural history of severe ischaemic stroke.
- As of common limitations to observational studies, our study may subject to selection bias and inaccurate data recording. To overcome such limitations, we provided regular training and monitoring to site researchers to promote adherence to protocol and ensure Good Clinical Practice.

INTRODUCTION

Acute ischaemic stroke is a leading cause of mortality and morbidity in the world. About one third of patients recruited in trials of intravenous thrombolysis for acute ischaemic stroke presented with severe neurological deficits.[1, 2] Severe stroke is usually related to large infarction in middle cerebral artery (MCA) territories, termed as large hemispheric infarction (LHI)[3] or massive MCA infarction,[4] and is associated with poor outcomes at short-term[5] and long-term.[6] In addition, brainstem infarction can be fatal even the lesion could be relatively small. Apart from initially severe stroke, malignant MCA infarction is another type of severe stroke associated with a high risk of death. It is a clinical syndrome characterised by a rapid increase in the severity of neurological deficits associated with cerebral oedema, which results in massive hemispheric brain swelling, with or without haemorrhagic transformation, leading to transtentorial herniation, death or very poor functional outcomes.[7]

Despite its devastating consequences, little evidence is available to inform the prevention and management of patients with either initially severe or malignant-course strokes. Although a number of interventions are recommended for general management of acute ischaemic stroke, we do not know which patients with very severe stroke benefit most from conventional stroke-specific therapies such as thrombolysis,[8] anti-platelet agents,[9] and anticoagulants.[10] Due to this gap of knowledge, international guidelines have been published for management of LHI[3] and malignant stroke with oedema[11]; however, most of the clinical recommendations are derived from general stroke guidelines as patients with severe stroke are often excluded from clinical trials investigating interventions for stroke.[12]

In addition, there is insufficient data on the effect of hypothermia,[13] corticosteroids[14] and osmotic therapy[15] for the treatment of stroke, and certainly insufficient in severe stroke, despite their frequent use in practice.[11] Three randomised controlled trials (RCTs), HAMLET,[16] DESTINY[17] and DECIMAL,[18] investigated decompressive hemicraniectomy (DHC) for patients with supratentorial infarction and all reported that DHC reduced mortality as compared with medical management. However, as the benefit of DHC is evident only in highly selected patients and the improved survival is gained at the cost of persistent morbidity in many survivors, DHC is underused in practice despite the recommendation in clinical guidelines.[3, 11]

Lack of effective interventions is partly due to our limited knowledge on mechanisms that underpin the malignant evolution of stroke in some patients. Few studies have systematically investigated either modifiable risk factors for the development of stroke worsening or those affecting the prognosis of severe stroke. A systematic review of predictors of life-threatening brain oedema in MCA infarction was published in 2008, which included 23 observational studies with 1185 patients and identified 27 factors associated with brain oedema; however, even the best predictor reported in this review has only moderate predictive value.[19] It is noticeable that all included studies are small and may lack of power to detect predictive value. So far the largest observational study on severe stroke, derived from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL), was published in 2012.[5] By comparing 243 stroke patients with an initial NIHSS score $\geq$ 20 with 1672 patients with NIHSS < 20, the study found that the presence of severe stroke on admission was associated with multiple clinical factors, brain imaging and blood biomarkers; in addition, favourable outcome at 3 months of patients

with initially severe stroke was predicted by several modifiable factors.[5] Early identification of these risk factors and interventions for modifiable factors would be useful for the prediction and management of severe stroke. However, this study used an 'arbitrary' cut-off score of NIHSS ≥ 20 on admission to define 'severe stroke', which may not fully reflect clinical features of this complex condition. In addition, the study did not investigate factors associated with the evolution from mild stroke to severe stroke in hospital, which is a very important issue for acute stroke management.

In summary, there are uncertainties in the causes, risk factors, clinical course, management and outcomes of severe ischaemic stroke, thus this multi-centre prospective cohort study is designed to investigate into these areas in a real-world setting in tertiary hospitals in China. Particularly, as malignant brain oedema is, based on our clinical observation, possibly the most common cause of neurological worsening following acute ischaemic stroke, we will explore predictors for its evolution and strategies specifically targeting its prevention and treatment.

METHODS AND ANALYSIS

This is a multi-centre, registry-based, prospective cohort study, which will start in March 2017 and end in February 2020. We will recruit patients with acute ischaemic stroke admitted to the Department of Neurology of nine participating hospitals (details in the Acknowledgements section). Central ethics approval is obtained from The Biomedical Research Ethics Committee of West China Hospital, Sichuan University (Reference No. 2017(130)). Appropriate local Ethics Committee approvals are sought for each participating

hospital and proof of local approval must be sent to the leading centre before recruitment can be started in each centre. The study must be run according to local law and regulation. This study is registered in ClinicalTrials.gov (NCT03222024). Figure 1 is a summary of study processes.

Figure 1 Flowchart of study processes for clinical features, management and outcomes of severe ischaemic stroke

Participants

Inclusion and exclusion criteria

In each participating hospital, stroke patients admitted to the Department of Neurology will be screened for eligibility by their responsible doctors. Inclusion criteria: a) Aged 18 years or over; b) Symptoms and signs of clinically definite acute stroke; c) Time of stroke onset is known and within 30 days of admission; and d) CT or MRI brain scanning has reliably excluded both intracranial haemorrhage and structural brain lesions which can mimic stroke (e.g. brain tumour). Exclusion criteria: a) Likely to be unavailable for follow-up, e.g. no fixed home address; or b) Refuse to give consent to participate. All patients (or their legal proxies) will be provided with a written Patient Information Sheet and be fully informed the aim and content of this study. Each patient will be asked to sign an informed consent form before they are recruited.

Definition of severe ischaemic stroke

We searched PubMed with search terms (stroke OR ischemi* OR ischaemi* OR infarct OR infarction) AND (severe OR malignant OR massive OR large OR hemispheric OR edema OR oedema OR swelling OR herniation OR space-occupying) for clinical trials, observational studies and reviews. We summarised commonly reported definitions of 'severe stroke' and had a panel discussion with doctors and nurses working in stroke wards and neurological intensive care unit (NICU) of participating hospitals, and reached consensus on the following operational definition of 'severe stroke' to be used in the current study: a) severe neurological deficits, assessed by the National Institute of Health Stroke Scale (NIHSS) scored 15 or over, b) loss of consciousness, assessed by the Glasgow Coma Scale (GCS) scored 8 or less, or item 1a of NIHSS scored 1 or over, or c) intubation, mechanical ventilation, or admitted to NICU for any reason on admission or during current hospitalisation for ischaemic stroke.

We define our patients as three groups: a) initially severe stroke: patients who fulfill the above pre-specified operational definition of severe stroke at onset of symptoms; b) late-developed severe stroke (*i.e.* malignant-course stroke): patients who do not initially fulfill the definition of severe stroke, but experience clinical worsening and develop severe stroke within 7 days after stroke onset; and c) non-severe stroke: patients do not have either initially severe stroke or late-developed severe stroke. We define clinical worsening as a) neurological deterioration with an increase of NIHSS score of 4 or more as compared to baseline NIHSS, b) a decline of consciousness, which leads to a GCS score of 8 or less, or item 1a of NIHSS scored 1 or over, c) need for invasive interventions such as DHC, or d) death in hospital.

In-hospital visits and data collection

After patients (or their proxies) sign the consent form, we will collect patients' baseline data within 24 hours after admission (visit 1, day 0). Subsequent visits will be conducted on day 3 after admission or earlier if the patient experiences clinical worsening (as defined above) at anytime between day 0 and day 3 (visit 2), on day 7 after admission or earlier if clinical worsening occurs at anytime between visit 2 and day 7 (visit 3), and on the day before discharge or on day 30 after admission, whichever is earlier (visit 4). If the patient dies or is discharged before a planned visit, visit 4 will be conducted accordingly with the planned visit omitted.

A paper-based structured Case Report Form will be used to record information for each patient. Data collected at each visit are summarised in Table 1. Particularly, at visit 1, we will record demographics (age and sex), medical history (e.g. hypertension, atrial fibrillation), clinical characteristics of current stroke (e.g. initial stroke severity by NIHSS, consciousness level by GCS), results of routine blood tests on admission (e.g. white blood cell count, renal function), and stroke features on initial brain imaging (e.g. early infarct signs). For subsequent visits, we will assess stroke characteristics (e.g. change in stroke severity) and brain imaging features (e.g. brain swelling, haemorrhagic transformation), and record current medical treatment for each patient (e.g. thrombolysis, endovascular interventions, anti-platelet agents, anticoagulation, osmotics, DHC). If the patient has an examination (e.g. brain CT) more than once between two adjacent visits, results of the most recent examination to the latter visit will be recorded. At visit 4, we will record treatment interventions used during hospitalisation. We

will also record if the patient is referred to Neurosurgery Department for DHC or to Rehabilitation Department for further rehabilitation.

Follow-up assessments

At 3 months and 1 year after stroke onset, a trained researcher (a neurologist or postgraduate in Neurology) blind to all relevant medical information will contact the patient to deliver a structured telephone interview and collect the data on survival status (survival or death) and functional outcome (assessed by scores on modified Rankin scale, mRS) (Table 1).

Clinical outcomes

In-hospital outcomes include symptomatic haemorrhagic transformation and brain oedema by day 7 of admission, and survival status (death or survival) by discharge; follow-up outcomes include survival status and functional outcome (assessed by mRS) at 3 months and 1 year.

Table 1 Data collection during hospitalisation and up to 1 year after stroke onset

Data	Visit 1 (day 0)	Visit 2 (day 3)	Visit 3 (day 7)	Visit 4 (discharge)	Follow-up 1 (3 months)	Follow-up 2 (1 year)
Demographics	×					
Medical history	×					
Stroke characteristics	×					
Vital signs	×	×	×	×		
NIHSS	×	×	×	×		
GCS	×	×	×	×		
Routine blood examination	×	*	*	*		
Brain CT/MRI	×	at least one repeated brain imaging				
Survival status				×	×	×
mRS					×	×

× required; * if applicable; NIHSS: National Institute of Health Stroke Scale; GCS: Glasgow Coma Scale; CT: computed tomography; MRI: magnetic resonance imaging; mRS: modified Rankin scale.

Provisional analysis plan

We have planned the following analyses:

(a) Clinical features, management, and outcomes of patients with severe ischaemic stroke

All patients will be included in this analysis. Comparisons will be performed between patients with initially severe stroke, patients with late-developed severe stroke, and those without severe stroke, for their demographics, medical history, stroke characteristics, in-hospital interventions, and survival and functional outcomes at discharge, 3 months, and 1 year. Particularly, clinical course of neurological deficits will be described for patients who develop severe stroke.

(b) Prognostic factors for patients with severe ischaemic stroke

Patients with initially severe stroke and those with late-developed severe stroke will be included in this analysis. Comparisons will be performed between patients with good functional outcomes (mRS ≤ 2) with those with poor functional outcomes (mRS ≥ 3) at 3 months, for their demographics, medical history, stroke characteristics, and in-hospital interventions. Subgroup analyses will be performed for the time of admission, comparing patients admitted within 24 hours, 2 to 7 days, and beyond 7 days.

(c) Causes for clinical worsening within 7 days after stroke onset, and risk factors and outcomes of patients with each cause

Patients admitted within 7 days after stroke onset will be included for this analysis. Comparisons will be performed between patients developing clinical worsening within 7 days after onset and those not developing clinical worsening, and further between patients with each cause of clinical worsening. Possible causes include but are not limited to cerebral events such as brain swelling, intracranial haemorrhage and recurrent stroke, and non-cerebral events such as pulmonary infection, myocardial infarction and extracranial bleeding. Patients with each cause of clinical worsening and those without clinical worsening will be compared for demographics, medical history, clinical and radiological characteristics of current stroke, interventions, and outcomes at discharge, 3 months and 1 year. For the subgroup of patients who develop malignant brain oedema (i.e. initially severe stroke or late-developed severe stroke, with imaging evidence of brain swelling) compared to patients without malignant brain oedema, we will perform multivariate analysis to explore clinical and radiological factors that independently predict the development of malignant brain oedema.

Statistical analyses

Data will be described in mean (standard deviation, SD) or median (range) for continuous variables and counts (percentages) for categorical variables. Two group comparisons will be conducted by independent Student-t test or one-way ANOVA test for continuous variables and Chi-square test or Fisher's exact test for dichotomous variables. Associations between potential risk factors and outcomes will be assessed by odds ratio (ORs) and relevant 95%

confidence intervals (95% CIs). Multivariate logistic regression will be used to investigate the effects of potential risk factors on the development malignant brain oedema.

Sample size estimation

This is an observational study with a primary aim to describe the clinical features and outcomes of patients with severe ischaemic stroke, which would often not require sample size estimation. Therefore, we calculate the sample size for the logistic analysis for predicting malignant brain oedema, for which we anticipate to test 5 to 10 variables as potential predictors. Based on the criteria of at least 10 events per variable,[20, 21] we will need 50 to 100 patients with malignant brain oedema. Assuming a proportion of 4% of general patients with ischaemic stroke would develop malignant brain oedema,[1] a sample of 1250 to 2500 patients is required. In this observational study, we aim to recruit 2500 patients in order to allow a possible withdrawal rate of 10% and provide sufficient information on different subgroups of patients for further analyses.

Data management

Site data will be collected by responsible doctors at each participating hospital and sent securely to the central office in West China Hospital, Sichuan University. Researchers of the Central Management Team and relevant regulatory authorities will have access to the information, for which the consent will be sought from each patient at the very beginning of the study. Paperwork with personal information will be stored in a locked filling cabinet in the central office. Clinical data recorded on Case Report Forms will be entered to an electronic

database (IBM SPSS, v21.0. Armonk, NY: IBM Corp.). Study data will be analysed and published in the anonymised form.

Data and safety monitoring

The Steering Committee consists of the principal investigator (ML, committee chair) based on West China Hospital, Sichuan University (the leading research centre) and chief investigators of eight participating hospitals (FG, DY, XL, BW, CW, JD, HZ, TL; details in the Acknowledgements section). The Committee will be responsible for overseeing the conduct of study to ensure compliance with Good Clinical Practice guidelines and the study protocol. Interim analyses will be performed annually to assess the adherence of study administration to protocol and the progress of study conduction. The Committee will advise the Central Management Team on necessary modifications or discontinuation of the study.

The Central Management Team (ML, SW, RY, SZ, BW) based on the leading research centre is responsible for all aspects of day to day management of the study, including coordinating the recruitment of participating hospitals, providing training and study materials, organising training and study meetings, organising central data collection and checking, performing data analysis, and coordinating the production of study reports and publications. Upon advice on study design modification from the Steering Committee, the Central Management Team will report to the Ethics Committee and obtain the approval before implementing the changes. Ethics Committee, which is independent from investigators and the sponsor of this study, will perform annual audits for the study conduct.

Patient and Public Involvement

This is an investigator-initiated observational study, where clinical doctors raised the research question and designed the study. Patients will be involved by providing their clinical information for analysis, with their written consent. The results of current study will inform practice and be used for patient education about the development and prognosis of severe ischaemic stroke, and thus facilitate patients' decision on acute management.

DISCUSSION

This paper describes the design of a multi-centre, registry-based, prospective observational study, which provides a real-world setting to explore causes, risk factors, clinical course, management and outcomes of severe ischaemic stroke. To our knowledge, this will be the largest observational study that systematically investigate severe ischaemic stroke. By exploring causes and clinical course of severe stroke including the development of late-developed severe stroke, this study will inform when severe stroke is likely to occur and why. These findings will suggest the timing for intensive monitoring for patients at risk and optimal strategies for treatment. This study will also provide information on which patients with severe ischaemic stroke could benefit from conventional therapies of stroke management, thus optimise individualised treatment for stroke patients with severe neurological deficits. Furthermore, by investigating factors existing prior to stroke and in acute phase (including in-hospital interventions) that are associated with the subsequent malignant brain oedema, we will be able to focus on modifiable factors as they are potential targets for preventive interventions. In addition, we will analyse factors that influence the effects of available

treatment strategies for malignant brain oedema, with an aim to find out individuals who may benefit from certain intervention. In summary, the current study will improve our knowledge of the development of severe ischaemic stroke at acute phase and factors influencing its outcomes, which will eventually facilitate optimisation of individualised interventions for its prevention and treatment.

Limitations

As a prospective cohort study, current study cannot avoid common limitations of observational studies such as selection bias and inadequacy of data recording. To overcome these possible limitations, we select tertiary hospitals and require researchers to have clinical and research experience in stroke, in order to ensure a similar high quality of medical services and Good Clinical Practice. We also conduct regular site monitoring and researcher training meetings twice per year, to promote adherence to protocol. We only include tertiary hospitals, because such hospitals are where most stroke patients will be admitted thus could reflect a real-world setting of stroke care in China.

ETHICS AND DISSEMINATION

Central ethics approval is obtained from The Biomedical Research Ethics Committee of West China Hospital, Sichuan University (Reference No. 2017(130)). Appropriate local Ethics Committee approvals are sought for each participating hospital and proof of local approval must be sent to the leading centre before recruitment can be started in each centre. All patients will be fully informed of the study with written information and will be asked to sign the consent form before they are recruited. We will present our findings at the national and international conferences and peer-reviewed journals in stroke and neurology.

ACKNOWLEDGEMENTS

We would like to thank Professor Peter Sandercock, University of Edinburgh, who provides advice on study design of this study and comments on the manuscript of this protocol. A number of people have already contributed to the development of the study, particularly clinical and research staff in participating hospitals who support the study, without whom the study would not be possible. We thank Jinyao He (West China Hospital, Sichuan University) for her administrative coordination of this project. We would like to thank Chief Investigators of eight participating hospitals: Fuqiang Guo (Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital), Xiaogang Li (Affiliated Hospital of Southwest Medical University), Bihua Wu (Affiliated Hospital of North Sichuan Medical College), Dongdong Yang (Affiliated Hospital of Chengdu University of Traditional Chinese Medicine), Jingfeng Duan (Mianyang Central Hospital), Chun Wang (People's Hospital of Deyang City), Tianjin Ling (The First People's Hospital of Ziyang), and Hao Zhang (Jiangyou People's Hospital).

Nine tertiary hospitals in western China, including five teaching hospitals, are participating in the study: West China Hospital, Sichuan University; Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital; Affiliated Hospital Of Southwest Medical University; Affiliated Hospital of North Sichuan Medical College; Chengdu University of Traditional Chinese Medicine; Mianyang Central Hospital; People's Hospital of Deyang City; The First People's Hospital of Ziyang; and Jiangyou People's Hospital.

AUTHORS' CONTRIBUTIONS

ML and SW conceived and designed the study; ML is the grant holder; SW, RY and YX conducted the systematic review of literature on severe stroke that underpinned the rationale of the current study; SZ and BW provided advice on clinical and imaging issues; SW wrote the first draft and all authors critically appraised the protocol; all authors have read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

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ADDITIONAL FILFES

Additional file 1 SPIRIT checklist

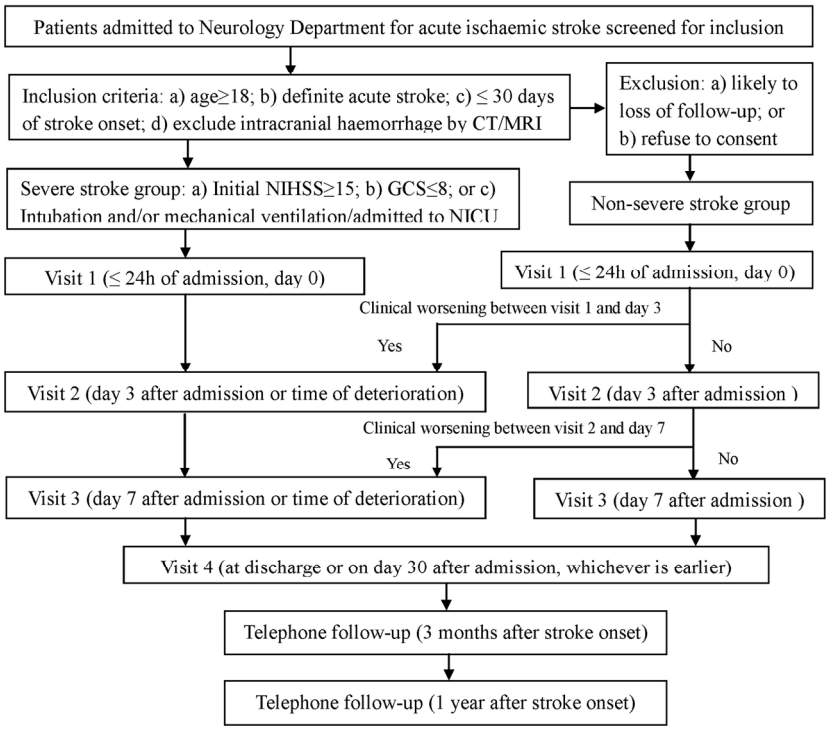

Figure 1 Flowchart of study processes for clinical features, management and outcomes of severe ischaemic stroke

165x130mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3, 8
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	Footnote
Funding	4	Sources and types of financial, material, and other support	P20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P20
	5b	Name and contact information for the trial sponsor	P20
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	P20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	P16, 19-20

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P5-7
	6b	Explanation for choice of comparators	NA
Objectives	7	Specific objectives or hypotheses	P7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	P8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	NA
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	P9-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

This is an observational study

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P7-8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P9-11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA

This is an observational study.

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	P16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	P13-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P7-8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	P16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	P15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P20-21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	P15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P19
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix.
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Clinical features, management and outcomes of severe ischaemic stroke in tertiary hospitals in China: protocol for a prospective multi-centre registry-based observational study

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Clinical features, management and outcomes of severe ischaemic stroke in tertiary hospitals in China: protocol for a prospective multi-centre registry-based observational study

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ABSTRACT

Introduction

Severe ischaemic stroke is a devastating condition with high mortality and morbidity; however, there is insufficient evidence on its management. The aim of this study is to investigate causes, risk factors, clinical course, management and outcomes of severe ischaemic stroke in a real-world setting in tertiary hospitals in China.

Methods and analysis

This is a prospective, multi-centre, registry-based observational study. We will recruit 2500 patients with acute ischaemic stroke from nine tertiary hospitals in western China. Patients with acute ischaemic stroke admitted to the Department of Neurology within 30 days of stroke onset will be included. Patients will be visited within 24 hours after admission, on day 3, day 7 and at discharge, to collect data on their clinical state, blood biomarkers, and brain imaging. Severe stroke is defined as severe neurological deficits (National Institute of Health Stroke Scale [NIHSS] ≥15 or in coma) on admission or clinical worsening (NIHSS increased by ≥4 scores) during hospitalisation. Patients will be followed up by structured telephone interviews at 3 months and 1 year after stroke onset. In-hospital outcomes include symptomatic haemorrhagic transformation and brain oedema by day 7 of admission, and survival status (death or survival) by discharge; follow-up outcomes will include survival status and functional outcome (assessed by modified Rankin scale, mRS) at 3 months and 1 year. The current study will improve our knowledge about the development of severe

ischaemic stroke at acute phase and factors influencing its outcomes, which will eventually facilitate optimisation of individualised interventions for its prevention and treatment.

Ethics and dissemination

Ethics approval is obtained from The Biomedical Research Ethics Committee of West China Hospital, Sichuan University (Reference No. 2017(130)). We will present our findings at the national and international conferences and peer-reviewed journals in stroke and neurology.

Trial registration: ClinicalTrials.gov NCT03222024

KEYWORDS

Ischaemic stroke, severe, malignant, causes, risk factors, clinical course, management, prognosis

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a large multi-centre registry-based prospective cohort study to systematically investigate clinical features, management and outcomes of patients with severe ischaemic stroke in tertiary hospitals in China.
- We chose tertiary hospitals because most patients with severe ischaemic stroke in China are cared in these hospitals, which would reflect a real-world practice pattern.
- Another strength is that we used a comprehensive definition of severe stroke, incorporating initial neurological function and clinical worsening during hospitalisation, to better cover patients requiring intensive management in acute phase.
- We provided intensive in-hospital assessments and long-term follow-up to understand natural history of severe ischaemic stroke.
- As of common limitations to observational studies, our study may subject to selection bias and inaccurate data recording. To overcome such limitations, we provided regular training and monitoring to site researchers to promote adherence to protocol and ensure Good Clinical Practice.

INTRODUCTION

Acute ischaemic stroke is a leading cause of mortality and morbidity in the world. About one third of patients recruited in trials of intravenous thrombolysis for acute ischaemic stroke presented with severe neurological deficits, known as severe ischaemic stroke.[1, 2] Severe stroke is usually related to large infarction in middle cerebral artery (MCA) territories, termed as large hemispheric infarction (LHI)[3] or massive MCA infarction,[4] and is associated with poor outcomes at short-term[5] and long-term.[6] In addition, brainstem infarction can be fatal even the lesion could be relatively small. Apart from initially severe stroke, malignant MCA infarction is another type of severe stroke associated with a high risk of death. It is a clinical syndrome characterised by a rapid increase in the severity of neurological deficits associated with cerebral oedema, which results in massive hemispheric brain swelling, with or without haemorrhagic transformation, leading to transtentorial herniation, death or very poor functional outcomes.[7]

Despite its devastating consequences, little evidence is available to inform the prevention and management of patients with either initially severe or malignant-course strokes. Although a number of interventions are recommended for general management of acute ischaemic stroke, we do not know which patients with very severe stroke benefit most from conventional stroke-specific therapies such as thrombolysis,[8] anti-platelet agents,[9] and anticoagulants.[10] Due to this gap of knowledge, international guidelines have been published for management of LHI[3] and malignant stroke with oedema[11]; however, most of the clinical recommendations are derived from general stroke guidelines as patients with

severe stroke are often excluded from clinical trials investigating interventions for stroke.[12] In addition, there is insufficient data on the effect of hypothermia,[13] corticosteroids[14] and osmotic therapy[15] for the treatment of stroke, and certainly insufficient in severe stroke, despite their frequent use in practice.[11] Three randomised controlled trials (RCTs), HAMLET,[16] DESTINY[17] and DECIMAL,[18] investigated decompressive hemicraniectomy (DHC) for patients with supratentorial infarction and all reported that DHC reduced mortality as compared with medical management. However, as the benefit of DHC is evident only in highly selected patients and the improved survival is gained at the cost of persistent morbidity in many survivors, DHC is underused in practice despite the recommendation in clinical guidelines.[3, 11]

Lack of effective interventions is partly due to our limited knowledge on mechanisms that underpin the malignant evolution of stroke in some patients. Few studies have systematically investigated either modifiable risk factors for the development of stroke worsening or those affecting the prognosis of severe stroke. A systematic review of predictors of life-threatening brain oedema in MCA infarction was published in 2008, which included 23 observational studies with 1185 patients and identified 27 factors associated with brain oedema; however, even the best predictor reported in this review has only moderate predictive value.[19] It is noticeable that all included studies are small and may lack of power to detect predictive value. So far the largest observational study on severe stroke, derived from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL), was published in 2012.[5] By comparing 243 stroke patients with an initial National Institute of Health Stroke Scale (NIHSS) score ≥ 20 with 1672 patients with NIHSS < 20, the study found that the presence of severe stroke on admission was

associated with multiple clinical factors, brain imaging and blood biomarkers; in addition, favourable outcome at 3 months of patients with initially severe stroke was predicted by several modifiable factors.[5] Early identification of these risk factors and interventions for modifiable factors would be useful for the prediction and management of severe stroke. However, this study used an 'arbitrary' cut-off score of NIHSS ≥ 20 on admission to define 'severe stroke', which may not fully reflect clinical features of this complex condition. In addition, the study did not investigate factors associated with the evolution from mild stroke to severe stroke in hospital, which is a very important issue for acute stroke management.

In summary, there are uncertainties in the causes, risk factors, clinical course, management and outcomes of severe ischaemic stroke, thus this multi-centre prospective cohort study is designed to investigate into these areas in a real-world setting in tertiary hospitals in China. Particularly, as malignant brain oedema is, based on our clinical observation, possibly the most common cause of neurological worsening following acute ischaemic stroke, we will explore predictors for its evolution and strategies specifically targeting its prevention and treatment.

METHODS AND ANALYSIS

This is a multi-centre, registry-based, prospective cohort study, which will start in March 2017 and end in February 2020. We will recruit patients with acute ischaemic stroke admitted to the Department of Neurology of nine participating hospitals (details in the Acknowledgements section). Central ethics approval is obtained from The Biomedical Research Ethics Committee of West China Hospital, Sichuan University (Reference No.

2017(130)). Appropriate local Ethics Committee approvals are sought for each participating hospital and proof of local approval must be sent to the leading centre before recruitment can be started in each centre. The study must be run according to local law and regulation. This study is registered in ClinicalTrials.gov (NCT03222024). Figure 1 is a summary of study processes. The reporting of this protocol complies with the SPIRIT recommendation (Additional file 1).

Figure 1 Flowchart of study processes for clinical features, management and outcomes of severe ischaemic stroke

Patient and public involvement

Patients and public were not involved in the design of the study. Participation of patients with ischaemic stroke will provide data to answer the research questions of current study. We will disseminate the study findings to stroke patients in our routine practice in neurology wards and clinics, and through public education activities and stroke academic conferences.

Participants

Inclusion and exclusion criteria

In each participating hospital, stroke patients admitted to the Department of Neurology will be screened for eligibility by their responsible doctors. Inclusion criteria: a) Aged 18 years or over; b) Symptoms and signs of clinically definite acute stroke; c) Time of stroke onset is known and within 30 days of admission; and d) CT or MRI brain scanning has reliably excluded both intracranial haemorrhage and structural brain lesions which can mimic stroke (e.g. brain tumour). Exclusion criteria: a) Likely to be unavailable for follow-up, e.g. no fixed home

address; or b) Refuse to give consent to participate. All patients (or their legal proxies) will be provided with a written Patient Information Sheet and be fully informed the aim and content of this study. Each patient (or their proxies if the patient is incapable in decision making) will be asked to sign an informed consent form before they are recruited.

Definition of severe ischaemic stroke

We searched PubMed with search terms (stroke OR ischemi* OR ischaemi* OR infarct OR infarction) AND (severe OR malignant OR massive OR large OR hemispheric OR edema OR oedema OR swelling OR herniation OR space-occupying) for clinical trials, observational studies and reviews. We summarised commonly reported definitions of 'severe stroke' and had a panel discussion with doctors and nurses working in stroke wards and neurological intensive care unit (NICU) of participating hospitals, and reached consensus on the following operational definition of 'severe stroke' to be used in the current study: a) severe neurological deficits, assessed by the NIHSS scored 15 or over, b) loss of consciousness, assessed by the Glasgow Coma Scale (GCS) scored 8 or less, or item 1a of NIHSS scored 1 or over, or c) intubation, mechanical ventilation, or admitted to NICU for any reason on admission or during current hospitalisation for ischaemic stroke.

We define our patients as three groups: a) initially severe stroke: patients who fulfill the above pre-specified operational definition of severe stroke at onset of symptoms on admission; b) late-developed severe stroke (*i.e.* malignant-course stroke): patients who do not initially fulfill the definition of severe stroke on admission, but experience clinical worsening and develop severe stroke within 7 days after stroke onset; and c) non-severe stroke: patients do not have

either initially severe stroke or late-developed severe stroke. We define clinical worsening as a) neurological deterioration with an increase of NIHSS score of 4 or more as compared to baseline NIHSS, b) a decline of consciousness, which leads to a GCS score of 8 or less, or item 1a of NIHSS scored 1 or over, c) need for invasive interventions such as DHC, or d) death in hospital.

In-hospital visits and data collection

In-hospital visits will be performed by on-site neurologists or trained postgraduate students in the department of Neurology in each participating hospital. After patients (or their proxies) sign the consent form, we will collect patients' baseline data within 24 hours after admission (visit 1, day 0). Subsequent visits will be conducted on day 3 after admission or earlier if the patient experiences clinical worsening (as defined above) at anytime between day 0 and day 3 (visit 2), on day 7 after admission or earlier if clinical worsening occurs at anytime between visit 2 and day 7 (visit 3), and on the day before discharge or on day 30 after admission, whichever is earlier (visit 4, the average hospital stay for patients with ischaemic stroke is about 2 weeks, and can be longer for some patients with severe stroke). If the patient dies or is discharged before a planned visit, visit 4 will be conducted accordingly with the planned visit omitted.

A paper-based structured Case Report Form will be used to record information for each patient. Data collected at each visit are summarised in Table 1. Particularly, at visit 1, we will record demographics (age and sex), medical history (e.g. pre-stroke disability [assessed by modified Rankin scale], hypertension [blood pressure consistently above 140/90 mmHg, or

treated hypertension on medication], diabetes mellitus, atrial fibrillation, history of stroke), clinical characteristics of current stroke (e.g. initial stroke severity by NIHSS, consciousness level by GCS), results of routine blood tests on admission (e.g. white blood cell count, renal function indices including serum creatinine concentration), and stroke features on initial brain imaging (site and size of cerebral infarction, extent of cerebral swelling, and presence of haemorrhagic transformation according to criteria by Wardlaw and Sellar [20]). For subsequent visits, we will assess stroke characteristics (e.g. change in stroke severity by NIHSS, change of consciousness level by GCS) and brain imaging features (e.g. brain swelling, haemorrhagic transformation), and record current medical treatment for each patient (e.g. thrombolysis, endovascular interventions, anti-platelet agents, anticoagulation, statins, anti-cerebral oedema therapies, DHC). If the patient has an examination (e.g. brain CT) more than once between two adjacent visits, results of the most recent examination to the latter visit will be recorded. At visit 4, we will record treatment interventions used during hospitalisation. We will also record if the patient is referred to Neurosurgery Department for DHC or to Rehabilitation Department for further rehabilitation.

Follow-up assessments

At 3 months and 1 year after stroke onset, a trained researcher (a neurologist or postgraduate in Neurology) blind to all relevant medical information will contact the patient to deliver a structured telephone interview and collect the data on survival status (survival or death, and cause for death) and functional outcome (assessed by scores on modified Rankin scale, mRS) (Table 1).

Clinical outcomes

In-hospital outcomes include symptomatic haemorrhagic transformation (defined as significant clinical worsening accompanied by clear evidence of significant intracranial haemorrhage on the brain scan) and symptomatic brain oedema (defined as significant clinical worsening accompanied by evidence of significant brain swelling including shift of the midline away from the side of the ventricle or effacement of the basal cisterns or uncal herniation on the brain scan) by day 7 of admission, and survival status (death or survival) by discharge; follow-up outcomes include survival status and functional outcome (assessed by mRS) at 3 months and 1 year.

Table 1 Data collection during hospitalisation and up to 1 year after stroke onset

Data	Visit 1 (day 0)	Visit 2 (day 3)	Visit 3 (day 7)	Visit 4 (discharge)	Follow-up 1 (3 months)	Follow-up 2 (1 year)
Demographics	×					
Medical history	×					
Stroke characteristics	×					
Vital signs	×	×	×	×		
NIHSS	×	×	×	×		
GCS	×	×	×	×		
Routine blood examination	×	*	*	*		
Brain CT/MRI	×	at least one repeated brain imaging				
Survival status				×	×	×
mRS					×	×

× required; * if applicable; NIHSS: National Institute of Health Stroke Scale; GCS: Glasgow Coma Scale; CT: computed tomography; MRI: magnetic resonance imaging; mRS: modified Rankin scale.

Provisional analysis plan

We have planned the following analyses:

(a) Clinical features, management, and outcomes of patients with severe ischaemic stroke

All patients will be included in this analysis. Comparisons will be performed between patients with initially severe stroke, patients with late-developed severe stroke, and those without severe stroke, for their demographics, medical history, stroke characteristics, in-hospital interventions, and survival and functional outcomes at discharge, 3 months, and 1 year. Particularly, clinical course of neurological deficits will be described for patients who develop severe stroke, for subgroups of patients admitted within 24 hours, 2-7 days, and after 7 days of stroke onset.

(b) Prognostic factors for patients with severe ischaemic stroke

Patients with initially severe stroke and those with late-developed severe stroke will be included in this analysis. Comparisons will be performed between patients with good functional outcomes (mRS ≤ 2) with those with poor functional outcomes (mRS ≥ 3) at 3 months, for their demographics, medical history, stroke characteristics, and in-hospital interventions. Subgroup analyses will be performed for the time of admission, comparing patients admitted within 24 hours, 2 to 7 days, and beyond 7 days.

(c) Causes for clinical worsening within 7 days after stroke onset, and risk factors and outcomes of patients with each cause

Patients admitted within 7 days after stroke onset will be included for this analysis. Comparisons will be performed between patients developing clinical worsening within 7 days after onset and those not developing clinical worsening, and further between patients with each cause of clinical worsening. Possible causes include but are not limited to cerebral events such as brain swelling, intracranial haemorrhage and recurrent stroke, and non-cerebral events such as pulmonary infection, myocardial infarction and extracranial bleeding. Patients with each cause of clinical worsening and those without clinical worsening will be compared for demographics, medical history, clinical and radiological characteristics of current stroke, interventions, and outcomes at discharge, 3 months and 1 year. For the subgroup of patients who develop malignant brain oedema (i.e. initially severe stroke or late-developed severe stroke, with imaging evidence of brain swelling) compared to patients without malignant brain oedema, we will perform multivariate analysis to explore clinical and radiological factors that independently predict the development of malignant brain oedema.

Statistical analyses

Data will be described in mean (standard deviation, SD) or median (range) for continuous variables and counts (percentages) for categorical variables. Two group comparisons will be conducted by independent Student-t test or Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test for dichotomous variables. Associations between potential risk factors and outcomes will be assessed by odds ratio (ORs) and relevant 95% confidence intervals (95% CIs). Multivariate logistic regression will be used to investigate the

effects of potential risk factors on the development malignant brain oedema. Cox proportional hazard model will be used to explore factors affecting prognosis at 3 months and 1 year. We will perform multiple imputation to account for missing data and also perform sensitivity analysis by excluding patients with missing data.

Sample size estimation

This is an observational study with a primary aim to describe the clinical features and outcomes of patients with severe ischaemic stroke, which would often not require sample size estimation. Therefore, we calculate the sample size for the logistic analysis for predicting malignant brain oedema, for which we anticipate to test 5 to 10 variables as potential predictors. Based on the criteria of at least 10 events per variable,[21, 22] we will need 50 to 100 patients with malignant brain oedema. Assuming a proportion of 4% of general patients with ischaemic stroke would develop malignant brain oedema,[1] a sample of 1250 to 2500 patients is required. In this observational study, we aim to recruit 2500 patients in order to allow a possible withdrawal rate of 10% and provide sufficient information on different subgroups of patients for further analyses.

Data management

Site data will be collected by responsible doctors at each participating hospital and sent securely to the central office in West China Hospital, Sichuan University. Researchers of the Central Management Team and relevant regulatory authorities will have access to the information, for which the consent will be sought from each patient at the very beginning of the

study. Paperwork with personal information will be stored in a locked filing cabinet in the central office. Clinical data recorded on Case Report Forms will be entered to an electronic database (IBM SPSS, v21.0. Armonk, NY: IBM Corp.). Study data will be analysed and published in the anonymised form.

Data and safety monitoring

The Steering Committee consists of the principal investigator (ML, committee chair) based on West China Hospital, Sichuan University (the leading research centre) and chief investigators of eight participating hospitals (FG, DY, XL, BW, CW, JD, HZ, TL; details in the Acknowledgements section). The Committee will be responsible for overseeing the conduct of study to ensure compliance with Good Clinical Practice guidelines and the study protocol. Interim analyses will be performed annually to assess the adherence of study administration to protocol and the progress of study conduction. The Committee will advise the Central Management Team on necessary modifications or discontinuation of the study.

The Central Management Team (ML, SW, RY, SZ, BW) based on the leading research centre is responsible for all aspects of day to day management of the study, including coordinating the recruitment of participating hospitals, providing training and study materials, organising training and study meetings, conducting central data collection and checking, performing data analysis, and coordinating the production of study reports and publications. Upon advice on study design modification from the Steering Committee, the Central Management Team will report to the Ethics Committee and obtain the approval before implementing the changes.

Ethics Committee, which is independent from investigators and the sponsor of this study, will perform annual audits for the study conduct.

DISCUSSION

This paper describes the design of a multi-centre, registry-based, prospective observational study, which provides a real-world setting to explore causes, risk factors, clinical course, management and outcomes of severe ischaemic stroke. To our knowledge, this will be the largest observational study that systematically investigate severe ischaemic stroke. By exploring causes and clinical course of severe stroke including the development of late-developed severe stroke, this study will inform when severe stroke is likely to occur and why. These findings will suggest the timing for intensive monitoring for patients at risk and optimal strategies for treatment. This study will also provide information on which patients with severe ischaemic stroke could benefit from conventional therapies of stroke management, thus optimise individualised treatment for stroke patients with severe neurological deficits. Furthermore, by investigating factors existing prior to stroke and in acute phase (including in-hospital interventions) that are associated with the subsequent malignant brain oedema, we will be able to focus on modifiable factors as they are potential targets for preventive interventions. In addition, we will analyse factors that influence the effects of available treatment strategies for malignant brain oedema, with an aim to find out individuals who may benefit from certain intervention. In summary, the current study will improve our knowledge of the development of severe ischaemic stroke at acute phase and factors influencing its

outcomes, which will eventually facilitate optimisation of individualised interventions for its prevention and treatment.

Limitations

As a prospective cohort study, current study cannot avoid common limitations of observational studies such as selection bias and inadequacy of data recording. To overcome these possible limitations, we select tertiary hospitals and require researchers to have clinical and research experience in stroke, in order to ensure a similar high quality of medical services and Good Clinical Practice. We also conduct regular site monitoring and researcher training meetings twice per year, to promote adherence to protocol. We only include tertiary hospitals, because such hospitals are where most stroke patients will be admitted thus could reflect a real-world setting of stroke care in China.

ETHICS AND DISSEMINATION

Central ethics approval is obtained from The Biomedical Research Ethics Committee of West China Hospital, Sichuan University (Reference No. 2017(130)). Appropriate local Ethics Committee approvals are sought for each participating hospital and proof of local approval must be sent to the leading centre before recruitment can be started in each centre. All patients will be fully informed of the study with written information and will be asked to sign the consent form before they are recruited. We will present our findings at the national and international conferences and peer-reviewed journals in stroke and neurology.

ACKNOWLEDGEMENTS

Nine tertiary hospitals in western China, including five teaching hospitals, are participating in the study: West China Hospital, Sichuan University; Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital; Affiliated Hospital Of Southwest Medical University; Affiliated Hospital of North Sichuan Medical College; Chengdu University of Traditional Chinese Medicine; Mianyang Central Hospital; People's Hospital of Deyang City; The First People's Hospital of Ziyang; and Jiangyou People's Hospital.

We would like to thank Professor Peter Sandercock, University of Edinburgh, who provides advice on study design of this study and comments on the manuscript of this protocol. A number of people have already contributed to the development of the study, particularly clinical and research staff in participating hospitals who support the study, without whom the study would not be possible. We would like to thank Chief Investigators of eight participating

hospitals: Fuqiang Guo (Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital), Xiaogang Li (Affiliated Hospital of Southwest Medical University), Bihua Wu (Affiliated Hospital of North Sichuan Medical College), Dongdong Yang (Affiliated Hospital of Chengdu University of Traditional Chinese Medicine), Jingfeng Duan (Mianyang Central Hospital), Chun Wang (People's Hospital of Deyang City), Tianjin Ling (The First People's Hospital of Ziyang), and Hao Zhang (Jiangyou People's Hospital).

AUTHORS' CONTRIBUTIONS

ML and SW conceived and designed the study; ML is the grant holder; SW, RY and YX conducted the systematic review of literature on severe stroke that underpinned the rationale of the current study; SZ and BW provided advice on clinical and imaging issues; SW wrote the first draft and all authors critically appraised the protocol; all authors have read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

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ADDITIONAL FILFES

Additional file 1 SPIRIT checklist

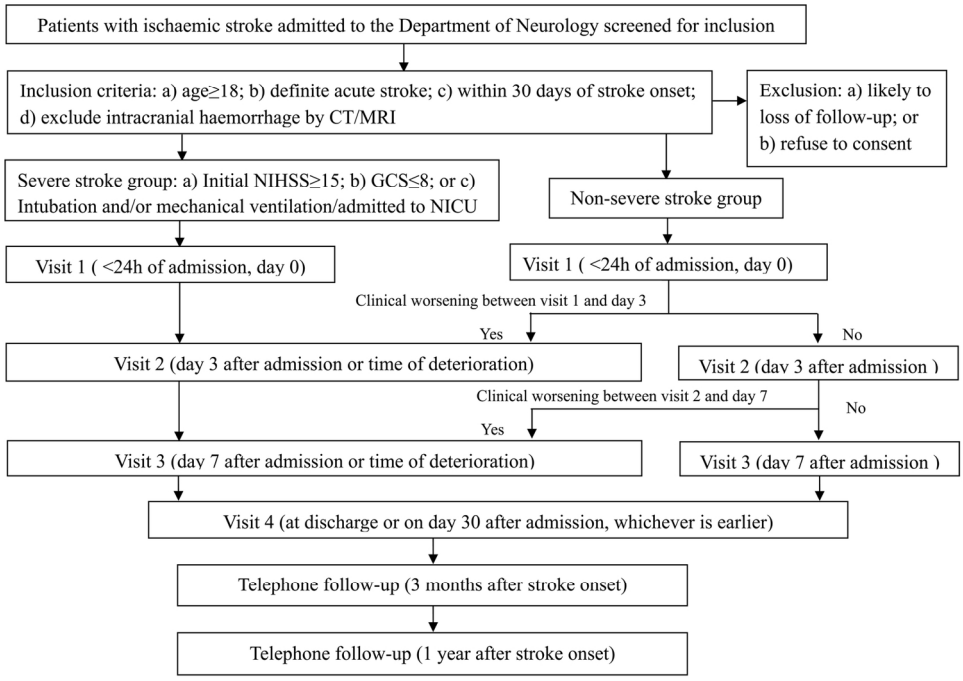

Figure 1 Flowchart of study processes for clinical features, management and outcomes of severe ischaemic stroke

151x104mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_page 1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_pages 3 and 8
	2b	All items from the World Health Organization Trial Registration Data Set	_NA_____
Protocol version	3	Date and version identifier	_Footnote____
Funding	4	Sources and types of financial, material, and other support	_page 22_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_page 21_____
	5b	Name and contact information for the trial sponsor	_page 22_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_page 22_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_pages 17, 20-21

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	__pages 5 and 7
	6b	Explanation for choice of comparators	__NA_____
Objectives	7	Specific objectives or hypotheses	__page 7_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	__page 7_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	__page 7_____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	__page 8_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_NA_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	__NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__NA_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	__NA_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	__pages 9-12____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	__Figure 1_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__page 16_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	__pages 7-8____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__NA_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__NA_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___NA_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___NA_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___NA_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	__pages 10-12___
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	__NA_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	__pages 16-17_
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	__pages 15-16_
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__pages 15-16__
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	__NA_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__page 17_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__NA_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	__NA_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___pages 17-18_
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___pages 7-8_
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__pages 17-18____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_page 8_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__pages 16-17___
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__page 22_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__pages 16-17____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__NA_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	__page 20_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	___NA_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___NA_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	___NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.