Stroke in China: advances and challenges in epidemiology, prevention and management

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Abstract

With over 2 million new cases annually, stroke has the highest disability-adjusted life-years lost of any disease in China. The burden will increase further from population ageing, ongoing high prevalence of risk factors (e.g. hypertension), and inadequate management. Despite improved access to services, specialist stroke care is variable across the country, and especially patchy in rural areas. In-hospital outcomes have improved due to greater availability of reperfusion therapies and supportive care, but adherence to secondary prevention strategies and long-term care remains inadequate. Thrombolysis and stroke units are accepted as standard of care, but bleeding-risk concerns and organizational challenges hamper widespread adoption. Despite limited supporting evidence, Chinese herbal products and neuroprotective agents are widely used, while greater availability of neuroimaging results in over-diagnosis and over-treatment of ‘silent stroke’. Future efforts should focus on providing more balanced stroke services across the country, enhancing evidence-based practice, and encouraging greater translational research.
Introduction

Stroke is the second leading cause of death in the world and the leading cause of death in China,\textsuperscript{1,2} where one fifth of world’s population reside with very high rates of stroke.\textsuperscript{3} An earlier review, which summarised existing data on the epidemiology, prevention and management of stroke in China before 2007, called for further research to update the knowledge of burden, characteristics and practice patterns.\textsuperscript{4} Subsequently, a surge in research on stroke has occurred in China over the last decade, leading to better understanding of its causes, and advances in prevention and management.\textsuperscript{5–12} On the other hand, evidence-based stroke care has been incorporated in the healthcare system and in-hospital outcomes have improved, with no increase in mortality despite the rising prevalence and incidence in the past decade.

In this Review, we provide an update on the epidemiology, prevention, and management of stroke in China. We focus on modifiable risk factors and interventions that are affordable and potentially widely applicable for prevention and treatment in China. We identify gaps in delivery of evidence-based stroke care, and elucidate possible reasons for such gaps. We also explore the variations in stroke care across the country that are different from the high-income countries.\textsuperscript{13} Based on current progress and ongoing challenges, we provide suggestions for policy makers and healthcare providers to mitigate, or even reduce, the rising burden of stroke in China.

Epidemiology

Nationwide studies and periodic governmental reports indicate a high and increasing burden of stroke (Figure 1).\textsuperscript{5,6,14,15} For example, the National Epidemiological Survey of Stroke in China (NESS-China) involved 480 687 individuals (age $\geq$20 years) from 31 provinces between 2012-2013, reporting the age-standardised stroke prevalence of 1115/100 000 people, annual age-standardised (per 100 000) incidence and mortality of 247 and 115, respectively.\textsuperscript{5} These data indicate there were an estimate of 11 million prevalent cases of stroke, 2.4 million new strokes and 1.1
million stroke-related deaths annually in China. The China National Stroke Screening Survey conducted between 2013-2015 reported higher stroke prevalence and incidence in an older segment of population (age ≥40 years) compared to the NESS-China study. These data highlight a marked increase in stroke prevalence and incidence, with a generally stable mortality, compared with the rates reported last decade. Such temporal trends are comparable to the general trend of low-to-middle income countries (LMICs) where the stroke incidence is increasing, in contrast to the decreased incidence in high-income countries (Figure 1). Given that China has the highest number of prevalent cases of stroke in the world, more vigorous and effective actions are needed to reduce the burden of stroke.

In China, the prevalence of stroke still surpasses ischaemic heart disease; however, the Healthcare Access and Quality (HAQ) index ranks stroke as the second lowest among all preventable diseases in China, indicating an inadequate social and medical investment to stroke compared to other diseases. Since stroke incidence and mortality rates increase with age, the absolute number of patients who have and die from stroke will increase steadily as the Chinese population continues to grow and age, which will further increase the pressure on the Chinese health system.

Over half of the Chinese population live in rural areas, where stroke incidence is higher than in urban areas (298 vs. 204/100 000 person-years). The prevalence of stroke in rural areas has increased sharply in recent 10 years, whilst in urban areas the rate is relatively stable (Figure 2A). The substantial increase in rural prevalence probably reflects a rising incidence of stroke as well as an increased detection of cases. In contrast, stroke mortality is stable over the past 20 years, which is consistently higher in rural than urban areas (Figure 2B). There is a North-to-South geographical gradient in stroke incidence and mortality, with rates being highest in the Northeast and lowest in the South of China. However, the mortality-to-incidence ratio (MIR) of stroke estimated based on data from the NESS-China study shows a different pattern, with the highest MIR in Southwest and the lowest in Eastern and Southern coast (Figure 3A). These regional differences in MIR indicate striking disparities in both
access and quality of stroke care across the country; this is consistent with the regional distribution pattern of the HAQ index of stroke (highest in Beijing, lowest in Tibet). The distribution of MIR and HAQ is associated with variation in the proportion of registered medical doctors per 1000 of the population, being highest in the Northern and Eastern and lowest in Southwest of China (Figure 3B); and in the proportion of secondary and tertiary hospitals that have certified stroke centres, being relatively high in Eastern and Southern, and low in Northeast and Western China (Figure 3C). Since the reported MIR is based on a secondary analysis of published data, more reliable data from the original studies are needed to confirm these observed discrepancies in MIR between and within regions, and to explore the underlying reasons.

Risk factors and primary prevention

Hypertension, dyslipidaemia, diabetes, smoking, alcohol consumption, air pollution, dietary intakes low in fruit and vegetables, and high intake of sodium are the most common and modifiable risk factors for stroke in China. Hypertension, the single most important modifiable risk factor of stroke, was estimated to affect approximately 300 million adults in China between 2013-2014 (prevalence 28%), which represents an almost 50% increase from 153 million estimated in 2002. A geographical gradient is noted in the prevalence of hypertension, highest in Northern and Eastern China. While improved, patient awareness, treatment and control of hypertension are encouraging, the proportion of people whose hypertension is controlled remains under 20% in China, considerably lower than the UK and US. It is likely that these figures are lower in rural areas, despite an absence of a clear urban-rural difference in the prevalence of hypertension. Similarly, dyslipidaemia (prevalence 34%) and diabetes (prevalence 11%) are prevalent and poorly controlled in China, both associated with an increased risk of stroke. The rates of prevalence, awareness, treatment and control are lower in rural than urban areas for both conditions. New evidence has emerged from large prospective studies about the relevance of a range of lifestyle factors for stroke in Chinese adults, which may account for the
North-to-South gradient of stroke. Smoking and excessive alcohol consumption contribute to an increased risk of stroke in China, particularly among men in whom up to two thirds smoke and over one third drink regularly, compared with <5% in women.7, 8 High rates of smoking and alcohol consumption in the Northeast correlate with high incidence and mortality for stroke.5 Note that smoking prevalence has been consistently high in the past decade, and is higher in rural than urban residents.23 Air pollution continues to be a great public health challenge in China, with the second highest level of PM$_{2.5}$ fine particulate matter among 79 countries, and PM$_{2.5}$ has been consistently increasing over the last 20 years.24 Compared with clean fuels, the domestic use of solid fuels, which is popular in rural areas, is an important source for PM$_{2.5}$ and is associated with higher stroke mortality.25 While the stroke mortality attributable to PM$_{2.5}$ has decreased at a national level, the high mortality belt has gradually moved from Northern and Western China to Central and Southwest regions in recent 20 years.26 The traditional Northern Chinese diet (characterised by high intake of refined cereal products and salted vegetables) is associated with an elevated risk of stroke, as compared to the traditional Southern Chinese diet (characterised by high intakes of rice, vegetables and fruit, and less salt).27 Although personal daily consumption of vegetables and fruit of Chinese residents has gradually increased since 1980s, it is still below national recommended levels, and consistently lower in rural than urban areas.28 Sodium intake is associated with increased risk of both hypertension and stroke, of which the daily individual intake in the North of China is about twice of that in the South.29 Given the high prevalence of hypertension and stroke in Northern China, a cluster randomised controlled trial is underway evaluating a potentially widely applicable intervention, a potassium enriched, low-salt substitute, for the prevention of stroke across 600 villages in 5 Northern provinces (NCT02092090). Other regional-specific interventions that should be promoted may include more intensive smoking restrictions in the smoking belt in Northeast, Northern and Central China,23 the promotion of clean fuels in rural areas,25 and increasing the supply of fresh vegetables and fruit in North.27
The present high rates of stroke indicate that the impact of primary prevention strategies is unsatisfactory. Poor control of hypertension, high prevalence of smoking and alcohol consumption, and unhealthy diet and lifestyles in Northern regions and rural areas likely contribute to the high rates of stroke in China. Better control of risk factors requires not only more effective public education and greater responsibilities of individuals, but also changes in government laws and regulations related to taxation, advertising, urban development and construction of healthy cities. For example, the Chinese government launched a programme of Stroke Screening and Intervention for High-risk Population in 2011, as part of a national non-communicable diseases (NCDs) programme, where 6 million people across 31 provinces have been screened for vascular risk factors by 2016 and nearly 1 million high-risk individuals have received appropriate intervention. In 2017, the State Council of China released a national medium- to long-term plan on the prevention and treatment of NCDs, with an aim to reduce the mortality of cardiocerebrovascular diseases by 15% by 2025, through an emphasis on promoting healthy lifestyles, public education, early screening for chronic diseases, and the development of national platforms for quality control of healthcare. Stroke societies (Panel 1) have been actively leading the activities against stroke, particularly since the foundation of the Chinese Stroke Society in 2002. In conjunction with the World Stroke Organisation, the Chinese Stroke Society, the Chinese Stroke Association, and other stroke initiatives have vigorously organised professional members across the country to provide regular public education, maximised around the ‘World Stroke Day’.

**Stroke aetiology**

Reliable assessment of pathological and aetiological subtypes of acute stroke is pivotal to instituting appropriate treatment and secondary prevention for the individual patient. However, data specifically pertaining to Chinese patients is scarce or too diverse to be conclusive, but more reliable data are now available from large community- and hospital-based studies. A nationwide community-based study indicates that ischaemic stroke accounts for approximately 70% of all incident stroke
cases, with intracerebral haemorrhage (ICH) and subarachnoid haemorrhage in 24% and 4%, respectively, and 2% are undetermined or other types; these proportions are similar to multicentre hospital-based studies. Although the proportional frequency of ICH among patients with stroke is higher in Chinese than Western populations, there is a wide variation across the country, being higher in the Central and lower in coastal regions. A dramatically high proportion of ICH has repeatedly been reported in Changsha, a city in Central China, over the last 20 years, for reasons still not fully understood. Hospital-based studies have revealed a variation in the aetiological subtypes of acute ischaemic stroke (according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification), with a general trend of increase in large arterial atherosclerosis (LAA) and decline in undetermined subtype over the past 10 years (appendix). This trend is in line with other Asian populations, and likely reflecting an increased access to vascular imaging. The proportion of ischaemic stroke due to small-artery occlusion is about 30% on average and even higher specifically for lacunar infarction, whereas the proportion of cardioembolic stroke remains low in Chinese patients (about 10%) compared to those in Western populations (30%) (appendix). This may be due partly to the under-diagnosis of atrial fibrillation (AF) in Chinese patients. The wide variation in the aetiological subtypes of stroke may be explained by the discrepancies in study design, subtype definitions actually used, and time periods across studies. Future large-scale studies are needed to provide more reliable and precise data on the proportion of aetiological subtypes and temporal changes, by performing repeated assessments in the same stroke population across different time periods.

Subtypes of ICH are less well reported than ischaemic stroke. One multicentre study assessed aetiological subtypes of non-traumatic ICH and reported that hypertensive angiopathy was the most common aetiology, followed by undetermined subtype, cerebral amyloid angiopathy, vascular structural lesions, medication-derived haemorrhage, and systemic diseases. Largely consistent with a study in Taiwan,
these findings suggested that Chinese people have higher proportions of hypertensive angiopathy and structural lesions, and lower proportions of medication-derived haemorrhage and cerebral amyloid angiopathy, as compared with Western populations.44

Patients with stroke or those who die from stroke in LMICs including China are younger than patients in high-income countries, reflecting partly difference in demography and risk factors of different populations.3, 45 This may explain the lower proportion of cardioembolic stroke and cerebral amyloid angiopathy in China. The low proportion of medication-related ICH in China42, 43 may be due to the under-use of anticoagulation and thrombolysis in practice. Given ongoing ageing of the population, and a foreseeable increase in the use of bleeding-risk treatment for indicated individuals in future, cerebral amyloid angiography and medication-related ICH are likely to increase. In addition, evidence is consistently highlighting the higher proportional frequency of ICH33, 34 and small-artery occlusion35-39 in Chinese patients, which share the common underlying mechanism of hypertension-related acute cerebral small vessel diseases, and their features and management are currently investigated in observational studies (ChiCTR-OOC-17010562, ChiCTR-COC-17013056).

**Neuroimaging and diagnosis of stroke**

Non-contrast CT is widely available in hospitals in China, where around 90% of patients with ischaemic stroke receive brain CT (Table 1), while about 50% of patients receive MRI.46 As neuroimaging is increasingly being used for routine health screening and in general clinic checkups in cities (e.g. CT, MRI or ultrasound for headache or dizziness), the increased imaging detection of silent pathological signs can cause over-diagnosis of stroke and challenge doctors in their decision over the prescribing of medicines for secondary prevention. For example, about one fifth of community-dwelling Chinese residents (≥20 years) have silent cerebral infarcts on brain CT or MRI,5 10% have silent cerebral microbleeds on MRI,47 and approximately one third have carotid atherosclerotic plaques on ultrasound
assessment. If these silent pathological signs are misinterpreted as cerebral infarcts or even overt stroke, it can lead to the over prescribing of aspirin and statins, which may also influence the reporting of stroke for epidemiological data on the surveillance of stroke rates. Whether silent cerebral infarcts should be actively treated with aspirin for secondary prevention is under investigation (NCT03318744) and studies for asymptomatic carotid plaques are ongoing (appendix).

**Management of acute stroke**

The Chinese Stroke Society and the Chinese Society of Neurology have together published a series of national clinical guidelines to promote evidence-based stroke care, while two ongoing nationwide register platforms serve to monitor and evaluate the quality of stroke care: the National Stroke Centre of the Stroke Prevention and Control Project Committee (since 2012), and the China Stroke Centre Alliance of the Chinese Stroke Association (since 2015). Other stroke registers have also provided data on the quality of stroke care in China (Table 1), which indicate that the use of evidence-based therapies (i.e. stroke unit care, thrombolysis, antiplatelet, lipid lowering agents, antihypertensives, and anticoagulation) have gradually increased over the past 20 years, although therapies with high perceived risk of bleeding (e.g. thrombolysis and anticoagulation) and those require specific facilities (i.e. stroke unit) and skills (e.g. decompressive hemicraniectomy) are still underused. We discuss management of stroke in the order how patients with stroke are cared in clinical practice.

**Acute management of ischaemic stroke**

Antiplatelets and statins are the most commonly prescribed medications in acute phase of ischaemic stroke in China, where about 90% of patients commence antiplatelet treatment within 48 hours after admission and are maintained on this at discharge. Statins prescribed to hospitalised patients with stroke has dramatically increased in the past 20 years. Despite limited evidence for their efficacy, Chinese herbal products, neuroprotective agents and dehydrating anti-cerebral oedema agents
are widely used in clinical practice. Several studies are underway to clarify the
efficacy of Chinese herb products and neuroprotective agents in acute stroke
(appendix). While stroke unit care is an accepted standard of care to produce
favourable outcomes, there are only few studies investigating its utilisation and
organisation in China. Whether the facilities and quality of care of Chinese stroke
units meet the international standards is uncertain; a study showed that only one third
of patients with stroke receive such care, and even fewer receive care that satisfy
key organisational and staffing parameters. There is limited data on decompressive
hemicraniectomy and post-discharge rehabilitation. Although the safety and
efficacy of mechanical clot retrieval has been well established in several randomised
controlled trials, minimum standards of training and quality control reporting have yet
to be established in China.

Effective therapies for hyperacute treatment of ischaemic stroke rely on timely
restoration of blood supply to salvageable brain tissue. Currently, only 20% of
patients with stroke are admitted to hospital within 3 hours in China (Table 1).
Delays in admission are associated with several factors, particularly that of early
recognition of the symptoms of acute stroke. Only about one in five patients
recognise the initial symptoms as stroke and a similar proportion call an emergency
number. To address this issue, a stroke 1-2-0 educational programme was launched
in China, and efforts to increase public awareness of core stroke symptoms are
ongoing (NCT03167346). Many cities and provinces have released a stroke map to
facilitate patients to locate the nearest stroke centre, which has been widely
disseminated to the public through mass and social media. In addition, a national
telestroke centre platform has been initiated in 2014 and the nationwide network is
under construction to guide timely stroke care in rural hospitals. Less than 3% of
Chinese patients with ischaemic stroke received intravenous thrombolysis, much
lower than that in high-income countries, as reported in two studies recently published
in 2018 (Table 1). Although admission delay is an explanation for this, the
treatment is given to less than 20% of eligible patients (Table 1). Apart from the high
personal cost, the main reason for such under-use of intravenous thrombolysis is an excessive concern over the bleeding risk among patients, families and doctors.\textsuperscript{58} It should be noted that these data possibly underestimate the current situation, because the above studies were completed in 2015.\textsuperscript{55, 57} Given the promising results of late-window reperfusion trials,\textsuperscript{65-67} Chinese doctors are now cautiously applying intravenous thrombolysis and endovascular interventions to a broader range of eligible patients. Therefore, the proportion of patients who have received reperfusion therapies in practice may be higher than the rate reported in the existing studies, which needs to be updated.

\textit{Acute management of ICH}

Approximately two thirds of Chinese patients with ICH receive early antihypertensive therapy and 10\% receive some type of neurosurgical intervention.\textsuperscript{68} Open surgery for haematoma evacuation and minimally invasive surgery are conducted in many hospitals with neurosurgery in cities, while the latter is more widely used in local hospitals where the access to neurosurgery is limited.

\textit{Secondary prevention}

Medications for secondary prevention are initiated in hospital for most patients with stroke but adherence is poor among community-dwelling patients with stroke.\textsuperscript{69-71} For example, in a multicentre observational study with 1913 patients with minor ischaemic stroke, 92\% (835/905) of patients with LAA, 91\% (421/461) of patients with small-artery occlusion, and 72\% (63/88) of patients with cardioembolic stroke received antiplatelet in hospital, but less than half of these patients on medication in hospital maintained the medication one year later.\textsuperscript{72} Socioeconomic factors are one of the main reasons precluding long-term use of such treatment, including inadequate health insurance and reimbursement policies, and unawareness of the need for long-term use of these medications by patients and doctors.\textsuperscript{69, 71} More research is required to explore strategies to improve cost-effectiveness and adherence to the secondary prevention of stroke.\textsuperscript{73} For example, using a single pill that contains several
cardiovascular medications for secondary prevention is a promising strategy to improve the adherence, since over 90% of stroke patients in community require at least two types of medication for secondary prevention.\textsuperscript{74}

About 2\% of Chinese adults aged over 40 years have AF, which is increased from <1\% noted 10 years earlier.\textsuperscript{75} About 10\% of Chinese patients with stroke had AF in previous reports,\textsuperscript{76} but this proportion may be higher in a study based on Holter electrocardiogram monitoring over 6 days after admission.\textsuperscript{77} However, prolonged cardiac monitoring for patients with stroke is scarcely used in practice, despite recommendations by Chinese and international guidelines, which possibly results in the under-diagnosis of AF. The proportion of patients with ischaemic stroke and AF who receive oral anticoagulation in hospital or at discharge is steadily improving, with 30\% receive anticoagulants by discharge but only 10\% at one year after stroke; in contrast, over 60\% of patients with stroke and AF receive antiplatelets in hospital, despite a decrease by 10\% in the use over the past 10 years (appendix).\textsuperscript{57, 72, 76, 78-82}

The community-dwelling patients also have the preference for use of antiplatelets over oral anticoagulants, where only 2\% of patients receive anticoagulants, mostly warfarin and fewer than 2\% on novel oral anticoagulants.\textsuperscript{81} The main reason for the under-use of oral anticoagulation is the concern over bleeding risk, by both doctors and patients, which is considered much higher in Asians than other populations.\textsuperscript{83}

The total number of carotid angioplasty and stenting performed for patients with carotid atherosclerosis in China has increased over the past decade. In 2016, 9310 patients received carotid stenting among 100 selected Chinese hospitals with advanced interventional facilities, which is greater than the 3668 patients who received carotid endarterectomy.\textsuperscript{84} Unlike the West where extracranial carotid atherosclerosis is more common, Chinese people have a greater prevalence of intracranial atherosclerosis.\textsuperscript{85} This leads to active exploration of better targeting of those who may benefit more than others from intra-arterial interventions, where the safety has been shown in small studies\textsuperscript{86} and more trials are ongoing (appendix).

\textit{Rehabilitation}
A three-stage rehabilitation network for stroke was launched in China in early 2000s. Since then, the proportion of stroke patients who receive in-hospital rehabilitation assessment has increased, and often considered part of routine stroke care. Yet, still about 40% of patients do not have access to rehabilitation in hospital (Table 1), and of whom do receive some type of therapy, it is most often acupuncture, passive massage, or isolated physical therapy for motor function, with only a small proportion of patients received formal physiotherapy, occupational therapy, speech-language therapy, or psychotherapy. This may imply there are neglected areas of training for stroke rehabilitation in China, related to input to maximise recovery in cognitive, language and emotional function, with psychological support an apparent high need for Chinese stroke patients. About 20% of patients receive outpatient rehabilitation after hospital discharge, but there is uncertainty over whether and to what extent there is any professional guidance. The research evidence on rehabilitation is scarce and needs further investigation.

**Outcomes after stroke**

Hospital-based studies provided data on outcomes within one year after stroke, which were not available previously. For acute ischaemic stroke, the reported case fatality increases from <5% at 1 month to 10% at 3 months and 15% at 1 year, and about one third of patients are dead or disabled by 3 months and at 1 year (appendix). The continuously increased risk of death over the year after stroke emphasises the need to explore the causes of death and improve care for severe stroke, which is under investigation in Chinese patients (NCT03222024). For ICH, the reported case fatality varies from about 10% at 1 month to 25% at 3 months and 30% at 1 year (appendix). About half of patients with ICH are dead or disabled at 1 month and 3 months and the proportion slightly decreases by 1 year.

With consistent albeit slow improvement in the quality of stroke care, outcomes for patients with stroke have gradually improved over the last decade. Such improvement in outcome is reflected in the stable stroke mortality over the past 30 years despite an increase in incidence. Generally, prognosis for patients with acute
stroke appears to be better in China than in Western countries, in part related to differences in demography (younger age) and milder neurological severity and pathological subtypes compared to patients with stroke in Western countries. The earlier occurrence of stroke in Chinese people than Western populations may be related to unhealthy lifestyle in young Chinese such as high prevalence of adolescent smoking and alcohol drinking. However, the data of stroke outcomes in Chinese patients might be biased in relation to referral patterns to hospitals, mainly tertiary care, which are located in big cities, and where there is greater access to health and other services compared to rural areas in China. Thus, the case fatality and functional outcome patterns might have an under-estimate, and more data are required across time and regions, particularly rural areas.

**Conclusions and future directions**

The prevalence and incidence of stroke are increasing, and there are substantial geographical and rural-urban variations in rates, reflecting the regional disparities in the prevalence of risk factors, and access and quality of stroke care in China. Public awareness for healthy lifestyles and the control of risk factors are still suboptimal and needs further intensive action. The increasing use of imaging technology raises challenges for diagnosis and treatment of silent pathological signs. Chinese patients with stroke are younger and have more small vessel and intracranial atherosclerotic diseases, compared to Western patients. Stroke outcome appears to be improved over the past 10 years, in line with the stable stroke mortality despite an increase in incidence, possibly due to the improved in-hospital stroke care.

However, a number of challenges remain and require further research and action (Panel 2, 3). Although a framework of evidence-based stroke care has been incorporated in the existing health system, how well organisational and staffing requirements are being met and of the implementation of interventions are generally unknown. Evidence-based stroke care has improved in urban areas, particularly for interventions with low risk of adverse effects. Neuroprotective agents and Chinese herbal products, although with limited evidence of efficacy, are commonly used. In
contrast, stroke unit care and other proven interventions are under-used, often due to organisational challenges and unnecessarily high perceived risk. Early secondary prevention and rehabilitation in hospital have improved, but long-term adherence is unsatisfactory. As most stroke research has been done in urban areas, there are limited data on treatment patterns and stroke outcomes in rural areas. In addition, there is no detailed data on community-based stroke care. To fill these evidence-practice gaps, an increasing number of studies on stroke management are ongoing (appendix). Coordinated efforts from government, local and hospital leaders, and doctors are required to support more high-quality research, and to provide more balanced resources and evidence-based stroke care across the country, with sensitivity to the specific needs of regions.
Search strategy and inclusion criteria

Panel 1: Stroke societies and initiatives in China
- Chinese Stroke Society (founded in 2002), affiliated to Chinese Medical Association
- Stroke Prevention and Control Society (founded in 2010), affiliated to Chinese Preventative Medicine Association
- Stroke Prevention and Control Project Committee (founded in 2012), affiliated to National Health Commission
- Chinese Stroke Association (founded in 2015), affiliated to China Association for Science and Technology

Panel 2: Research priorities for stroke in China
- More research in community and rural areas to explore stroke outcome and management patterns, in order to allow comparisons between patients in urban and rural areas, and between China and the West
- Longitudinal studies with repeated assessments at different time periods in the same group of patients to explore temporal trends of risk factors, treatment patterns, and stroke outcomes
- Prospective studies and clinical trials for the natural history and management of silent cerebral infarcts and asymptomatic carotid plaques
- Studies for aetiology and management of small cerebral vessel diseases, including intracerebral haemorrhage
- Data is needed on the current status of the implementation of emergency services and stroke unit care according to certain quality standards
- Providing evidence for the development of accessible and cost-effective strategies for long-term secondary prevention and rehabilitation
- Early identification of patients at particularly high risk of bleeding to more precisely implement individualised treatment on blood flow restoration
- High quality clinical trials are required to address the uncertain efficacy of widely used Chinese herb products and neuroprotective agents

Panel 3: Regional-specific needs to combat stroke in China
The nationwide needs to combat stroke in China, particularly in certain regions:
- Northeast China: more intensive action to control hypertension and smoking and alcohol drinking, and to promote diet with low sodium and high fruit and vegetables
- Northern China: more intensive action to promote diet with low sodium and high fruit and vegetables
- Central China: more intensive action to control smoking and air pollution; more research to explore mechanisms underlying high prevalence of intracerebral haemorrhage
- Southwest China: more investment to improve access and quality of stroke care; more intensive action to control hypertension and air pollution
<table>
<thead>
<tr>
<th>Study period</th>
<th>Participants</th>
<th>Admission time</th>
<th>CT accessibility</th>
<th>Stroke unit care</th>
<th>Intravenous thrombolysis</th>
<th>Antiplatelet</th>
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</thead>
<tbody>
<tr>
<td>Chen 1997**</td>
<td>1095 doctors from 247 hospitals</td>
<td>1993-1994</td>
<td>88% (683/775)</td>
<td>30.3% (1449/4782)**</td>
<td>4% (41/1095)†</td>
<td>54% (590/1095)†</td>
</tr>
<tr>
<td>Chengdu Stroke Registry*</td>
<td>2070 patients with ischaemic stroke</td>
<td>2002-2006</td>
<td>&lt;3h: 10.3% (214/2070)</td>
<td>&lt;3h: 21.3%</td>
<td>0.9% (20/2070)</td>
<td>83.0% (1719/2070)</td>
</tr>
<tr>
<td>ChinaQUEST*</td>
<td>4783 patients from 62 hospitals</td>
<td>2006</td>
<td>&lt;3h: 21.3%</td>
<td>89.2% (4267/4782)**</td>
<td>1.9% (91/4783)</td>
<td>80.6% (3853/4783)</td>
</tr>
<tr>
<td>CNSR I*</td>
<td>12173 patients from 131 hospitals</td>
<td>2007-2008</td>
<td>&lt;6h: 21.6% (448/2070)</td>
<td>&lt;3h: 21.5% (2514 of known time)**</td>
<td>0.98% (120/12173) of all patients;</td>
<td>&lt;48h: 80.3% (9706/12090) of eligible patients</td>
</tr>
<tr>
<td>CNSR II*</td>
<td>19604 patients from 219 hospitals</td>
<td>2012-2013</td>
<td></td>
<td>1.23% (243/19604) of all patients;</td>
<td>10.0% (120/1203) of eligible patients</td>
<td>&lt;48h: 84.6% (16149/19093) of eligible patients</td>
</tr>
<tr>
<td>INTERSTROKE**</td>
<td>5859 patients from upper-middle income countries (3987 from China)*</td>
<td>2007-2015</td>
<td></td>
<td></td>
<td>2.9% (168/5859)</td>
<td>Discharge: 71.0% (8285/11677) of eligible patients</td>
</tr>
<tr>
<td>GOLDEN BRIDGE-AIS*</td>
<td>4800 patients from 40 hospitals</td>
<td>2014-2015</td>
<td></td>
<td></td>
<td></td>
<td>62.5% (25/40) of hospitals</td>
</tr>
</tbody>
</table>

Control group: 0.95% (23/2400) of all patients; 11.3% (23/204) of eligible patients
Discharge: 96.7% (2253/2330) of eligible patients
Discharge: 92.9% (2141/2305) of eligible patients
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Chen 1997&lt;sup&gt;99&lt;/sup&gt;</th>
<th>Chengdu Stroke Registry&lt;sup&gt;99&lt;/sup&gt;</th>
<th>ChinaQUEST&lt;sup&gt;99&lt;/sup&gt;</th>
<th>CNSR I&lt;sup&gt;98&lt;/sup&gt;</th>
<th>CNSR II&lt;sup&gt;98&lt;/sup&gt;</th>
<th>INTERSTROKE&lt;sup&gt;98&lt;/sup&gt;</th>
<th>GOLDEN BRIDGE-AIS&lt;sup&gt;97&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid lowering</td>
<td>...</td>
<td>11.9% (246/2070)</td>
<td>30.2% (1444/4783)</td>
<td>42.6% (2402/5634)</td>
<td>66.3% (8475/12791)</td>
<td>72.1% (4222/5859)</td>
<td>Control group: 93.0% (1439/1547) of eligible patients</td>
</tr>
<tr>
<td>Chinese herb products</td>
<td>66% (728/1095)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>89.7% (1857/2070)</td>
<td>79.1% (3784/4783)</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Neuroprotective agents</td>
<td>...</td>
<td>68.1% (1410/2070)</td>
<td>75.9% (3632/4783)</td>
<td>...</td>
<td>...</td>
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</tr>
<tr>
<td>Glycerol or manitol</td>
<td>69% (750/1095)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>23.5% (486/2070)</td>
<td>intravenous diuretics</td>
<td>...</td>
<td>...</td>
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<td>...</td>
</tr>
<tr>
<td>Anti-hypertension</td>
<td>33% (365/1095)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>33.9% (702/2070)</td>
<td>61.6% (2945/4782)</td>
<td>56.4% (4620/8196)</td>
<td>65.6% (9684/14758)</td>
<td>66.2% (3881/5859)</td>
<td>Control group: 77.5% (1372/1771) of eligible patients</td>
</tr>
<tr>
<td>immediately after admission</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>1% (11/1095)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>14.2% (52/366)</td>
<td>11.8% (37/314)</td>
<td>19.7% (221/1124)</td>
<td>21.0% (332/1578)</td>
<td>...</td>
<td>Control group: 28.5% (39/137) of eligible patients</td>
</tr>
<tr>
<td>In-hospital rehabilitation</td>
<td>...</td>
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<td>...</td>
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<td>...</td>
</tr>
<tr>
<td>Decompressive hemicraniectomy</td>
<td>...</td>
<td>14.2% (31/219)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

ChinaQUEST: The China QUality Evaluation of Stroke care and Treatment (QUEST) study; CNSR: China National Stroke Registry; CT: computed tomography; GOLDEN BRIDGE-AIS: Intervention to Bridge the Evidence-based Gap in Stroke Care Quality; TIA: transient ischaemic attack. <sup>†</sup>For each study, the report with most relevant data was included as the main report and was cited along with the study ID. When the data were unavailable in the main report, data were extracted from other relevant reports of the study with the reference cited with the corresponding data. <sup>‡</sup>The proportion of doctors who would routinely provided the therapy after admission to patients with ischaemic stroke.
Figure legends

Figure 1 Prevalence, incidence, and mortality of stroke in China compared with low- to middle-income countries and high-income countries

Prevalence data are the crude prevalence of cerebrovascular diseases in Chinese people of all ages (due to absence of age-specific prevalence) per 100 000 people. Sample size: year 1993 [215 163 people], 1998 [216 101], 2003 [193 689], 2008 [177 501], and 2013 [273 688]. Incidence data are age-standardised stroke incidence in Chinese people aged 40-74 years (standardised by China census population 2000), per 100 000 person-years. Sample size: year 2013 [633 859 people] and 2014 [726 451]. Mortality data are age-standardised mortality of cerebrovascular diseases in Chinese people of all ages (standardised by China census population 2010), per 100 000 person-years. Sample size is based on the national population: year 2003 [1292 million people], 2004 [1300 million], 2005 [1308 million], 2006 [1314 million], 2007 [1321 million], 2008 [1328 million], 2009 [1335 million], 2010 [1341 million], 2011 [1347 million], 2012 [1354million], 2013 [1361 million], 2014 [1368 million], and 2015 [1375 million]. Data in side panels from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010.

Figure 2 Prevalence and mortality of stroke in urban and rural areas of China

(A) Prevalence data are the crude prevalence of cerebrovascular diseases in Chinese people of all ages (due to lack of age-specific prevalence, per 100 000 people); (B) Mortality data are age-standardised mortality of cerebrovascular diseases in Chinese people of all ages (standardised by China census population 2010, per 100 000 person-years).

Figure 3 Geographical distribution of mortality-to-incidence ratio, coverage of registered medical doctors, and proportion of hospital with stroke centre in secondary or tertiary hospitals in China

(A) Mortality-to-incidence (MIR) ratio for 7 geographical regions of China was calculated from the incidence and mortality data of stroke in the National Epidemiological Survey of Stroke in China (NESS-China). (B) Doctor coverage (per 1000 people) was calculated from the number of registered medical doctors and the population in each of the 31 provinces and municipalities in mainland China. (C) Number of certified stroke centres was retrieved from the websites of the National Stroke Center and the China Stroke Center Alliance, which are two qualified organisations to officially certify stroke centres in China. The number of secondary or tertiary hospitals was extracted from the National Bureau of Statistics of China.
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ML, SW, BW, PS, WW, and ZC conceived the review. ML designed and drafted the outline of the review and coordinated the writing process. SW, CW, YW, and YC performed the literature search, data collection, analysis and checking, and developed tables and figures. ML, SW, and BW evaluated the quality of the included studies, wrote the first draft, and revised each version of the manuscript. YW, YH, LC, CP, JJ, TZ, XL, SZ, PX, DF, XJ and K-SW provided necessary data and commented the manuscript. ML, ZC, CA, PS and LW interpreted data and revised the manuscript. All authors contributed to critical appraisal for important intellectual content, provided relevant research data, and approved the final version.

Declaration of interests

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