Multicentre registration of wake-up stroke in China (MCRWUSC): a protocol for a prospective, multicentre, registry-based cohort study

Zengyu Zhang, Hualan Yang, Zhilan Tu, Gaurav Nepal, Rajeev Ojha, Yan Xi, Jianlan Qiao, Mengting Hu, Chao Li, Fuchun Lin, Lili Zhou, Pengpeng Jin, Shuangxing Hou

ABSTRACT

Introduction Wake-up stroke (WUS) is a type of acute ischaemic stroke (AIS) that occurs during sleep with unknown time of symptom onset. The best treatment is usually not suitable for WUS, as thrombolysis is usually provided to patients who had a symptomatic AIS within a definite 4.5 hours, and WUS remains a therapeutic quandary. Efforts to explore the onset time characteristics of patients who had a WUS and the risk factors affecting poor prognosis support a role for providing new insights by performing multicentre cohort study.

Methods and analysis This multicentre, nationwide prospective registry will include 21 comprehensive stroke centres, with a goal of recruiting 550 patients who had a WUS in China. In this study, clinical data including patient’s clinical characteristics, stroke onset time, imaging findings, therapeutic interventions and prognosis (the National Institutes of Health Stroke Scale Score and the modified Rankin Scale Score at different time points) will be used to develop prediction models for stroke onset time and prognostic evaluation using the fast-processing of ischemic stroke software. The purpose of this study is to identify risk factors influencing prognosis, to investigate the relationship between the time when the symptoms are found and the actual onset time and to establish an artificial intelligence-based model to predict the prognosis of patients who had a WUS.

Ethics and dissemination This study is approved by the ethics committee of Shanghai Pudong Hospital (Shanghai, China) and rest of all participating centres. The findings will be disseminated through peer-reviewed publications and conference presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

This will be a real-world study for patients who had a wake-up stroke in Chinese population.

This is the first study to focus on sleep–awake cycle and the sleep, awake time on the day before stroke onset by collecting lots of time points.

Imaging data of MRI and/or CT perfusion will be collected within 24 hours after stroke onset and the fast-processing of ischemic stroke software will be used for data analysis.

As a limitation, uncontrollable selection bias may occur in the recruitment process at multiple centres.

INTRODUCTION

Acute ischaemic stroke (AIS) is the leading cause of death among the diseases afflicting the Chinese people. Patients who had an AIS arriving within a suitable time frame are treated with recanalisation therapy, that is, intravenous thrombolysis with alteplase and/or mechanical thrombectomy (MT). Intravenous thrombolysis with alteplase is indicated in patients who had an AIS presenting within 4.5 hours of onset regardless of vascular territory involved. MT is indicated in patients who had an AIS presenting within 24 hours of onset with large vessel occlusion in the anterior circulation. However, up to 30% of patients who had an AIS have an ambiguous onset time and up to 20% encounter a wake-up stroke (WUS). WUS is an AIS that has an uncertain time of onset and is detected after the patient wakes up from sleep. This has caused patients to be frequently excluded from the recanalisation therapy, resulting in increased functional impairment and a poor prognosis. The best treatment is usually not suitable for patients who had a WUS because thrombolysis is usually provided to patients who had an AIS within the first definite 4.5 hours of symptom onset. Therefore, studying the stroke onset time range as well as clinical and imaging features will be helpful to explore whether the active treatment in the acute phase is beneficial and provide an essential reference and basis for the diagnosis and treatment of WUS.

Thomalla et al studied 1005 individuals with WUS and discovered that the majority of patients developed AIS between 6:00 and 10:00. This view is of great value for the treatment choice...
of patients who had a stroke, but more research is needed to prove this point and it is better to narrow the scope. Imaging has been used to determine the onset time of patients with WUS in recent years. Numerous studies have demonstrated the diagnostic utility of a variety of MRI sequences, including diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), fluid-attenuated inversion recovery (FLAIR), gradient-recalled echo and susceptibility-weighted imaging. DWI allows for the detection of the infarct core within minutes of AIS onset, as well as the size, location and onset time of the infarct. DWI is more sensitive than unenhanced MRI at detecting small infarct foci. PWI can be used to identify areas of severe hypoperfusion. Similarly, FLAIR is capable of detecting acute ischaemic foci within a few hours of ischaemia. The DWI–FLAIR mismatch is used to delineate the ischaemic penumbra within which thrombolysis with recombinant tissue plasminogen activator is effective regardless of the time frame. The DWI–FLAIR mismatch can also be used to determine the time of lesion formation and may represent the approximate time range of AIS onset. However, DWI–FLAIR mismatch still has some shortcomings. Due to its limited sensitivity and negative predictive value, it may overestimate the actual onset time, excluding many patients who would benefit from thrombolysis. At the same time, subjective judgement, a lack of standards, and parameter settings all have the potential to impact the outcomes. Thrombectomy was discovered that only 48% of patients who had a WUS demonstrated a DWI–FLAIR mismatch. Galinovic et al evaluated the MRI characteristics of 145 patients with WUS and concluded that DWI–FLAIR mismatch could not consistently quantify onset time and that mismatch determination by radiologist was subjective. Thus, multimodal neuroimaging is required to increase the accuracy and specificity of determining the onset time of patients who had a WUS.

The imaging evaluation of collateral circulation can provide a basis for predicting the prognosis of patients who had a WUS. Studies have shown that collateral status can predict the outcome of AIS. There are several imaging modalities to evaluate collateral circulation. Among these evaluation methods, digital subtraction angiography is the gold standard for evaluating all levels of collateral circulation, and CT angiography is also a common method to assess the establishment of collateral circulation. The volume of ischaemic penumbra and infarct core is often calculated by using CT perfusion (CTP) images, created by enhanced image processing software. Campbell et al found significant benefits of reperfusion in all time strata (4.5–6 hours, 6–9 hours and wake-up time) in patients who had an AIS without risk variation of symptomatic haemorrhage. These findings support similar efficacy of alteplase in perfusion mismatch-selected patients in both 4.5–9 hours and WUS time windows. Similarly, Campbell et al observed that individuals with AIS 4.5–9 hours after onset or patients who had a WUS who received alteplase had better functional outcome than patients who received placebo. While alteplase increased the frequency of symptomatic intracerebral haemorrhage (sICH), this increase did not eliminate the overall net benefit of thrombolysis.

Additional studies have failed to provide sufficient evidence to evaluate if recanalisation therapy improves the overall outcome in patients with WUS. Kim et al evaluated the relationship between WUS and functional outcome in 2289 patients with AIS. Patients with WUS had a considerably higher initial National Institutes of Health Stroke Scale (NIHSS) Score than their non-WUS counterparts. Patients with WUS had a greater likelihood of experiencing adverse outcomes and had a substantial effect on the modified Rankin Scale (mRS) Score increasing functional dependence. However, numerous investigations have demonstrated no substantial difference in clinical severity or outcomes between WUS and stroke with known onset time, implying the feasibility of reperfusion therapy for patients who had a WUS. Considering aforementioned literature, there is still some debate about whether or not to treat patients who had a WUS with recanalisation therapy. As a result, further research is needed to validate the feasibility of recanalisation therapy for patients with WUS.

The aim of our study is to collect data on the time characteristics of patients with WUS, to explore the relationship between the time when the symptoms were found and the stroke onset time, to identify risk factors associated with poor prognosis and to determine whether there is a relationship between therapeutic strategy and prognosis. Then, using the afore-mentioned data, we intend to develop an artificial intelligence (AI)-based prediction model that can be used for early warning and proper intervention selection and to improve prognosis for patients who had a WUS.

**METHODS**

**Design**

This project will establish a registry-based prospective cohort database of patients who had a WUS in China. The information including demographic characteristics, medical history, family history, basic clinical information, imaging evaluation for stroke, stroke onset time characteristics, treatment method, prognosis and follow-up information will be collected. After the patient is admitted in hospital, all the information will be extracted prospectively. For patients not evaluated for CTP in the emergency department, we can reduce patient’s selection bias by collecting corresponding scoring metrics (each imaging examination has a corresponding score) based on the case report form. The study design is displayed in figure 1 and flowchart of patient’s enrolment is depicted in figure 2.

**Setting**

The study protocol has been approved by the ethics committee. Recruitment of patients was started in January 2019 and will end in June 2023.

**Patient and public involvement**

Subjects with AIS will be recruited from multiple centres across China. Before the implementation of the study, the subjects or one of their family members will be explained clearly about the purpose and procedures of the study.
and an informed consent form will be signed. In the course of the study, the subjects’ personal privacy and data confidentiality will be protected and health managers will be specified to maintain further contact with the patient. The feedbacks of patients will also be regularly recorded into the system.

**Inclusion criteria**

1. Aged 18–80 years.
2. Patients with diagnosis of AIS in accordance to the 2018 Chinese guideline for the diagnosis and treatment of AIS.
3. Patients without impaired consciousness.
4. Patients with no neurological impairment before sleep and with neurological deficits noticed after wake up.
5. The time from onset to enrolment is less than 24 hours, and the time of AIS onset here is defined as the

---

**Figure 1** The multicentre registration of wake-up stroke (WUS) in China study design.

**Figure 2** The flowchart of patient’s enrolment. GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; WUS, wake-up stroke.
midpoint between the sleep onset or when the patient was last known to be normal and the time of wake-up in accordance to the study of Ma et al.27

6. Patients who had an AIS or local guardian/near kin should sign the informed consent.

Exclusion criteria
1. No features of infarction in DWI–MRI.
2. Patients who declined participation in registration and follow-up investigation. The completed data includes all registration and clinical information of patients for 9±7 days. Patients presenting with one or more of the following conditions will be withdrawn from this study: A. The patient dissatisfies the inclusion criteria.
B. The patient withdraws the informed consent form.
C. Any situation where the investigators believe that the patient should discontinue from this study for safety reasons or conflict of interest of the patient.
D. The patient who is lost to follow-up.

On termination of the study, patient’s endpoints should be evaluated.

Data collection
1. Baseline assessment data (Time 0).
   A. The demographic and clinical information will be collected. Patient’s information will be recorded including age, sex, height, weight, waist circumference, medical history (hypertension, diabetes, hypercholesterolaemia, coronary heart disease, etc), personal history (smoking, drinking, etc), family history, emotional state before going to sleep on the day of stroke and medication before admission.
   B. Clinical baseline assessment (clinical features, vital signs, physical examination).
   C. Functional score (NIHSS Score, Glasgow Coma Scale (GCS) Score, mRS Score, Barthel Index).
   D. Laboratory examination (blood routine, blood biochemistry, blood coagulation routine, etc).
   E. Imaging examination (CT of the head, MRI of the head, transcranial Doppler ultrasound (TCD), vascular ultrasound, etc).
2. Several different time points.
   The regular sleep and wake-up time of sleep; the last known normal time before the onset of stroke; wake-up time on the day of stroke; time taken to reach hospital after stroke; time to start of treatment; time to end of treatment.
3. Image evaluation: centres can either select A or B for image assessment.
   A. CT image evaluation data.
      Alberta Stroke Program Early CT Score (ASPECTS) on Non-Contrast CT (NCCCT); CTP core infarct volume; CTP mismatch rate.
      Absolute mismatch region (penumbra) volume; formation of collateral circulation.
   B. MRI image evaluation data.
      MRI–DWI ASPECTS Score; volume of core infarct area in DWI (apparent diffusion coefficient) image.

Volume of ischaemic penumbra in PWI images; infarct volume in FLAIR images.

Collateral circulation; macrovascular occlusion.

4. Therapeutic interventions.
   A. Intervention protocols: intravenous thrombolysis, arterial thrombolysis, thrombectomy, drug therapy, etc.
   B. Additional medications for various comorbidities.
   C. Follow-up data collection.

Treatment plan
This study is not a randomised controlled trial, so the treatment options are not limited, but it needs to be truly recorded. After admission, the doctor will determine the most suitable treatment strategy for the patient’s prognosis according to the patient’s baseline clinical characteristics and treat the patient accordingly.27

After the completion of study, subgroup analysis will be performed by comparing the excellent and poor prognosis for each treatment strategy in order to ascertain the prognostic factors of patients who had a WUS.

According to the 2019 update of 2018 AHA/ASA (the American Heart Association/American Stroke Association) guideline, intravenous alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose will be given as bolus over 1 min) will be administered within 4.5 hours of stroke. Symptoms recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset>4.5 hours from last known normal or at baseline state and who have a DWI–MRI lesion smaller than one-third of the middle cerebral artery (MCA) territory and no visible signal change on FLAIR.27 MT will be done in selected patients with AIS within 6–16 hours of last known normal who have large artery blockage in the anterior circulation and meet the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) or DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) trials eligibility criteria. MT will be done in selected individuals with AIS within 16–24 hours of their last known normal who have significant artery blockage in the anterior circulation and meet DAWN eligibility criteria.27 In this registry-based study, patients with WUS will be treated acutely in accordance with the afore-mentioned recommendations.

Variables
Primary endpoint
The primary efficacy endpoint will be early neurological improvement (NIHSS Score decrease by ≥4 points within 24 hours), early neurological deterioration (NIHSS Score increase by ≥4 points within 24 hours) and functional independence (defined as mRS ≤2) at 90 days. The primary safety endpoint is sICH and all-cause mortality at 24 hours and 90 days.
Secondary endpoints
Secondary efficiency endpoints will include: Global Outcome Score, Barthel Index and categorical shift in mRS at 90 (±10) days after WUS onset.

Exploratory purpose
First, how to more quickly and effectively determine the time range of WUS occurrence? The study is to establish a clinical database for exploring the relationship between possible onset time of symptom and the time range of onset inferred from ischaemic penumbra, to look for the possible onset time range of possible symptoms in some cases only by asking for several different time points about sleep, wake-up and onset of symptom. Further to provide a faster judgement of the time range of onset and basis for follow-up treatment measures even without the assistance of high-end imaging machines. And to detect whether mobile phones or other electronic devices which can monitor sleep time can be used to indirectly assess the possible stroke onset. Second, collecting imaging data to investigate the ischaemic penumbra and exploring the relationship between the ischaemic penumbra and WUS. The specific aims and objectives are as follow:

1. To evaluate the onset time by evaluation of multimodal neuroimaging, such as DWI–FLAIR mismatch and DWI–PWI mismatch, to infer to a certain extent whether the estimated onset time in accordance to the study of Thomalla et al. or to obtain even a smaller time range of stroke onset and to establish a predictive model for onset time of patients who had a WUS.
2. To establish a model for evaluating prognosis of patients who had a WUS and further to find out the factors affecting prognosis by comparing each treatment strategy.
3. To evaluate the current situation of medical service and socioeconomic benefits of patients who had a WUS in China, explore and summarise the clinical morbidity and imaging features of Chinese WUS population and observe the effects of intervention in acute phase of WUS on their efficacy and prognosis.

Collection and analysis of imaging data
The CT and MRI equipment used by the participating centres are all from mainstream brands such as Siemens, Philips or GE. For the selection of image inspection items, we only do registration studies and do not impose any restrictions. When setting the parameters, each centre conducts routine imaging examinations in accordance with the procedure and parameters of the ‘Guidelines for Stroke Vascular Imaging Examination in China’. CTP imaging data will be exported to DICOM style for unified analysis with the fast-processing of ischemic stroke (F-STROKE) software, which provides a fully automatic CTP processing combined with manual rerun mechanism. Further, F-STROKE used the similar algorithm and standard definitions of ischaemic parameters with Rapid Processing of Perfusion and Diffusion.\(^\text{28}\) And the F-STROKE software package with automatic segmentation and calculation will be quite accurate in measuring baseline ischaemic core volume and penumbra volume.\(^\text{28, 29}\)

F-STROKE calculates (1) time to maximum (\(T_{\text{max}}\)), (2) relative cerebral blood flow, (3) relative cerebral blood volume and (4) mean transit time but with only arterial inflow function input.\(^\text{28}\)

Statistical analysis
According to the sample size design scheme of this register study, the sample size has been taken to be 25 times of the number of independent variables. About 20 independent variables are expected to be included in the analysis. Taking into account a lost-to-follow-up and culling rate of 10%, estimated number of patients to be included in the study is 550. Data are recorded, stored and analysed by SPSS V.22.0 for windows operating system. Measurement data will be expressed as mean±SD, and comparison between groups will be performed by analysis of variance. The enumeration data are analysed as rate, and comparison between groups is to be conducted using \(\chi^2\) test. \(P<0.05\) will be considered statistically significant.

DISCUSSION
So far, there has been a few researches on WUS in national and international level and reports on the factors related with the prognosis are limited. In China, there is a lack of multicentre research on WUS population and most studies are retrospective type. So, a relatively perfect national WUS population registration research cohort database may be beneficial. This study, in collaboration with the Institute of Science and Technology for Brain-inspired Intelligence of Fudan University, aims to establish a predictive model for onset time and prognostic evaluation with the help of F-STROKE software.\(^\text{28}\) This will help provide evidence-based medical evidence for the diagnosis and treatment of patients who had a WUS and the selection of related techniques. Although some studies suggest that stroke after waking occurs in a short time before waking up,\(^\text{10}\) but big data research combined with imaging is still needed, especially in the Asian population. Moreover, if there is a faster and simpler method to estimate the time of stroke onset, we can more purposefully select the patient who need upscale imaging examination in the early stages of the disease because medical resources are in short supply in most countries, and choose better treatment methods for patients in places with poor medical conditions.

Major innovations of our study are: First, among patients who had a stroke of various stroke onset periods, we can estimate the onset time by combining their imaging data. In addition, we can analyse the impact of WUS on sleep–wake cycle, and further analysis will be done to determine the onset time of stroke. For example, early awakening phenomenon of patients who wake up earlier than the usual wake-up time in the WUS population may be related to stroke occurrence, or whether the stroke is a contributory factor that stimulates the early wake-up in patients.
Second, we propose the combined evaluation methods using three imaging parameters: DWI–FLAIR mismatch, collateral circulation and large vessel occlusion, in order to improve the accuracy of imaging evaluation of the onset time for WUS. Furthermore, we hope to document the risk factors influencing the prognosis and search for poor prognostic factors for patients with WUS. And on this basis, we can find the evaluation criteria that can be used for early warning signs through AI modelling. Together, we are expected to provide new insights for the selection of early warning signs, diagnosis and treatment methods and the relationship between different sensitivity points and basic CT findings, which will be more quickly and effectively for the selection of therapeutic strategies in patients with WUS.

However, this study has several limitations. In terms of sample selection, many seriously ill patients over 80 years who have a higher incidence of WUS will not be included in the study. Another limitation could be selection bias due to involvement of researchers from various centres and broad selection criteria. In terms of inclusion and exclusion criteria, the conditions are relatively broad, and more interference factors are not considered. In terms of prognostic evaluation, there are few indicators to be examined, and detailed cognitive evaluation will not be done in the follow-up.

Data availability statement
Assessments of functional scores and cognitive scales are completed by trained neurologists, and neuroimaging findings are independently judged by two imaging practitioners. During the study, clinical monitors will regularly verify the informed consent of the subjects, case reports and preservation of the raw data. This project is an observational cohort study with no expected adverse events. Standard follow-up training is required, and clinicians and health managers are required to network with patients.

ETHICS AND DISSEMINATION
Ethics approval
This study has obtained ethical approval from the ethics committee of Shanghai Pudong Hospital (ID number: GNXM-01) and rest of all participating centres, in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent
Written informed consent will be obtained based on the patient’s ability to provide written informed consent and the availability of a legal guardian/next of kin.

Dissemination
The findings of this study will be submitted for publication in a peer reviewed academic journal. Our results will also be disseminated through presentation at the conference.

Author affiliations
1Department of Neurology, Shanghai Pudong Hospital, Fudan University, Shanghai, China
2Department of Internal Medicine, Maharajgunj Medical Campus, Tribhuvan University Institute of Medicine, Kathmandu, Nepal
3Department of Neurology, Maharajgunj Medical Campus, Tribhuvan University Institute of Medicine, Kathmandu, Nepal
4Department of Radiology, Shanghai Pudong Hospital, Fudan University, Shanghai, China
5School of Pharmacy, Hubei University of Science and Technology, Hubei, China
6Department of Chronic Disease Management, Shanghai Pudong Hospital, Fudan University, Shanghai, China

Acknowledgements Thanks to the centres and all the members who participated in the multicentre registration of wake-up stroke in China (MCRWUSC) study. The authors thank MCRWUSC investigators for their participation in revising the protocol and collecting data. We thank the patient advisers for the information they provided.

Contributors SH and PJ designed the registry. ZZ and HY wrote the manuscript. ZT, QN, RO, YY, JO, MH and LZ revised the manuscript. CL and FL participated in revising the protocol and collected the data. All authors read and approved the manuscript. ZZ and HY contributed equally to this work.

Funding This work was supported by grants from the Research and Popularization of Appropriate Intervention Techniques for Stroke High-risk Groups in China by the Stroke Prevention and Treatment Engineering Committee of the National Health Commission (GN-2018R0008), Beijing Emerging Health Industry Development Foundation Project (XXCY2018-011) and the Key Discipline Project of Shanghai Pudong Hospital (Zdk2020-09).

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD
Zengyu Zhang http://orcid.org/0000-0002-2751-3901

REFERENCES
10 Thomalla G, Boutitie F, Fiebach JB, et al. Stroke with unknown time of symptom onset: baseline clinical and magnetic resonance...
imaging data of the first thousand patients in wake-up (efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomized, Doubleblind, placebo-controlled trial). Stroke 2017;48:770–3.


