Neurological diseases in China 1

Traumatic brain injury in China

Ji-Yao Jiang, Guo-Yi Gao, Jun-Feng Feng, Qing Mao, Li-Gang Chen, Xiao-Feng Yang, Jin-Fang Liu, Yu-Hai Wang, Bing-Hui Qiu, Xian-Jian Huang

Lancet Neurol 2019; 18: 286–95

See Comment page 228

This is the first in a Series of four papers about neurological diseases in China

Department of Neurosurgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China (Prof J-Y Jiang MD, Prof G-Y Gao MD, J-F Feng MD, Q Mao MD); **Department of Neurosurgery, The Affiliated Hospital of Southwest Medical University, Luzhou, China** (Prof L-G Chen MD); **Department of Neurosurgery, First Affiliated Hospital, Zhejiang University, Hangzhou, China** (Prof X-F Yang MD); **Department of Neurosurgery, Xiangya Hospital, Southcentral University, Changsha, China** (Prof J-F Liu MD); **Department of Neurosurgery, Wuxi Taihu Hospital, Wuxi, China** (Prof Y-H Wang MD); **Department of Neurosurgery, Southern Hospital, Southern Medical University, Guangzhou, China** (Prof B-H Qiu MD); **and Department of Neurosurgery, The First Affiliated Hospital of Shenzhen University, Shenzhen, China** (X-J Huang MD)

Correspondence to: Professor Ji-yao Jiang, Department of Neurosurgery, RenJi Hospital, School of Medicine, Shanghai Jiao Tong University. Shanghai 200127, China.
jiyaojiang@126.com

China has more patients with traumatic brain injury (TBI) than most other countries in the world, making this condition a major public health concern. Population-based mortality of TBI in China is estimated to be approximately 13 cases per 100 000 people, which is similar to the rates reported in other countries. The implementation of various measures, such as safety legislation for road traffic, establishment of specialised neurosurgical intensive care units, and the development of evidence-based guidelines, have contributed to advancing prevention and care of patients with TBI in China. However, many challenges remain, which are augmented further by regional differences in TBI care. High-level care, such as intracranial pressure monitoring, is not universally available yet. In the past 30 years, the quality of TBI research in China has substantially improved, as evidenced by an increasing number of clinical trials done. The large number of patients with TBI and specialised trauma centres offer unique opportunities for TBI research in China. Furthermore, the formation and development of research collaborations between China and international groups are considered essential to advancing the quality of TBI care and research in China, and to improve quality of life in patients with this condition.

Introduction

More than 50 million people have a traumatic brain injury (TBI) each year worldwide, with approximately half the world's population likely to have one or more TBIs over the course of their lifetime.[1] At the end of 2017, China had a population of more than 1·39 billion, representing approximately 18% of the world population. The absolute numbers of patients with TBI in China exceed those of most other countries, causing a huge burden to society and families.[1]

Road traffic incidents are the most common cause of TBI in China.[1] However, over the past three decades, several road traffic safety measures have been implemented, correspondingly reducing rates of traffic-related TBI.[1] Additionally, since the 1980s, the care of patients with TBI has substantially improved as a result of enhanced brain monitoring technology, implementation of new guidelines for management of TBI, and additional neurosurgical training programmes.[1] A greater number of resources (such as financial support from the government) and modern facilities (such as specialised trauma centres) with neurosurgical intensive care units, intracranial pressure monitors, CT, MRI, digital subtraction angiography, and EEG are now available, further improving care of patients with TBI.[1] However, implementation of these various measures has not been widespread and there are large regional differences within China (ie, mostly rural *vs* urban areas, and western *vs* eastern China) due to differences in access and quality of health care.[1] Compared with high-income countries, China has fewer preventive strategies to combat TBI and fewer clinical trials in patients with TBI.[1] However, TBI research in China is changing and moving from retrospective clinical data analyses to prospective randomised controlled trials.

This Review covers the epidemiology, advances in treatment options, and prospects for future research in TBI in China. We also highlight remaining challenges and discuss the implications of improved TBI research and care on the lives of patients with TBI in China.

Epidemiology of TBI

For the past 30 years, nationwide data for the incidence of TBI in China have not been available. However, several large-scale, population-based studies done in the 1980s showed an incidence of TBI of 55·4–64·1 cases per 100 000 people per year.[2–4] This equates to approximately 770 060–890 990 new cases of TBI every year in China.[2–4] This incidence is much lower than that reported for high-income countries, such as USA [823·7 cases per 100 000 per year] and New Zealand [811·0 per 100 000 per year]),[1] possibly reflecting incomplete patient demographic data, such as for patients who were more difficult to formally diagnose (eg, those with mild TBI), or to identify (such as for those in rural areas).

Between 1983 and 1985, the prevalence of TBI was investigated by the Chinese government in 23 provinces and cities across China (figure 1).[2,3] The prevalence values are in the hundreds per 100 000 people, except in the outliers of Chongqing (68·2 cases), Guizhou (1056·7 cases), and Guangdong (1419·6 cases). However, the absence of more recent epidemiological data for TBI in China makes interpretation of these results difficult.

Causes of TBI

Between 2001 and 2016, 125 474 cases of acute TBI were reported across 18 retrospective clinical studies in China,[5–22] of which the most common causes of TBI in China were road traffic incidents (66 465 [53·0%]), falls (35 911 [28·6%]), violence (8532 [6·8%]), and other causes (14 566 [11·6%]), such as sports injuries (figure 2). Differences were also found between adult and paediatric populations. In 94 761 adults with TBI, road traffic incidents accounted for 52 640 (55·6%), falls

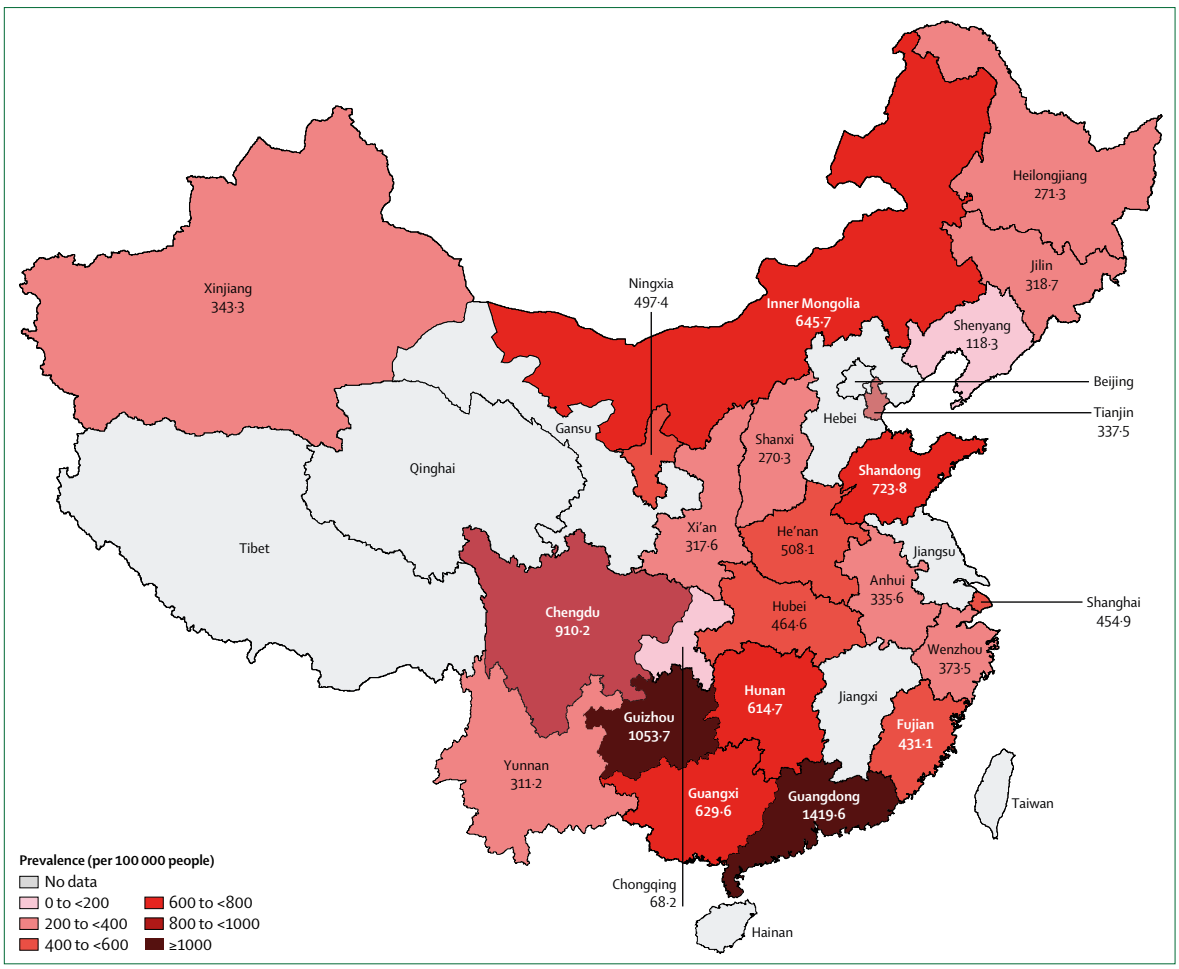

Figure 1: **Prevalence of traumatic brain injury in China between 1983 and 1985**

for 25 448 (26·9%), and violence for 5983 (6·3%) of TBI cases. In 30 713 children with TBI, traffic incidents accounted for 13 825 (45·0%), falls for 10 463 (34·1%), and violence for 2549 (8·3%) of TBI cases.

The distribution of TBI causes has changed between 2001 and 2016 in China.[5–22] The number of TBI cases due to traffic-related incidents has decreased from 46 189 (56·0%) between 2001 and 2010 to 6451 (52·9%) between 2011 and 2016.[5–22] However, the number of TBI cases due to falls was similar across the same period (22 297 [27·0%] between 2001 and 2010 *vs* 3151 (25·8%) between 2011 and 2016). On the other hand, TBI due to violence has increased from 4854 cases (5·9%) between 2001 and 2010 to 1129 (9·3%) between 2011 and 2016.[5–22] The burden of TBI from road traffic incidents in China is now higher than that reported in Europe and the USA, where falls are now the leading cause of TBI in individuals ≥55 years of age.[1,23] We anticipate a further decline in the rate of road traffic-related TBI and an increase in the rate of fall-related TBI in China, consistent with the changing epidemiological patterns of TBI reported in high-income countries.[1,23,24]

Traffic-related TBI

The high rate of TBIs caused by road traffic incidents in China coincided with the rise of automobiles, whereby numbers of automobiles in China increased by nearly five times (from 60 million in 2000 to 295 million in 2016).[25] In the same period, the number of traffic-related deaths and injuries increased by 367%, from 83 000 to 388 000 people.[25] Peak mortality was 97 000 in 2004 and the peak injury was 508 000 in 2001.[25] As traffic-related deaths and injuries were also related to alcohol misuse, the Ministry of Public Safety issued the alcohol penalty law in 2011 which declared that all drivers found to be over the legal alcohol limit (≥80 mg alcohol in 100 ml blood) were liable to prison sentences. Since then, alcohol-related traffic incidents have declined rapidly, with the number of injuries decreased by 64·2% (508 308 to 181 528) between 2001 and 2015.[25] Traffic-related mortality also decreased by 44·3% (97 456 to 54 279 incidents) between 2004 and 2015 (appendix).[25] The decline of traffic-related deaths and injuries, particularly after 2011, must be at least partially related to the implementation of the alcohol penalty law in China.

See Online for appendix

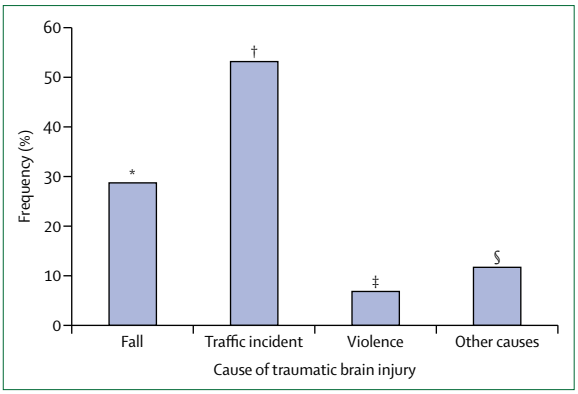

Figure 2: **Causes of traumatic brain injury from 2001 to 2016 in China**[5–22]
*n=35 911. †n=66 465. ‡n=8532. §n=14 566.

The number of mopeds (called electric bicycles in China) has markedly increased over the past 10 years and contributes to traffic congestion. The registered number of mopeds increased by 124%, from 101 million in 2008 to 226 million in 2016.[25] In 2016, the number of deaths due to accidents by moped-riders increased 2·74 times (a total of 1883 more patients) and injuries by 2·40 times (a total of 13 700 more patients), compared with 687 deaths and 5702 injuries in 2008 (appendix).[25]

The following reasons might be related to the increase of moped incidents: the number of mopeds has markedly increased;[25] the speed of mopeds can reach as high as 100 km/h; moped riders often do not wear helmets and do not always obey the traffic laws; moped riders are allowed on sidewalks and thus, compete with pedestrians; and electric mopeds are silent, which reduces pedestrian awareness of nearby mopeds. To reduce the incidence of moped-related incidents, the Chinese Ministry of Public Security issued the national moped laws in April 2018, which include the following items: the upper limit of speed must be less than 25 km/h, the maximum power must be less than 400 watts, electric voltage must be less than 48 volts, total weight of the moped (including the battery) must be less than 55 kg, and the height and width must be less than 1·1 m and 45 cm, respectively.

Violence-related TBI

After road traffic incidents and falls, violence-related TBI is the third major cause of TBI in China (figure 2).[5–22] A survey in 11 Chinese hospitals showed that 2254 (10%; 1890 [84%] men and 364 [16%] women) of 23 816 hospitalised head trauma patients with TBI was caused by violence.[22] Most patients with violence-related TBI were young and middle-aged adults (356 [16%] aged ≤20 years, 1216 [54%] aged 21–40 years, 576 [26%] aged 41–60 years, and 106 [5%] aged >60 years).[22] Violence-related TBI was mainly caused by blunt objects (1260 [56%]), with sharp or cutting instruments (271 [12%]), gunshots (10 [<1%]), and others causes (713 [32%]) such as fist injury less common. In the same survey, most patients (1869 [83%]) had mild TBI (Glasgow Coma Scale [GCS] 13–15), moderate TBI (GCS 9–12) was reported for 166 (7%) patients, and severe TBI (GCS 3–8) for 219 (10%) patients. Most patients (2072 [92%]) had a favourable outcome, 106 (4%) patients had an unfavourable outcome (dead, vegetative state, or severe disability), and the remaining 76 patients had lost records.[22] In summary, most TBIs in China were caused by blunt objects, with youg and middle-aged males most likely to suffer a TBI in this way, and favourable outcomes were seen in most of them.

Notably, TBI caused by gunshots are very rare (ten of 2254 violent cases), even though violence is the third major cause of TBI in China.[22] This low incidence of gun-related TBI is because China has the strictest gun control laws worldwide, in which ownership, distribution, and transportation of firearms is punishable by imprisonment.

Outcomes after TBI

Outcomes after TBI have substantially improved in China in the past two decades. A population-based study using data from the nationwide Disease Surveillance Points system (comprising 145 reporting sites selected by stratified cluster random sampling, covering a 1% representative sample of China's population) showed a decrease in age-adjusted TBI mortality from 17·06 per 100 000 people in 2008 to 12·99 in 2013.[26] This 2013 value is similar to that reported for Europe.[27] From 2008 to 2012, the Chinese Head Trauma Data Bank collected data for 11 937 cases of TBI from 47 hospitals in China.[28] For the 2776 (23%) patients with severe TBI, these data showed that 756 (27%) patients died and 1476 (53%) had an unfavourable outcome.[28] From a total of 20 831 patients with severe TBI reported between 2000 and 2016, the overall mortality of severe TBI was 5578 (27%; figure 3).[29–36] Therefore, the mortality of severe TBI in China is similar to the reported rates in Europe and North America[37,38]

Advances in TBI care

The improvements in outcome after TBI observed in the past two decades in China are attributable to advances in the domains of legislation, health-care policy, and clinical management. Since China became more open to the outside world, many Chinese neurosurgeons have received additional training in North America and Europe before returning to China. This experience stimulated Chinese head trauma experts to compose and issue a series of guidelines and consensus reports on surgical management, drug treatment, intracranial pressure monitoring, decompressive craniectomy, management of post-traumatic hydrocephalus, coma arousal procedures, cranioplasty for traumatic cranial defect, prevention and management of post-traumatic epilepsy, and prevention and management of stress ulcers after TBI.[39–47] These guidelines and consensus reports have markedly changed how Chinese neurosurgeons treat TBI from experience-based medicine to evidence-based medicine eg, intracranial

monitoring values contributed significantly in determining a decompressive craniectomy.[16,48,49] This shifting of treatment management might have played an important role in improving the outcome of patients with TBI in China.

Additionally, Chinese medical facilities, such as neurosurgical intensive care units, have also substantially improved since the 1980s. Prehospital management and speed of transfer to nearby trauma hospitals (level I or level II) have also gradually improved. For example, a study indicated that time from emergent call to ambulance arrived at injury site was on average 11·8 (SD ±2·2) min in Pudong New District of Shanghai, for 77 patients with TBI.[50] The 120 free-call emergency telephone system was set up in 1986 to facilitate rapid response to medical emergencies and quick transportation of patients without delay. Well-equipped ambulances with physicians and nurses are also now available throughout the country, including remote areas of China.[51] Furthermore, helicopters are now available in some large cities for quick transportation of severely injured patients, including patients with acute TBI.[52] The improved availability of neurosurgical services across China ensures that the vast majority of patients with acute TBI can get a rapid diagnosis and access to treatment when they arrive at hospitals.

In the past decade, the implementation of modern imaging, including CT, MRI, and digital subtraction angiography, has advanced care for patients with TBI.[53] In China, CT scans are done for patients with TBI in all hospitals with departments of neurosurgery.[53] In some level I hospitals in urban parts of China, there are portable CT scanners in neurosurgical intensive care units or operating rooms to provide CT scans quickly and conveniently. Monitoring equipment is available in many TBI centres, including monitoring of intracranial pressure, brain temperature, brain oxygen, brain activity (monitored by EEG), and brain microdialysis. Intracranial pressure monitoring is widely used to evaluate the intracranial status of patients with TBI. It is estimated that more than 5000 intracranial pressure monitoring devices are now in clinical use, with more than 40 000 intracranial pressure catheters applied to patients with TBI each year in China.[28] In the past decade, the addition of intracranial pressure monitoring has markedly improved decision making and management of patients with severe TBI.[28–36] However, brain oxygen monitoring is only rarely used for patients with severe TBI because catheters for brain oxygen monitoring are still financed by patients' families, with government health insurance or public health insurance reimbursement still unavailable. Catheter use is therefore still largely confined to selected centres with an interest in TBI research. Bedside EEG is more widely used to facilitate the diagnosis of post-traumatic (non-convulsive) seizures and enhances early prediction of outcome in comatose patients with TBI.

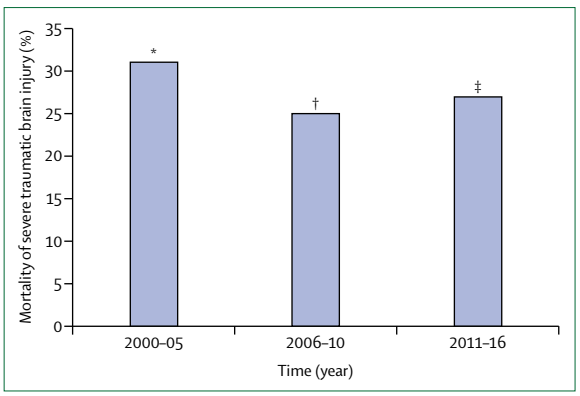

***Figure* 3: Severe traumatic brain injury and death from 2000 to 2016 in China[29-36]**

*n=1518. †n=2908. ‡n=1152.

TBI research

International collaborations are increasingly being established, facilitating the integration of Chinese research into the international community. For example, in HIT V, a multicentre randomised controlled trial, researchers examined the effects of nimodipine in 21 Chinese patients with subarachnoid haemorrhage after TBI.[54] CRASH-2 was a randomised, placebo-controlled trial that tested the effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with severe haemorrhage.[55] Another trial investigated the effects of progesterone on the outcome of patients with acute severe TBI.[56]

An international collaboration of the CENTER-TBI project[57] prospectively collected registry data (12 844 cases in China, 21 968 cases in European countries) aiming to characterise patients with TBI and comparative effectiveness research. This comparative effectiveness research is currently ongoing to explore structural and process-related differences between Europe and China and their relation to outcome on discharge.

Chinese neurosurgeons are actively seeking more international collaborations to strengthen the integration of Chinese clinical research into the international community. The Chinese government has awarded tens of grants per year to support prospective TBI clinical research projects in the past 3 years, including international collaborations (appendix). Since the 1980s, the number of Chinese publications on TBI research in international peer-reviewed journals has increased from almost none 30 years ago to hundreds of publications per year since the 2010s, based on PubMed search. For example, in 2018 alone, 202 Chinese papers on TBI were published in English-language journals (the majority of which are peer-reviewed), with 125 papers still published in Chinese journals according to the China National Knowledge Infrastructure, which is a Chinese version of PubMed. On November 12, 2018, we found 56 randomised controlled trials on TBI by Chinese neurosurgeons or neurologists on the ClinicalTrials.gov

For more on the **Chinese Clinical Trial Registry** see http://www.chictr.org.cn

website and the Chinese Clinical Trial Registry (appendix). In the following sections, we present some examples of completed or ongoing Chinese clinical studies across the spectrum of TBI.

Brain monitoring

Some controversy persists worldwide concerning the effectiveness of intracranial pressure monitoring in TBI.[58,59] A retrospective, observational, multicentre study[48] of 22 Chinese hospitals in 1443 patients with acute moderate (GCS 9–12) or severe (GCS 3–8) TBI included 838 patients in the intracranial pressure monitoring group and 605 patients in the group that had no intracranial pressure monitoring.[48] The intracranial pressure monitoring group was not different in either 6 -month mortality or 6-month unfavourable outcome compared with the non-monitored group. Specifically, for patients with severe TBI, the monitoring group was not different in either 6-month mortality or an unfavourable outcome. However, for patients with very severe (GCS 3–5) TBI, multivariate logistic regression showed that the intracranial pressure monitoring group had a significantly lower 6-month mortality rate compared with the non-monitored group. It might, therefore, be beneficial to monitor intracranial pressure in patients with very severe TBI.[48]

A prospective, observational clinical trial of 122 patients with acute TBI investigated the effects of intracranial pressure monitoring by using an external ventricular drain or intraparenchymal fibreoptic monitor.[49] The results showed that patients monitored with external ventricular drains had a significantly higher 6-month post-injury survival rate compared with patients monitored with intraparenchymal fiberoptic monitors. There was no difference between the two groups when comparing the number of device-related complications. Based on these findings, routine placement of an external ventricular drain in patients with TBI might be beneficial.[49]

Brain tissue oxygen pressure and brain temperature can also be monitored in patients with TBI. A study[60] of 112 patients admitted to a single Chinese hospital for severe TBI showed that intracranial pressure, cerebral perfusion pressure, and brain tissue oxygenation pressure were useful indicators of prognosis. A multicentre, prospective, observational study measured brain temperature in 51 patients with acute TBI and found that a postoperative peak temperature of more than 39°C was associated with both a higher severity of injury on admission and a worse prognosis. Thus, brain temperature might be a crucial indicator for predicting prognosis of patients with TBI.[61]

Decompressive craniectomy for refractory intracranial hypertension

Refractory intracranial hypertension caused by massive cerebral contusion, intracerebral or subdural haematomas, and brain oedemas in patients with severe TBI is associated with a poorer clinical outcome.[1] There is an internationally recognised consensus of surgical treatment for traumatic intracranial hypertension.[62] However, the optimum technique for surgical decompression for refractory intracranial hypertension remains disputed.[63,64]

A multicentre, randomised controlled trial[65] and a single centre, randomised controlled trial[66] compared large decompressive craniectomy (defined as 12 cm×15 cm) versus routine small decompressive craniectomy (defined as 6 cm×8 cm) on favourable outcome (good recovery and moderate disability) of patients with severe TBI with refractory intracranial hypertension caused by unilateral massive frontotemporoparietal contusion, intracerebral or subdural haematoma, or brain oedema. Both randomised controlled trials showed that patients that underwent large decompressive craniectomy had a significantly improved outcome compared with patients that underwent routine small decompressive craniectomy. These results suggest that a large decompressive craniectomy procedure (≥12 cm×15 cm or 15 cm diameter) should be used for patients with severe TBI with refractory intracranial hypertension. A large decompressive craniectomy procedure is also recommended (level II A evidence) in the guidelines for management of patients with severe TBI.[67] Furthermore, the Chinese head trauma committee also recommends unilateral or bilateral large decompressive craniectomy to treat patients with severe TBI with refractory intracranial hypertension.[42] The indications for unilateral or bilateral large decompressive craniectomy include progressive neurological deterioration, intracerebral haematoma, contusion or oedema with midline shift more than 5 mm and cisternal compression on CT, and intracranial pressure higher than 30 mm Hg for longer than 30 min.[42]

Surgical decompression as the last step therapy for refractory intracranial hypertension resulting from massive cerebral contusion and oedema commonly leads to a large cranial defect that, in turn, can result in serious complications (eg, subdural effusions, depressed scalp through the cranial defect with brain shift, and hydrocephalus shortly after surgical decompression). In China, surgical cranioplasty was commonly done at least 6 months after decompressive craniectomy up until 2016. Evidence supporting the safety and efficacy of early cranioplasty after decompressive craniectomy is still inconclusive. A case-control cohort study[68] compared the outcomes between patients who received early cranioplasty at 5–8 weeks after decompressive craniectomy and patients who received late cranioplasty at least 12 weeks after decompressive craniectomy. The Glasgow Outcome Score and the Karnofsky Performance Score were statistically better in patients who received early cranioplasty than in those who received late cranioplasty.[68,69] Furthermore, patients that received early cranioplasty also had improved cerebral perfusion compared with patients that received late cranioplasty.[70] The Chinese head trauma

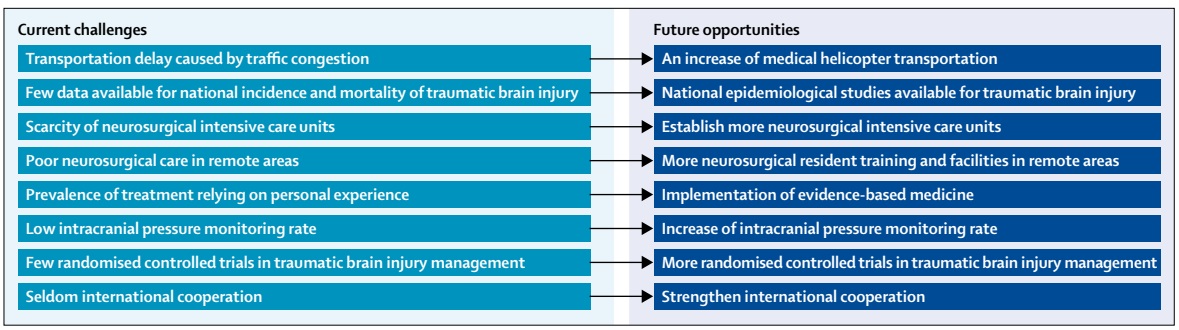

Figure 4: **Current challenges and future opportunities for improving care and outcomes of patients with traumatic brain injury in China**

committee recommends early cranioplasty if there are no contraindications.[45]

Hypothermia for severe TBI

Since the 1990s, mild-to-moderate hypothermia has been applied to treat more than a thousand patients with severe TBI in China, Europe, Japan, and the USA. However, whether mild-to-moderate hypothermia improves the outcome of patients with severe TBI is still controversial. Short-term mild hypothermia (<48 h) has not been effective for patients with severe TBI because of rebound intracranial pressure increase during early rewarming, which may have detrimental effects on outcome.[71] Long-term hypothermia might avoid the risks of a rebound increase of intracranial pressure. A multicentre, randomised controlled trial of 232 patients with severe TBI in the USA and Canada applied short-term (48 h) mild (33°C) hypothermia to patients within 2·5 h of injury and found no improvement in outcome.[72] By contrast, randomised controlled trials done in China compared the effects of long-term mild (>5 days) hypothermia to normothermia on the outcome of patients with severe TBI.[73–76] These studies found that long-term mild hypothermia following severe TBI significantly decreased intracranial pressure, improved brain tissue oxygenation and improved the outcome of patients.[73–76] Remarkably, long-term mild hypothermia did not show rebound intracranial pressure and did not lead to severe complications, especially pneumonia. However, the data of these three single centre randomised controlled trials are still not regarded as convincing evidence of the benefit of long-term mild hypothermia following severe TBI.[73–76] A multicentre randomised controlled trial is underway to confirm the effectiveness of long-term mild hypothermia for severe TBI (NCT01886222).[77]

Right median nerve stimulation

Approximately 10–15% of patients with severe TBI remain in a coma or a form of vegetative state, such as a permanent vegetative state.[1,78] Rehabilitation for patients with severe TBI is a complex process, especially so with the recovery of consciousness and cognition in comatose patients. Unfortunately, there is no level I evidence available to improve functional outcome in comatose patients. However, a single centre, randomised controlled trial of 437 patients in a coma with severe TBI showed that right median nerve stimulation-treated patients had an obvious increase in mean GCS, and a higher proportion of those patients regained consciousness and a lower proportion ended in vegetative state when compared with patients who did not receive right median nerve stimulation treatment.[78] However, multicentre, randomised controlled trials are needed to confirm the therapeutic effects of right median nerve stimulation treatment on comatose patients with severe TBI. A randomised controlled study in 26 centres across Asia is currently assessing the efficacy of right median nerve stimulation treatment on traumatic coma patients initiated 7–14 days after TBI (NCT02645578). The purpose of this trial is to evaluate the effectiveness of early right median nerve stimulation treatment intervention on comatose patients with TBI and to identify the characteristics of patients who might respond to treatment.[79] The Chinese head trauma committee recommends right median nerve stimulation treatment as early as possible in neurosurgical intensive care units for applicable patients because of its safety and possible therapeutic benefits.[44]

Chronic subdural haematoma

A multicentre, randomised controlled trial was carried out to compare the outcomes between atorvastatin treatment and placebo for conservative management of chronic subdural haematoma.[80] The inclusion criteria included symptomatic patients who were aged 18–90 years, a diagnosis of unilateral or bilateral supratentorial chronic subdural haematoma by CT scan, no chronic subdural haematoma surgery, and no statin treatment received in the previous 6 months. 98 patients took atorvastatin and another 98 patients received placebo. The haematoma volume reduction in patients who received atorvastatin was 12·55 mL more than those taking the placebo at 8 weeks after treatment. 45 patients (46%) in the atorvastatin group significantly improved their neurological function, compared with 28 patients (29%) in the placebo group. No significant adverse events were reported, therefore, atorvastatin might be a safe and

efficacious non-surgical method for treating patients with chronic subdural haematoma. These findings might change first-line therapy of chronic subdural haematoma in the future.

Epilepsy prophylaxis after TBI

A prospective observational study of patients with blunt TBI at urban level I trauma centres in the USA (n=272) and China (n=250) investigated the incidence of early clinical seizures following TBI.[81] All patients from the USA trauma centre received seizure prophylaxis with levetiracetam, but no seizure prophylaxis was given to Chinese patients. Overall, ten (4%) patients who received seizure prophylaxis had early seizures, compared with seven (3%) patients who did not receive any prophylaxis. Thus, these results suggest that there was no benefit of routine early seizure prophylaxis following blunt TBI.

Challenges and opportunities in TBI care

Despite advances in the care of patients with TBI and in outcome data (such as age-adjusted TBI mortality and the mortality after severe TBI) that are similar to those of high income countries,[26–38] challenges in the care for TBI still remain in China. For example, there is no national incidence reporting of TBI in China. Delays in transportation from the scene of an accident to hospital are common because of major traffic queues in most Chinese cities. Only very few patients with severe TBI are transported to hospitals by helicopter or medical airplanes even though helicopter landing sites are available in some level I or II hospitals.[52] This delay of emergency treatment results in the loss of the so-called golden hour for patients with severe TBI, especially for those who need emergency surgical intervention for removal of large intracranial haematomas or decompressive craniectomy for reduction of refractory intracranial hypertension. Furthermore, prehospital care on TBI is still suboptimal, with appropriate prehospital TBI management training programmes urgently needed in China.[82] Because of a scarcity of neurosurgical-intensive care units in most Chinese hospitals, most patients with severe TBI are still treated by physicians in general intensive care units without the presence of an attending neurosurgeon. There is also a shortage of trained neurosurgeons and limited access to specialist care, especially in the western regions of China and outside of large cities.[83] There are only about 15 000 neurosurgeons nationwide, who are required to treat millions of cases with CNS diseases, including more than a million cases of TBI every year.[83] Furthermore, the implementation of evidence-based management across China is still in the early stages and needs much improvement. Despite the efforts towards standardisation, use of treatments without proven therapeutic effects is still common, and many neurosurgeons still rely on personal experience to treat patients with TBI.[29,36] Both national government health insurance and public commercial health insurance companies do not pay for intracranial pressure procedures or other brain monitoring catheters throughout the country. Increased awareness of these shortages should guide health policy and lead to investments to overcome these shortcomings in TBI treatment, and will further improve the outcomes in patients with TBI in China.

The Chinese government has committed a great amount of financial support towards improving medical facilities, including those for care of TBI.[53] In July, 2018, the Ministry of Chinese Health issued a document requesting that all level I and II hospitals set up a department of traumatology for all trauma patients, including those with TBI.[84] Moreover, a greater number of level I and II hospitals now have a medical helicopter landing site to facilitate quick transportation of patients with TBI in large cities that are notorious for traffic queues.[84] Many neurosurgical intensive care units have been established in hospitals caring for patients with acute TBI to ensure essential access to neurosurgeons experienced in TBI management. Medical universities and colleges train about 500 resident neurosurgeons annually to meet the clinical demand in the whole of China, especially in the western regions.[83] In 2009, the Ministry of Chinese Health issued a document to state that all medical students graduated from medical schools are required to undergo 2–3 years of resident training prior to completing a national resident test for a clinical licence. Furthermore, an additional 3–4 years of neurosurgical professional training has been launched in more than ten big cities in China. Importantly, Chinese neurosurgeons now increasingly accept the implementation of evidence-based management, instead of guidelines informed by personal experience, to treat patients with TBI.[83] Additionally, many young Chinese neurosurgeons have learned modern knowledge and

Search strategy and selection criteria

We searched for articles published in English at PubMed and articles published in Chinese at China National Knowledge Infrastructure, from Jan 1 1984 to Nov 12 2018, and the references from relevant articles. The search terms "traumatic brain injury", "epidemiology", "head injury", "head trauma", "hypothermia", "outcome", "children", "intracranial pressure monitoring", "mortality", "pediatric", "guideline", "expert consensus", "prognosis", "traffic accident", "clinical trial", "decompressive craniectomy", "intracranial hypertension", "coma", "electrical stimulation", "cranioplasty", "complication", "atorvastatin", and "chronic subdural haematoma" were used. We also searched the National Bureau of Statistics of China for relevant data using several variations of search terms such as "mobile vehicle", "traffic accident", and "moped". We generated the final reference list on the basis of relevance to the scope of this Review.

skills in European countries and North America before returning to China, mostly through grants. This partnership facilitates the development of international collaborations and is essential to increase the profile of TBI research in China.

Conclusions and future directions

A great deal of progress in TBI prevention and care (such as establishing more neurosurgical intensive care units, increased availability of brain monitors, the development of brain imaging, and the establishment of evidence-based guidelines) have contributed towards improved treatment of TBI in China. However, there are still many improvements to be made, especially in achieving standardisation of TBI care across China. These improvements can be accomplished through training programs for young neurosurgeons, advancing medical facilities in remote areas, and greater support for conducting randomised controlled trials for TBI care (figure 4). The large number of patients with TBI in China and the high level of care available in many centres offers unique opportunities for randomised controlled trials and comparative effectiveness research. These opportunities should be grasped by the international community and China to welcome new and strengthen existing collaborations. Such international cooperation is extremely important for Chinese neurosurgeons to further improve outcomes and quality of life in patients with TBI.

Contributors

All authors contributed to this Review, by searching the literature, analysing the data, and drafting the report and reviewing it. All authors have approved the final version.

Declaration of interests

The National Natural Science Foundation of China provides financial support to J-YJ (81772058), G-YG (81671198), J-FF (81771317), and QM (81571883) for traumatic brain injury research. J-YJ, G-YG, J-FF, QM, L-GC, X-FY, J-FL, Y-HW, B-HQ, and X-JH declare no competing interests.

References

1 Maas AIR, Menon DK, Adelson PD, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol* 2017; **16:** 987–1048.

2 Zhu GL, Song JR, Zhang DX, Wang WZ, Xu ZL. The epidemiology of head injury in rural and minority areas of China. *Chin J Neurosurg* 1989; **5:** 44–47.

3 Yang YC, Li SC, Cheng XM, Wang WZ, Wu SP. The epidemiology of craniocerebral injury in 6 cities of China. *Chin J Neurosurg* 1987; **3:** 23–25.

4 Wang CC, Schoenberg BS, Li SC, Yang YC, Cheng XM, Bolis CL. Brain injury due to head trauma. Epidemiology in urban areas of the People's Republic of China. *Arch Neurol* 1986; **43:** 570–72.

5 Wu X, Hu J, Zhuo LF, et al. Epidemiology of traumatic brain injury in eastern China, 2004: a prospective large case study. *J Trauma* 2008; **64:** 1313–19.

6 Liu Y, Yao HJ, Xi CH, et al. Characteristic analysis of clinical epidemiology of 4196 traumatic brain injury inpatients in Jiangsu province in 2004. *Suzhou Univ J Med Sci* 2008; **28:** 402–05.

7 Tian HL, Geng Z, Cui YH, et al. Risk factors for posttraumatic cerebral infarction in patients with moderate or severe head trauma. *Neurosurg Rev* 2008; **31:** 431–36.

8 Xiao GM, Wei J, Yan WQ, Wang WM, Lu ZH. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. *Crit Care* 2008; **12:** R61.

9 Hu J, Yao HJ, Liu Y, et al. An investigation of hospitalized patients with traumatic brain injury associated with facies cranii injury in eastern China. *Chin J Neurosurg Dis Res* 2009; **8:** 47–52.

10 Zhao QJ, Zhang XG, Wang LX. Mild hypothermia therapy reduces blood glucose and lactate and improves neurologic outcomes in patients with severe traumatic brain injury. *J Crit Care* 2011; **26:** 311–15.

11 Yuan Q, Liu H, Wu X, et al. Characteristics of acute treatment costs of traumatic brain injury in eastern China—a multi-centre prospective observational study. *Injury* 2012; **43:** 2094–99.

12 Li JL, Sheng LP, Chen RH, et al. Epidemiology survey of 2671 cases of traumatic brain injury. *J Trauma Surg* 2013; **15:** 492–96.

13 Wang HQ, Xin T, Sun XB, et al. Post-traumatic seizures—a prospective, multicenter, large case study after head injury in China. *Epilepsy Res* 2013; **107:** 272–78.

14 Zhang YH, Qiu J, Zhou JH, Xu LS, Xu MH. Epidemiological feature of traumatic brain injury in 0-to 18-years-old children: a report of 19 821 cases. *J Third Mil Med Univ* 2015; **37:** 480–84.

15 Xu HM, Pi HY, Ma LL, Su XY, Wang JR. Incidence of headache after traumatic brain injury in China: a large prospective study. *World Neurosurg* 2016; **88:** 289–96.

16 Yuan Q, Wu X, Cheng HW, et al. Is intracranial pressure monitoring of patients with diffuse traumatic brain injury valuable? An observational multicenter study. *Neurosurg* 2016; **78:** 361–68.

17 Li YM, Zhou JH, Chen FQ, Zhang JR, Qiu J, Gu JW. Epidemiology of traumatic brain injury older inpatients in Chinese military hospitals, 2001–2007. *J Clin Neurosci* 2017; **44:** 107–13.

18 Ma JH, Gao J, Wang SS, Hu XH. Clinical and epidemiological characteristics of 2025 hospitalized patients with traumatic brain injury in Xi'an city. *J Trauma Surg* 2017; **19:** 411–16.

19 Cheng PX, Yin P, Ning PS, et al. Trends in traumatic brain injury mortality in China, 2006–2013: a population-based longitudinal study. *PLoS Med* 2017; **14:** e1002332.

20 Shao JB, Zhu HP, Yao HY, et al. Characteristics and trends of pediatric traumatic brain injuries treated at a large paediatric medical center in China, 2002–2011. *PLoS One* 2012; **7:** e51634.

21 Li YM, Chen FQ, Zhang JR, et al. Epidemiological characteristics of Chinese paediatric traumatic brain injury inpatients. *Brain Inj* 2017; **31:** 1094–101.

22 Jiang JY, Feng H, Fu Z, et al. Violent head trauma in China: report of 2254 cases. *Surg Neurol* 2007; **68:** S2–5.

23 Brazinova A, Rehorcikova V, Taylor MS, et al. Epidemiology of traumatic brain injury in Europe: a living systematic review. *J Neurotrauma* 2016; published online Aug 25. DOI:10.1089/NEU.2015.4126.

24 Roozenbeek B, Maas AIR, Menon DKM. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 2013; **9**: 231–36.

25 National Bureau of Statistics of China. National data. http://data.stats.gov.cn (accessed Nov 12, 2018).

26 Cheng P, Yin P, Ning P, et al. Trends in traumatic brain injury mortality in China, 2006–2013: a population-based longitudinal study. *PLoS Med* 2017; **14:** e1002332.

27 Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis based on hospital discharge statistics and death certificates in 2012. *Lancet Public Health* 2016; **1:** e76–83.

28 Hui JY, Gong R, Liang YM, Gao GY, Bao YH, Jiang JY. Chinese head trauma data bank: factors of short-term prognosis. *Chin J Neurosurg* 2014; **30:** 56–58.

29 Zhou L. Clinical analysis of 688 cases of severe traumatic brain injury. *Chin J Traumatol* 2000; **16:** 147.

30 He CJ, Wang GZ, Liang J, Li B. Experience of the treatment of 172 cases of severe traumatic brain injury in plateau area. *Chin J Neurosurg* 2007; **23:** 236–36.

31 Yang SZ, Li LN, Li SD, et al. Research of clinical epidemiology of 6690 cases of craniocerebral injury. *Chin J Neuromed* 2006; **5:** 274–77.

32 Weng CQ, Zhou JD, Yang GX. Experience of the treatment of 2750 cases of severe traumatic brain injury. *Fujian Med J* 2006; **28:** 44–46.

33 Liu JY. Clinical analysis of 10730 cases of acute traumatic brain injury. *Chin J Neurosurg* 2007; **23:** 510–12.

34 Liu B, Zhang J, Wang ZT, Zhi DS. Analysis of the related factors of death in severe traumatic brain injury. *Chin J Neurosurg* 2007; **23:** 496–98.

35 Yuan Q, Liu H, Yao HJ, et al. The impact of intracranial pressure monitoring on severe traumatic brain injury prognosis and disease afflictions. *Chin J Neurosurg* 2013; **29:** 120–24.

36 Jiang JY, and the Chinese Head Trauma Study Collaborators. Head trauma in China. *Injury* 2013; **44:** 1453–57.

37 Stein SC, Georgoff P, Meghan S, Mizra K, Sonnad SS. 150 years of treating severe traumatic brain injury: a systematic review of progress in mortality. *J Neurotrauma* 2010; **27:** 1343–53.

38 Rosenfeld JV, Maas AI, Bragge P, Morganti-Kossmann MC, Manley GT, Gruen RL. Early management of severe traumatic brain injury. *Lancet* 2012; **380:** 1088–98.

39 Chinese Congress of Neurological Surgeons. Chinese surgical guidelines for management of traumatic brain injury. *Chin J Neurosurg* 2009; **25:** 100–01.

40 Chinese Congress of Neurological Surgeons. The Chinese guidelines for drug management of traumatic brain injury. *Chin J Neurosurg* 2008; **24:** 723–75.

41 Chinese Congress of Neurological Surgeons. Chinese expert consensus on intracranial pressure monitoring for traumatic brain injury. *Chin J Neurosurg* 2011; **27:** 1073–75.

42 Chinese Congress of Neurological Surgeons. Chinese expert consensus on decompressive craniectomy for traumatic brain injury. *Chin J Neurosurg* 2013; **29:** 967–69.

43 Chinese Congress of Neurological Surgeons. Chinese expert consensus on diagnosis and management of posttraumatic hydrocephalus. *Chin J Neurosurg* 2014; **30:** 840–43.

44 Chinese Congress of Neurological Surgeons. Chinese expert consensus on arousal methods of traumatic coma. *Chin J Neurosurg* 2015; **31:** 757–60.

45 Chinese Congress of Neurological Surgeons. Chinese expert consensus on cranioplasty after chinraumatic brain injury. *Chin J Neurosurg* 2016; **32:** 767–70.

46 Chinese Congress of Neurological Surgeons. Chinese expert consensus on prevention and management of posttraumatic epilepsy. *Chin J Neurosurg* 2017; **33:** 652–54.

47 Chinese Congress of Neurological Surgeons. Chinese expert consensus on prevention and management of stress ulcer after TBI. *Chin J Neurosurg* 2018; **34**: 649–52.

48 Yuan Q, Wu X, Yu J, et al. Effects and clinical characteristics of intracranial pressure monitoring–targeted management for subsets of traumatic brain injury: an observational multicenter study. *Crit Care Med* 2015; **43:** 1405–14.

49 Liu H, Wang WM, Cheng F, et al. External ventricular drains versus intraparenchymal intracranial pressure monitors in traumatic brain injury: a prospective observational study. *World Neurosurg* 2015, **83:** 794–800.

50 Ni YQ, Yang JH, Gu JL, et al. Application of tranexamic acid in pre-hospital emergency care of patients with craniocerebral trauma. *Chin J Trauma* 2018; **34:** 293–298.

51 Chinabgao. China Report Hall. http://www.chinabgao.com report/4004947.html (accessed Nov 12, 2018).

52 Wang L, Li XX, Wei W, Wang Y. Quantitative analysis on literatures of helicopter-medical rescue in China. *Chin J Disaster Med* 2018, **6**: 485–488.

53 Lin SQ, Cai K. The analysis on allocation status and problem of the large medical equipment. *Chin Med Equip* 2016, **13:** 121–123.

54 Vergouwen MD, Vermeulen M, Roos YB. Effect of nimodipine on outcome in patients with traumatic subarachnoid haemorrhage: a systematic review. *Lancet Neurol* 2006; **5**: 1029–32.

55 CRASH-2 trial cooperators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010; **376:** 23–32.

56 Wright DW, Yeatts SD, Silbergleit R, et al. Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med* 2014; **371:** 2457–66.

57 Maas AI, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurg* 2015; **76:** 67–80.

58 Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012; **367:** 2471–81.

59 Stocchetti N, Carbonara M, Citerio G, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurol* 2017; **16:** 452–64.

60 Zhang QS, Zhang M, Lin HZ, Ji T, He Y, Li WP. Effect of brain oxygen, ICP, and CPP on the outcome of severe traumatic brain injury. *Chin J Pract Nerv Dis* 2014; **11:** 33–35.

61 Weng WJ, Yang C, Huang XJ, et al. Effects of brain temperature on the outcome of patients with traumatic brain injury: A prospective observational study. *J Neurotrauma* 2018; published online Sept 14. DOI:10.1089/NEU.2018.5881.

62 Stocchetti N, Maas AIR. Traumatic intracranial hypertension. *N Engl J Med* 2014; **370:** 2121–30.

63 Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011; **364:** 1493–502.

64 Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of decompressivecraniectomy for traumatic intracranial hypertension. *N Engl J Med* 2016; **375:** 1119–30.

65 Jiang JY, Xu W, Li WP, et al. Efficacy of standard trauma craniectomy for refractory intracranial hypertension with severe traumatic brain injury: a multicenter, prospective, randomized controlled study. *J Neurotrauma* 2005; **22:** 623–28.

66 Qiu W, Guo C, Shen H, et al. Effects of unilateral decompressive craniectomy on patients with unilateral acute post-traumatic brain swelling after severe traumatic brain injury. *Crit Care* 2009; **13:** R185.

67 Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurg* 2017; **80:** 6–15.

68 Wen L, Yang XF, Liu WG, et al. Cranioplasty of large cranial defect at an early stage after decompressive craniectomy performed for severe head trauma. *J Craniofac Surg* 2007; **18:** 526–32.

69 Li G, Wen L, Yang XF, et al. The effect of early cranioplasty on prognosis of patients with decompressive craniectomy due to head trauma. *Chin J Neurosurg* 2008; **24:** 750–52.

70 Wen L, Lou HY, Xu J, et al. The impact of cranioplasty on cerebral blood perfusion in patients treated with decompressive craniectomy for severe traumatic brain injury. *Brain Inj* 2015; **29:** 1654–60.

71 Clifton MG, Valadka PA, Aisuku IP, Okonkwo DO. Future of rewarming in therapeutic hypothermia for traumatic brain injury: a personalised plan. *Ther Hypothermia Temp Manag* 2011; **1:** 3–7.

72 Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the national acute brain injury study: hypothermia II): a randomized trial. *Lancet Neurol* 2011; **10:** 131–39.

73 Jiang JY, Yu MK, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *J Neurosurg* 2000; **93:** 546–49.

74 Zhi DS, Zhang S, Lin X. Study on therapeutic mechanism and clinical effect of mild hypothermia in patients with severe head injury. *Surg Neurol* 2003; **59:** 381–85.

75 Zhi DS, Zhang S, Zhou LG. Continuous monitoring of brain tissue oxygen pressure in patients with severe head injury during moderate hypothermia. *Surg Neurol* 1999; **52:** 393–96.

76 Qiu W, Shen H, Zhang Y, et al. Noninvasive selective brain cooling by head and neck cooling is protective in severe traumatic brain injury. *J Clin Neurosci* 2006; **13:** 995–1000.

77 Lei J, Gao GY, Mao Q, et al. Rationale, methodology and implementation of a nationwide multicenter randomized controlled trial of long-term mild hypothermia for severe traumatic brain injury (the LTH-1 trial). *Comtemp Clin Trials* 2015; **40:** 9–14.

78 Lei J, Wang L, Gao GY, Cooper E, Jiang JY. Right median nerve electrical stimulation for acute traumatic coma patients. *J Neurotrauma* 2015; **32:** 1584–89.

79 Wu X, Zhang C, Feng JF, Mao Q, Gao GY, Jiang JY. Right median nerve electrical stimulation for acute traumatic coma (the Asia coma electrical stimulation trial): study protocol for a randomised controlled trial. *Trials* 2017; published online July 10: DOI 10.1186/s13063-017-2045-x.

80 Jiang RC, Zhao SG, Wang RZ, et al. Safety and efficacy of Atorvastatin for chronic subdural hematoma in Chinese patients. *JAMA Neurol* 2018; **75:** 1338–46.

81 Khor D, Wu J, Hong Q, et al. Early seizure prophylaxis in traumatic brain injuries revisited: a prospective observational study. *World J Surg* 2018; **42:** 1727–32.

82 Kou K, Hou XY, Sun JD, Chu K. Current pre-hospital traumatic brain injury management in China. *World J Emerg Med* 2014; **5:** 245–54.

83 Zhang YQ, Xue CQ, Mao Y, You C. Current status and the development of Chinese neurosurgeons. *Chin J Neurosurg* 2011; **27:** 217–219.

84 National Health Commission of China. Continuously improve the trauma rescue capability. http://www.nhc.gov.cn/yzygj/s3594q/201807/79daad75e4c746118fb7d0237c7588bd.shtml (accessed Nov 12, 2018).