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Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective, multicentre, longitudinal, observational study

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Abstract:	Background Large scale collaborations are required to generate clinical evidence of traumatic brain injury (TBI) treatments. Current evidence is limited and mostly originates from western countries. China has a potential to generate strong evidence, but uncertainty exists how comparable the baseline, treatment and outcome is to other settings. We aimed to document the current care for TBI and its outcome in China by conducting a prospective, multicentre Chinese TBI registry. Methods This prospective, multi-centre, longitudinal, observational study was conducted in 56 centres across China. It collected data of hospitalized patients with a clinical diagnosis of TBI and indication for computerized tomography (CT) scanning. The primary endpoint was survival on discharge. Prognostic analyses were applied to identify predictors of mortality. Variations in mortality were compared between centres and regions within China. Mortality was compared to expected mortality estimated by CRASH basic model. The study was registered with ClinicalTrials.gov, number NCT02210221. Findings From 22nd, Dec, 2014, to 1st, Aug, 2017, 13627 patients with TBI from 56 centers were enrolled in the China CENTER-TBI registry. Data of 13138 patients from 52 hospitals in 22 provinces of China were analyzed. Most patients were male (9782 [74%]), with a median age of 48 (IQR: 33-61). The median Glasgow Coma Scale (GCS) was 13 (IQR: 9-15) and major cause (6548 [50%]) of injury was traffic incident. Overall hospital mortality was 4.8% (637), and in severe TBI 19.7% (552). Age, GCS, Injury Severity Score, pupillary reflex, CT findings, hypoxia and hypotension showed predictive value for mortality. Economic level and altitude of the regions were correlated significantly with death. Variation in mortality existed between centres or regions. The observed mortality was lower than expected (O/E ratio 0·49, 95% CI 0·45-0·53). Interpretation The results show differences in mortality between centres and regions, which indicates potential for identifying best practices in comparative effectiveness research. The risk

	factors identified in prognostic analyses may contribute to developing benchmarks for assessing quality of care. The main strength of the study is the large study size and wide coverage of centres across China. The main limitation is that outcome was evaluated at discharge without follow up.

Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective, multicentre, longitudinal, observational study

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Summary

Background

Large scale collaborations are required to generate clinical evidence of traumatic brain injury (TBI) treatments. Current evidence is limited and mostly originates from western countries. China has a potential to generate strong evidence, but uncertainty exists how comparable the baseline, treatment and outcome is to other settings. We aimed to document the current care for TBI and its outcome in China by conducting a prospective, multicentre Chinese TBI registry.

Methods

This prospective, multi-centre, longitudinal, observational study was conducted in 56 centres across China. It collected data of hospitalized patients with a clinical diagnosis of TBI and indication for computerized tomography (CT) scanning. The primary endpoint was survival on discharge. Prognostic analyses were applied to identify predictors of mortality. Variations in mortality were compared between centres and regions within China. Mortality was compared to expected mortality estimated by CRASH basic model. The study was registered with ClinicalTrials.gov, number NCT02210221.

Findings

From 22nd, Dec, 2014, to 1st, Aug, 2017, 13627 patients with TBI from 56 centers were enrolled in the China CENTER-TBI registry. Data of 13138 patients from 52 hospitals in 22 provinces of China were analyzed. Most patients were male (9782 [74%]), with a median age of 48 (IQR: 33-61). The median Glasgow Coma Scale (GCS) was 13 (IQR: 9-15) and major cause (6548 [50%]) of injury was traffic incident. Overall hospital mortality was 4.8% (637), and in severe TBI 19.7% (552). Age, GCS, Injury Severity Score, pupillary reflex, CT findings, hypoxia and hypotension showed predictive value for mortality. Economic level and altitude of the regions were correlated significantly with death. Variation in mortality existed between centres or regions. The observed mortality was lower than expected (O/E ratio 0·49, 95% CI 0·45-0·53).

Interpretation

The results show differences in mortality between centres and regions, which indicates potential for identifying best practices in comparative effectiveness research. The risk factors identified in prognostic analyses may contribute to developing benchmarks for assessing quality of care. The main strength of the study is the large study size and wide coverage of centres across China. The main limitation is that outcome was evaluated at discharge without follow up.

Funding

No specific funding was provided for the China TBI registry. The coordinating centre received support from the European Commission 7th Framework program (602150), in the context of CENTER-TBI.

Research in context

Evidence before this study

We searched PubMed for registry studies on traumatic brain injury (TBI) that reported on early outcome and its prediction on 1st, Nov, 2019, using search terms "traumatic brain injury AND prognosis AND registry study" without language or country restrictions. We found 152 articles, from which we identified 31 studies that met the search criteria. These articles analyzed the outcome and prognostic factors of TBI patients, however, multi-centre clinical registry studies of TBI in Chinese patient populations are scarce, of older dates and mostly do not contain data recorded in formats compatible with standardized common data elements. As a consequence, comparisons to other registries are not straightforward and the literature data may not reflect the current patterns of traumatic brain injury in China, which have evolved along with the substantial development of the socioeconomic status in China.

Added value of this study

To our knowledge, this is the first large scale Registry study on TBI in China that has captured data in an identical format as in CENTER-TBI Europen Registry Study, which is a prospective, multi-centre, longitudinal, observational study in 22 countries across Europe and Israel. The results of this study portray the profile of Chinese TBI patients' demographics, the prehospital management, the emergency and ICU treatment and the differences among Chinese centres. They present the real world of a big public health problem in a big country and provide a resource for future comparison between China and Europe.

Implications of all the available evidence

Heterogeneity of TBI and variation in healthcare may lead to different outcome of TBI patients in different centres or regions. Evidence from this study shows that patient characteristics, treatment approaches and mortality differ between centres, which provides opportunities for identification of best practices using comparative effectiveness research. Mortality was also related to regional features and economic level, which illustrates the need to tailor head trauma systems to better fit the situation in different areas. The results of this study, originating from China, a country with a large population, various geographical features, social development levels and with a huge burden of TBI, highlights the huge potential that collaborations with China may offer to advance the care for patients with TBI.

Introduction

Traumatic brain injury (TBI) presents a great challenge to public health worldwide. The heterogeneity of the disease, in terms of injury causes, mechanisms, approaches to treatment and outcome makes it a hugely complex problem compared to other diseases.[1] Large scale studies are required to better characterize the disease, to generate evidence in support of treatment recommendations and to improve outcome.[1] International collaborations offer the best potential to conduct such studies by increasing efficiency and generalizability and are strongly promoted by the International Initiative for Traumatic Brain Injury Research (InTBIR: https://intbir.nih.gov/), initiated as a collaboration of funding agencies.[2,3]

China has a large potential to contribute to such evidence, but uncertainty exists how comparable patient characteristics, treatment and outcome are to other settings. Some large clinical registry studies of TBI in Chinese patient populations exist, but these are of older dates or from local areas, and may not reflect the current patterns of traumatic brain injury in China, which have evolved along with the substantial development of the socioeconomic status in China. Moreover, most data of these studies were not recorded in formats compatible with standardized common data elements, making it not straightforward to compare with other registries.[4-6] In this study, we aimed to analyze epidemiological characteristics, management and outcome in an in-hospital cohort of TBI patients from centres in China.

Methods

Study design and participants

The China CENTER-TBI Registry is a prospective longitudinal observational study. It was modeled on the CENTER-TBI European Registry with an identical format for data collection and coding, and the study protocol and updated information was available on: www.center-tbi.eu.[7,8] Both studies included patients with a clinical diagnosis of TBI and indication for CT scanning. Data were prospectively collected from 56 Chinese neurosurgical centres in a 3-year period from 22nd, December, 2014 to 1st, August, 2017.

Patients were differentiated by care path into two strata: admission stratum (admitted to the general ward), and ICU stratum (primarily admitted to the intensive care unit). Patients discharged directly from the Emergency Room were not included.

Ethics statement: The study protocol was approved by the ethics committees of participating centres, who waived the need for informed consent as only routinely collected clinical data were recorded.

Data collection, handling, and storage

Clinical data of each patient was prospectively collected by one or more dedicated and trained physicians in each centre from patient medical records (paper or electronic) or personal interview. All data is in accordance with the medical records preserved in archives of each centre, which guarantees that all data is traceable. These variables included: demographics, medical history, injury characteristics, clinical and radiological severity upon arrival, emergency interventions, and care paths, including pre-hospital care system and transferals. Altitude and economic level were obtained from official government documents of National Bureau of Statistics.

Data were collected using a web-based electronic case report form (eCRF) and managed by the QuesGen data management platform. Data were coded in accordance with the Common Data Elements (CDE) scheme (https://www.commondataelements.ninds.nih.gov). All study data were de-identified and stored securely in the European data space under the supervision of Karolinska Institute International Neuroinformatics Coordinating Facility (KI-INCF). Automated data validation checks were run on data entry and central inspectors (GG and JH) continuously reviewed and checked uploaded data for data entry errors. More details for data collection, handling and storage are listed in appendix, p1-2.

Outcome

The primary outcome was survival at discharge. In case of in-hospital death, time and cause of death were recorded. Variations in primary outcome between centers and provinces were analyzed and predictors for primary outcome identified. The secondary outcomes of this study included: transferals, and emergency interventions.

Statistical analysis

We excluded patients in whom information on discharge status or clinical severity (e.g.

Glasgow Coma Scale (GCS) and pupillary light reflex) was lacking (N=489). Missing values for other baseline characteristics were classified as "unknown". Continuous variables were reported as median and interquartile ranges (IQR), and categorical data as numbers and percentages. Patients were classified according to the GCS into severe (GCS 3-8), moderate (GCS 9-12) and mild TBI (GCS 13-15).

Variations in primary outcome i.e. the hospital mortality between centers and provinces were analyzed in all 13138 patients using Logistic random effect models with a random intercept for center or province and adjustment for patient characteristics as fixed effects. Such models account for the fact that sample sizes per center may be small, introducing uncertainty, and for differences in patient populations between centers. Between-center variation was quantified with the median odds ratio (MOR), a measure based on the variance of the random effects. The MOR can be interpreted as the odds ratio for comparing two randomly selected centers. A MOR equal to one indicates no differences between centers. If there is considerable between-center variation, the MOR will be large. For example, a MOR of 2 for outcomes indicates that if two TBI patients with the same injury severity and characteristics presented to two random centers in our sample, one patient will have an over twofold probability of poor outcome.[9,10]

Kaplan-Meier survival analysis was performed in 13098 patients with discharge or death time, with patients discharged alive treated as censored data at the time of discharge and subsequently multivariable mixed effect Cox proportional hazards regression was applied to identify the risk factors for survival. To assess for proportionality, we checked if the survival curves crossed for each variable. Variables included formed a two-level hierarchical structure, with patients at level one and centre at level two. At the patient level, we included demographic and injury characteristics, clinical severity, and radiological findings. At the centre level, we included altitude and economic level. Altitude level was classified into three categories according to the geographical features of China, i.e., below 100 meters, between 100 and 500 meters and above 500 meters. The economic level was presented as GDP per capita of the province.

Observed 14 day mortality was compared to expected mortality determined by the CRASH basic model,[11] in 8351 patients with GCS <= 14 and all required covariates, and expressed as a ratio with 95% confidence intervals.

In secondary outcomes analyses, variations in emergency interventions and care paths between centers and provinces were analyzed using Logistic random effect models in all 13138 patients, and quantified with MOR.

Statistical analyses were performed using R (Version 3·5·0) statistical software, with Studio (Version 1·1·447) used as the implementation Integrated Development Environment (IDE). Kaplan-Meier survival analysis was performed with “survfit” function in “survival” package (Version 2·44-1·1). Multivariable mixed effect Cox proportional hazards regression was performed with “coxme” function in “coxme” package (Version 2·2-16). The logistic random effect regression models were fitted with the "glmer" function in "lme4" package (Version 1·1-19). A two-tailed p-value of 0·05 or less was used to define statistical significance. The study was registered with ClinicalTrials.gov, number NCT02210221.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
From 22nd, Dec, 2014, to 1st, Aug, 2017, 13627 patients with TBI from 56 centers were registered in the China CENTER-TBI registry. Among them, 489 patients lack necessary information including discharge status, GCS and pupillary reflex, and data of 13138 patients from 52 hospitals in 22 provinces of China met eligibility criteria and could be analyzed (figure 1, appendix p3 figure S1 and appendix p4 figure S2). 8317 were in the admission, 4747 in the ICU stratum and 74 lack stratum information. The median enrolment by centre was 137 patients (IQR: 51- 346, appendix p3 figure S1). Recruiting centres varied in terms of geographical and economic features, with the altitude level ranging from 2 to 1892 meters and the GDP per capita ranging from 28 to 129 thousand yuan (4142 to 18749 US dollars).

Characteristics of the patients enrolled, differentiated by stratum are presented in Table 1. The median age of all patients enrolled was 48 (IQR: 33-61) years, with 2217 (17%) > 65 years of age. Overall, males constituted 74% (n = 9782; ICU stratum 77%, n = 3661), and 95% of patients (n = 12539) were healthy or had only mild systemic diseases.

Road traffic incidents were the major cause of injury, occurring in 50% (n = 6548) of patients, followed by accidental fall (n = 4363; 33%) and other injury mechanisms (n = 1714; 13%). Ground level falls occurred in 18% (n = 2321) and falls from height in 16% (n = 2042). However, differences in injury mechanism were noted between provinces (appendix p5 figure S3).

We found that injury mechanisms differed by age (appendix p6 figure S4). Traffic incidents occurred more often in patients 18 to 65 years of age and decreased at higher ages, whilst ground level falls increased with age. Other injury mechanisms, mostly violence and suicide, peaked at ages 18-30.

Most of the injuries occurred on the streets or highways (n = 7287; 55%), whilst 22% (n = 2912) of patients were injured at home. The composition of injury places differed between strata. Compared with the general ward, a higher percentage of patients in the ICU were injured on streets or highways (n = 2890; 61%) and fewer at home (n = 850; 18%) (table 1).

Injuries causing TBI most commonly occurred between 9 am and 11 pm and peaked at 10 am (n = 1165; 8.9%), and patient arrival times showed similar trends (appendix p7 figure S5). At different arrival times, the causes of injury varied. Although road traffic incidents were the leading cause throughout the day, their proportion was relatively low in daytime. Conversely, the percentage of accidental falls, including ground level fall and fall from height, increased from 9 am to 7 pm (appendix p8 figure S6).

Overall, the median GCS was 13 (IQR: 9-15), and 2804 (21%), 2930 (22%) and 7404 (56%) respectively were classified as severe, moderate and mild TBI (table 1 and appendix p9 figure S7). ISS score showed that 886 (6·7%) patients suffered from mild to moderate injury (ISS 1-8), 4387 (33%) from serious injury (ISS 9-15), 4302 (33%) from severe injury (ISS 16-24) and 3563 (27%) from critical injury (ISS 25-75). 3646 (28%) patients suffered from major extracranial injuries (AIS non-head >= 3). 1365 patients (10%) had an abnormal pupillary light reflex, 279

(2·1%) arrived with systemic hypotension, and 1257 (9·6%) with hypoxia. Injury severity varied between admission and ICU stratum: ICU patients had lower GCS, more severe TBI, higher ISS, more major extracranial injuries, more pupillary abnormalities, more hypotension, and more hypoxia upon arrival, compared to general ward patients (table 1).

For primary outcome of 13138 patients, 637 (4·8%) patients died. Survival analysis estimated that 30-day survival rate was 94·5% (95%CI: 94·1% - 95·0%) and 90-day survival rate was 91·4% (95%CI: 90·1% - 92·7%) (figure 2). Of 2804 patients with severe TBI, 552 (19·7%) died. The leading cause of death was primary injury (n = 410, 64%), followed by secondary injury (n = 153, 24%), complications (n = 32, 5·0%), and systemic injury (n = 24, 3·8%). Survival time to death was related to death cause, primary brain injuries tend to cause early-stage mortality while death after 15 days was mainly due to complications (figure 2).

The CRASH basic model was fitted in 8351 patients with GCS <= 14 and all required covariates. The expected 14-day mortality was 1116 (13%), while 544 (6·5%) deaths within 14 days were observed (O/E ratio 0·49, 95% CI 0·45-0·53). Although overall mortality was lower than expected, the random effect model showed that odds of mortality varied substantially between provinces and hospitals (figure 3 and 4, appendix p13 table S1).

Potential predictors for primary outcome, i.e. hospital mortality were identified in univariate analysis (appendix p14-15 table S2). All variables met Cox's proportional hazard assumption. Multivariable mixed effect Cox regression showed that age, GCS, ISS, pupillary reflex, hypoxia, systemic hypotension, compressed basal cistern, midline shift > 5mm, altitude > 500 meters, and GDP per capita were significantly associated with survival in all cohort TBI patients and also in severe TBI patients (figure 5, appendix p10 figure S8).

The secondary outcomes included transferals and emergency interventions. A total of 3882 patients (30%) were transferred from another hospital to the study centre, with substantial variations in secondary referral rates across provinces (appendix p11 figure S9). Secondary referrals were more frequent in the ICU stratum (n = 1691, 36%), compared to the admission stratum (n = 2173, 26%, appendix p16 table S3).

A total of 2656 (20%) patients were emergently intubated, among which 154 received pre-hospital intubation, and 2502 were intubated in the emergency room before admission to the general ward or ICU (appendix p16 table S3).

Intracranial interventions, including ICP monitoring, external ventricular drainage (EVD), craniotomy and decompressive craniectomy were performed in 1509 (11%), 774 (5·9%), 2679 (20%) and 2170 (17%) patients respectively (appendix p16 table S3), with substantial variation occurring between provinces and centers (appendix p11 figure S9 and appendix p13 table S1). Overall, only 208 patients (1·6%) received extracranial surgery. Differences in treatments were demonstrated between strata (appendix p16 table S3).

Adjusting for center effects, it was shown that intracranial interventions, including ICP monitoring, EVD, craniotomy, and decompressive craniectomy decreased mortality in patients with severe TBI and absent pupillary light reflex, but not in those with normal pupillary response (appendix p12 figure S10).

Discussion

In this registry study, we present a contemporary picture of TBI in China. We found that, in China, adult patients in the ages 18-65 years old form the major part of the TBI population, that road traffic incidents remain the main cause of TBI and that most patients were in a normal healthy condition before the injury. Substantial differences in treatment and outcome were found between centres and regions. Overall, hospital mortality was 4·8%, which compares favorably to previous studies.[5]

These data indicate that the baseline of TBI in China has remained stable, compared with published cohort data collected from 2004, or from 2008 to 2009.[5,12] The proportion of severe TBI remains around 20%. In the present study, the median age is 48 years. These data indicate that unlike other regions, TBI in China remains a problem primarily of young and middle-aged adults, leading to huge losses in health and labor capacity.[13-15] Nonetheless, 18% of patients admitted to the ICU had been injured at home, illustrating that accidents occurring in daily life at home may lead to a serious head injury, which is in line with the evidence from other studies.[16] We anticipate that the changing demographics (ageing) of the population in China combined with further improvements in road traffic safety will lead to an increase of domestic injuries as cause of TBI in the near future, in particular in the elderly, thus following a trend observed in high income countries.[1]

On presentation to the emergency department, 1257 (9·6%) patients suffered hypoxia leading to a high rate of emergency intubations. Combined with the low rate (1·2%, n = 154) of on-scene intubations, these data indicate that the prehospital management of TBI patients needs further improvement regarding airway maintenance on-site or during transfer. Surgical interventions, including ICP device insertion, decompression, EVD and hematoma removal show clear therapeutic effects in patients with signs of brain herniation. The efficacy shown in this cohort likely reflects the greater severity of injuries, but from a clinical perspective it would be preferable to pre-emptively treat impending brain herniation, rather than to wait for its full development. Demonstrating effectiveness of these interventions in this cohort is of particular relevance given the lack of benefit reported in the overall populations of selected clinical trials.[17-19] Identification of subgroups most likely to benefit from these interventions should be a priority, that can be addressed in comparative effectiveness research.[20,21]

Of all patients admitted to the ICU with severe TBI, 64% did not receive an ICP device, thus implying that in many Chinese centres, clinical and image findings are still showing potential in driving treatments. The number of patients undergoing surgical treatments for extracranial injuries, was low in this cohort, likely reflecting admission policies of participating centres, where patients with more isolated TBI will be admitted to the neuro-intensive care unit, but patients with polytrauma to a general surgical ICU.

The overall mortality of 4·8% and of 19·7% in patients with severe TBI compares favorably to published series from high income countries and was lower than expected from the CRASH basic model.[11,22] The highest number of deaths occurred on the second day. Predictors of early mortality were in line with previous publications.[23-25] A unique finding from this cohort was that injury in higher altitude areas caused more death victims, and patients in areas of higher GDP had higher odds of mortality. Conceptually, these associations may be explained by centre effects, but this is rendered less likely by the random effects analysis which took centre into consideration. These results imply that the health policy to improve the care of TBI should also take into account the multiple geographic and developing levels, especially in China with variable natural, social, and economic status between provinces or regions.

We found substantial differences in case-mix, treatment and outcome across Chinese centres. Variations in injury mechanism and process of care were found between provinces, which is in line with reports from other studies.[8,26-28] Whilst the observed differences between provinces and centres offer potential to evaluate the performance of institute organization and professional behavior, they also indicate the need for initiatives to improve health care policy for TBI to take local aspects into consideration and to tailor head trauma systems to better fit the situation in different areas.

The China TBI registry was modelled on the CENTER-TBI European registry with an identical format for data collection and coding. The intrinsic "twin" studies feature illustrates the benefits of standardized data collection according to a common format, and highlights the relevance of understanding the heterogeneous nature of TBI and its treatments in different continents. Compared to the CENTER-TBI registry in Europe, Chinese patients had higher severity (median GCS 14 in China vs. 15 in Europe for admission stratum; median GCS 10 in China vs. 12 in Europe for ICU stratum) and more patients received craniotomy (8% in China vs. 1.5% in Europe for admission stratum; 42% in China vs. 16% in Europe for ICU stratum).[8] Chinese dataset provides evidence that different approaches may be appropriate for different settings. This supports the potential for comparing different registries and collaborative studies.[29,30]

The main strengths of our study are the large size of the cohort, the prospective recording of patient data and the multicentre organization for collecting data in China, covering 2/3 of all provinces, which increases representativeness of the data. The findings of this study provided a unique window to perceive the current profile of TBI in China, and the identical format to the CENTER-TBI registry in Europe permitted determination of similarities and differences between China and Europe. Some limitations should be recognized: *First,* we only analyzed data on patients admitted to 52 hospitals, not a nationwide population-based study. *Second,* data were collected from neuro-intensive care and neurosurgical units, and it should be recognized that patients with major extracranial injuries were underrepresented, as these are generally admitted to a general ICU in China. *Third*, outcome evaluation was limited to outcome on discharge and no information on long term complications and outcome collected. We consider it a priority for future studies in China to attempt to collect longer term outcomes. Despite these limitations, we consider our study to provide a representative picture of the current care for TBI across China, highlighting also differences in structure and processes of care, which provide both challenges and opportunities.

In conclusion, we prospectively collected demographic, clinical, treatment and hospital discharge data in a large cohort of patients with TBI in China. Despite observing substantial differences between centers or regions, mortality on discharge after adjustment for random effects and for case-mix and was better than expected according to the CRASH prognostic model. These data indicate that large scale collaborative studies between China and high income countries on TBI are feasible. The substantial differences between provinces and centres within China indicate the potential for comparative effectiveness research to explore best practices. Prognostic modelling confirmed the relevance of known predictors and identified new predictors including altitude and GDP. Clear therapeutic effects of third tier therapies were demonstrated in the most severely injured patients. Combined together, the results of this study indicate the feasibility of large scale collaborative studies including Chinese centres, inform policymaking for targeted TBI prevention and management, and provide evidence for decision making on clinical scenarios.

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Declaration of interest

GG, JJ and AIRM declare support to the CENTER-TBI project from the European Commission 7th Framework program.

AIRM declares consulting fees from PresSura Neuro, Integra Life Sciences and NeuroTrauma Sciences.

XW, JF, JH, QM, FL, and HL declare no competing interests.

Contributors' statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the concept, design, analysis, writing, or revision of the manuscript. All authors participated in the reported analyses and interpretation of results relevant to their domain of interest. GG, XW, JJ and AIRM prepared the draft manuscript and coordinated its finalization. JH performed the data extraction. XW, QM and JF performed statistical analyses and drafting of tables and figures. FL and HL revised the manuscript and gave support in statistical analyses and figures drafting. All authors approved the final manuscript.

Ethics statement

The China CENTER-TBI registry has been conducted in accordance with all relevant laws of the People's Republic of China, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of

Helsinki entitled “Ethical Principles for Medical Research Involving Human Subjects”. Ethical approval was obtained for all recruiting sites.

Data sharing statement:

Researchers who submit a methodologically sound study proposal that is approved by the management committee can have access to the study protocol, individual participant data, data dictionary, analytic code and analysis scripts. Proposals may be submitted online https://www.center-tbi.eu/data. A Data Access Agreement is required, and all access must comply with regulatory restrictions imposed on the original study.

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Figures and legends

Figure 1: Study population and selection process

Severe TBI patients: GCS 3-8, mild to moderate TBI patients: GCS 9-15.

Figure 2: Survival analysis and death causes

(A) Number of deaths on every single day after admission; (B) Kaplan-Meier curve for crude survival with 95% CI in the overall population within 90 days, showing that 30-day survival rate was 94.5% and 90-day survival rate was 91.4%; (C) Density plot of each death cause over time, in which the area under each death causes curve is 1, showing the time distribution of each death causes.

Figure 3: Variations in process of care for severe TBI patients between provinces

The log odds of discharge mortality per province compared with the overall average, showing the variations in mortality rate across China. The analyses were adjusted for baseline characteristics, clinical severity and CT result, and may reflect true differences in mortality.

Figure 4: Odds of mortality between centres

(A) Variation of mortality between centres in all TBI patients. (B) Variation of mortality between centres in severe TBI patients. The estimates are the (adjusted) log odds ratios for each centre for mortality, compared to the average centre. For example, a log odds of 1 means an exp(1)=2.7 times higher odds of mortality in that centre compared to the average centre. It is demonstrated that odds of mortality varied significantly between centres. Purple ones had odds of mortality significantly below average and green above average. Size of the diamond reflected the number of patients recruited in each centre.

Figure 5: Predictors for mortality in TBI patients

Multivariable mixed effect Cox regression showed that age, GCS, ISS, pupillary reflex, hypoxia, systemic hypotension, compressed basal cistern, midline shift > 5mm, altitude > 500 meters, and GDP per capita were significantly associated with mortality in TBI patients.

Manuscript with revisions highlighted

Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective, multicentre, longitudinal, observational study

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Summary

Background

Large scale collaborations are required to generate clinical evidence of traumatic brain injury (TBI) treatments. Current evidence is limited and mostly originates from western countries. China has a potential to generate strong evidence, but uncertainty exists how comparable the baseline, treatment and outcome is to other settings. We aimed to document the current care for TBI and its outcome in China by conducting a prospective, multicentre Chinese TBI registry.

Methods

This ~~a~~ prospective, multi-centre, longitudinal, observational study was conducted in 56 centres across China. It collected data of hospitalized patients with a clinical diagnosis of TBI and indication for computerized tomography (CT) scanning. The primary endpoint was survival on discharge. Prognostic analyses were applied to identify predictors of mortality. Variations in mortality were compared between centres and regions within China. Mortality was compared to expected mortality estimated by CRASH basic model. The study was registered with ClinicalTrials.gov, number NCT02210221.

Findings

From 22nd, Dec, 2014, to 1st, Aug, 2017, 13627 patients with TBI from 56 centers were enrolled in the China CENTER-TBI registry. Data of 13138 patients from 52 hospitals in 22 provinces of China were analyzed. Most patients were male (9782 [74%]), with a median age of 48 (IQR: 33-61). The median Glasgow Coma Scale (GCS) was 13 (IQR: 9-15) and major cause (6548 [50%]) of injury was traffic incident. Overall hospital mortality was 4.8% (637), and in severe TBI 19.7% (552). Age, GCS, Injury Severity Score, pupillary reflex, CT findings, hypoxia and hypotension showed predictive value for mortality. Economic level and altitude of the regions were correlated significantly with death. Variation in mortality existed between centres or regions. The observed mortality was lower than expected (O/E ratio 0·49, 95% CI 0·45-0·53).

Interpretation

The results show differences in mortality between centres and regions, which indicates potential for identifying best practices in comparative effectiveness research. The risk factors identified in prognostic analyses may contribute to developing benchmarks for assessing quality of care. The main strength of the study is the large study size and wide coverage of centres across China. The main limitation is that outcome was evaluated at discharge without follow up.

Funding

No specific funding was provided for the China TBI registry. The coordinating centre received support from the European Commission 7th Framework program (602150), in the context of CENTER-TBI.

Research in context

Evidence before this study

We searched PubMed for registry studies on traumatic brain injury (TBI) that reported on early outcome and its prediction on 1st, Nov, 2019, using search terms "traumatic brain injury AND prognosis AND registry study" without language or country restrictions. We found 152 articles, from which we identified 31 studies that met the search criteria. These articles analyzed the outcome and prognostic factors of TBI patients, however, multi-centre clinical registry studies of TBI in Chinese patient populations are scarce, of older dates and mostly do not contain data recorded in formats compatible with standardized common data elements. As a consequence, comparisons to other registries are not straightforward and the literature data may not reflect the current patterns of traumatic brain injury in China, which have evolved along with the substantial development of the socioeconomic status in China.

Added value of this study

To our knowledge, this is the first large scale Registry study on TBI in China that has captured data in an identical format as in CENTER-TBI Europen Registry Study, which is a prospective, multi-centre, longitudinal, observational study in 22 countries across Europe and Israel. The results of this study portray the profile of Chinese TBI patients' demographics, the prehospital management, the emergency and ICU treatment and the differences among Chinese centres. They present the real world of a big public health problem in a big country and provide a resource for future comparison between China and Europe.

Implications of all the available evidence

Heterogeneity of TBI and variation in healthcare may lead to different outcome of TBI patients in different centres or regions. Evidence from this study shows that patient characteristics, treatment approaches and mortality differ between centres, which provides opportunities for identification of best practices using comparative effectiveness research. Mortality was also related to regional features and economic level, which illustrates the need to tailor head trauma systems to better fit the situation in different areas. The results of this study, originating from China, a country with a large population, various geographical features, social development levels and with a huge burden of TBI, highlights the huge potential that collaborations with China may offer to advance the care for patients with TBI.

Introduction

Traumatic brain injury (TBI) presents a great challenge to public health worldwide. The heterogeneity of the disease, in terms of injury causes, mechanisms, approaches to treatment and outcome makes it a hugely complex problem compared to other diseases.[1] Large scale studies are required to better characterize the disease, to generate evidence in support of treatment recommendations and to improve outcome.[1] International collaborations offer the best potential to conduct such studies by increasing efficiency and generalizability and are strongly promoted by the International Initiative for Traumatic Brain Injury Research (InTBIR: https://intbir.nih.gov/), initiated as a collaboration of funding agencies.[2,3]

China has a large potential to contribute to such evidence, but uncertainty exists how comparable patient characteristics, treatment and outcome are to other settings. Some large clinical registry studies of TBI in Chinese patient populations exist, but these are of older dates or from local areas, and may not reflect the current patterns of traumatic brain injury in China, which have evolved along with the substantial development of the socioeconomic status in China. Moreover, most data of these studies were not recorded in formats compatible with standardized common data elements, making it not straightforward to compare with other registries.[4-6] In this study, we aimed to analyze epidemiological characteristics, management and outcome in an in-hospital cohort of TBI patients from centres in China.

Methods

Study design and participants

The China CENTER-TBI Registry is a prospective longitudinal observational study. It was modeled on the CENTER-TBI European Registry with an identical format for data collection and coding, and the study protocol and updated information was available on: www.center-tbi.eu.[7,8] Both studies included patients with a clinical diagnosis of TBI and indication for CT scanning. Data were prospectively collected from 56 Chinese neurosurgical centres in a 3-year period from 22nd, December, 2014 to 1st, August, 2017.

Patients were differentiated by care path into two strata: admission stratum (admitted to the general ward), and ICU stratum (primarily admitted to the intensive care unit). Patients discharged directly from the Emergency Room were not included.

Ethics statement: The study protocol was approved by the ethics committees of participating centres, who waived the need for informed consent as only routinely collected clinical data were recorded.

Data collection, handling, and storage

Clinical data of each patient was prospectively collected by one or more dedicated and trained physicians in each centre from patient medical records (paper or electronic) or personal interview. All data is in accordance with the medical records preserved in archives of each centre, which guarantees that all data is traceable. These variables included: demographics, medical history, injury characteristics, clinical and radiological severity upon arrival, emergency interventions, and care paths, including pre-hospital care system and transferals. Altitude and economic level were obtained from official government documents of National Bureau of Statistics.

Data were collected using a web-based electronic case report form (eCRF) and managed by the QuesGen data management platform. Data were coded in accordance with the Common Data Elements (CDE) scheme (https://www.commondataelements.ninds.nih.gov). All study data were de-identified and stored securely in the European data space under the supervision of Karolinska Institute International Neuroinformatics Coordinating Facility (KI-INCF). Automated data validation checks were run on data entry and central inspectors (GG and JH) continuously reviewed and checked uploaded data for data entry errors. More details for data collection, handling and storage are listed in appendix, p1-2.

Outcome

The primary outcome was survival at discharge. In case of in-hospital death, time and cause of death were recorded. Variations in primary outcome between centers and provinces were analyzed~~compared~~ and predictors for primary outcomee~~e were~~ identified. The secondary outcomes of this study included: transferals, and emergency interventions.

Statistical analysis

We excluded patients in whom information on discharge status or clinical severity (e.g.

Glasgow Coma Scale (GCS) and pupillary light reflex) was lacking (N=489). Missing values for other baseline characteristics were classified as "unknown". Continuous variables were reported as median and interquartile ranges (IQR), and categorical data as numbers and percentages. Patients were classified according to the GCS into severe (GCS 3-8), moderate (GCS 9-12) and mild TBI (GCS 13-15).

Variations in primary outcome i.e. the hospital mortality between centers and provinces were analyzed in all 13138 patients using Logistic random effect models with a random intercept for center or province and adjustment for patient characteristics as fixed effects. Such models account for the fact that sample sizes per center may be small, introducing uncertainty, and for differences in patient populations between centers. Between-center variation was quantified with the median odds ratio (MOR), a measure based on the variance of the random effects. The MOR can be interpreted as the odds ratio for comparing two randomly selected centers. A MOR equal to one indicates no differences between centers. If there is considerable between-center variation, the MOR will be large. For example, a MOR of 2 for outcomes indicates that if two TBI patients with the same injury severity and characteristics presented to two random centers in our sample, one patient will have an over twofold probability of poor outcome.[9,10]

Kaplan-Meier survival analysis was performed in 13098 patients with discharge or death time, with patients discharged alive treated as censored data at the time of discharge and subsequently multivariable mixed effect Cox proportional hazards regression was applied to identify the risk factors for survival. To assess for proportionality, we checked if the survival curves crossed for each variable. Variables included formed a two-level hierarchical structure, with patients at level one and centre at level two. At the patient level, we included demographic and injury characteristics, clinical severity, and radiological findings. At the centre level, we included altitude and economic level. Altitude level was classified into three categories according to the geographical features of China, i.e., below 100 meters, between 100 and 500 meters and above 500 meters. The economic level was presented as GDP per capita of the province.

Observed 14 day mortality was compared to expected mortality determined by the CRASH basic model,[11] in 8351 patients with GCS <= 14 and all required covariates, and expressed as a ratio with 95% confidence intervals.In 8351 patients with GCS <= 14 and all required covariates, observed mortality within 14 days was compared to expected mortality determined by the CRASH basic model,[11] and expressed as a ratio with 95% confidence intervals.

In secondary outcomes analyses, vVariations in emergency interventions and care paths between centers and provinces were also analyzed using Logistic random effect models in all 13138 patients, and quantified with MOR.

Statistical analyses were performed using R (Version 3·5·0) statistical software, with Studio (Version 1·1·447) used as the implementation Integrated Development Environment (IDE). Kaplan-Meier survival analysis was performed with “survfit” function in “survival” package

(Version 2·44-1·1). The logistic random effect regression models were fitted with the "glmer" function in "lme4" package (Version 1·1-19). Multivariable mixed effect Cox proportional hazards regression was performed with "coxme" function in "coxme" package (Version 2·2-16). The logistic random effect regression models were fitted with the "glmer" function in "lme4" package (Version 1·1-19). A two-tailed p-value of 0·05 or less was used to define statistical significance. The study was registered with ClinicalTrials.gov, number NCT02210221.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From 22nd, Dec, 2014, to 1st, Aug, 2017, 13627 patients with TBI from 56 centers were registered in the China CENTER-TBI registry. Among them, 489 patients lack necessary information including discharge status, GCS and pupillary reflex, and data of 13138 patients from 52 hospitals in 22 provinces of China met eligibility criteria and could be analyzed (figure 1, appendix p3 figure S1 and appendix p4 figure S2). 8317 were in the admission, 4747 in the ICU stratum and 74 lack stratum information. The median enrolment by centre was 137 patients (IQR: 51- 346, appendix p3 figure S1). Recruiting centres varied in terms of geographical and economic features, with the altitude level ranging from 2 to 1892 meters and the GDP per capita ranging from 28 to 129 thousand yuan (4142 to 18749 US dollars).

Characteristics of the patients enrolled, differentiated by stratum are presented in Table 1. The median age of all patients enrolled was 48 (IQR: 33-61) years, with 2217 (17%) > 65 years of age. Overall, males constituted 74% (n = 9782; ICU stratum 77%, n = 3661), and 95% of patients (n = 12539) were healthy or had only mild systemic diseases.

Road traffic incidents were the major cause of injury, occurring in 50% (n = 6548) of patients, followed by accidental fall (n = 4363; 33%) and other injury mechanisms (n = 1714; 13%). Ground level falls occurred in 18% (n = 2321) and falls from height in 16% (n = 2042). However, differences in injury mechanism were noted between provinces (appendix p5 figure S3~~2~~).

We found that injury mechanisms differed by age (appendix p6~~5~~ figure S4~~3~~). Traffic incidents occurred more often in patients 18 to 65 years of age and decreased at higher ages, whilst ground level falls increased with age. Other injury mechanisms, mostly violence and suicide, peaked at ages 18-30.

Most of the injuries occurred on the streets or highways (n = 7287; 55%), whilst 22% (n = 2912) of patients were injured at home. The composition of injury places differed between strata. Compared with the general ward, a higher percentage of patients in the ICU were injured on streets or highways (n = 2890; 61%) and fewer at home (n = 850; 18%) (table 1).

Injuries causing TBI most commonly occurred between 9 am and 11 pm and peaked at 10 am (n = 1165; 8.9%), and patient arrival times showed similar trends (appendix p7~~6~~ figure S5~~4~~). At different arrival times, the causes of injury varied. Although road traffic incidents were the leading cause throughout the day, their proportion was relatively low in daytime. Conversely, the percentage of accidental falls, including ground level fall and fall from height, increased from 9 am to 7 pm (appendix p8~~7~~ figure S6~~5~~).

Overall, the median GCS was 13 (IQR: 9-15), and 2804 (21%), 2930 (22%) and 7404 (56%) respectively were classified as severe, moderate and mild TBI (table 1 and appendix p9~~8~~ figure S7~~6~~). ISS score showed that 886 (6·7%) patients suffered from mild to moderate injury (ISS 1-8), 4387 (33%) from serious injury (ISS 9-15), 4302 (33%) from severe injury (ISS 16-24) and 3563 (27%) from critical injury (ISS 25-75). 3646 (28%) patients suffered from major extracranial injuries (AIS non-head >= 3). 1365 patients (10%) had an abnormal pupillary light reflex, 279 (2·1%) arrived with systemic hypotension, and 1257 (9·6%) with hypoxia. Injury severity varied between admission and ICU stratum: ICU patients had lower GCS, more severe TBI, higher ISS, more major extracranial injuries, more pupillary abnormalities, more hypotension, and more hypoxia upon arrival, compared to general ward patients (table 1).

For primary outcome of 13138 patients, 637 (4·8%) patients died. Survival analysis estimated that 30-day survival rate was 94·5% (95%CI: 94·1% - 95·0%) and 90-day survival rate was 91·4% (95%CI: 90·1% - 92·7%) (appendix p9 figure S27). Of 2804 patients with severe TBI, 552 (19·7%) died. The leading cause of death was primary injury (n = 410, 64%), followed by secondary injury (n = 153, 24%), complications (n = 32, 5·0%), and systemic injury (n = 24, 3·8%). Survival time to death was related to death cause, primary brain injuries tend to cause early-stage mortality while death after 15 days was mainly due to complications (appendix p9 figure S7figure 2).

The CRASH basic model was fitted in 8351 patients with GCS <= 14 and all required covariates. The expected 14-day mortality was 1116 (13%), while 544 (6·5%) deaths within 14 days were observed (O/E ratio 0·49, 95% CI 0·45-0·53). Although overall mortality was lower than expected, the random effect model showed that odds of mortality varied substantially significantly between provinces and hospitals (figure 3 A and 4, appendix p132 table S1).

Potential predictors for primary outcome, i.e. hospital mortality were identified in univariate analysis (appendix p143-154 table S2). All variables met Cox's proportional hazard assumption. Multivariable mixed effect Cox regression showed that age, GCS, ISS, pupillary reflex, hypoxia, systemic hypotension, compressed basal cistern, midline shift > 5mm, altitude > 500 meters, and GDP per capita were significantly associated with survival in all cohort TBI patients and also in severe TBI patients (figure 5, appendix p10 figure S8).

The secondary outcomes included transferals and emergency interventions. A total of 3882 patients (30%) were transferred from another hospital to the study centre, with substantial variations in secondary referral rates across provinces (appendix p11 figure S9 3 B and appendix p15 table S3). Secondary referrals were more frequent in the ICU stratum (n = 1691, 36%), compared to the admission stratum (n = 2173, 26%, appendix p16 table S3).

A total of 2656 (20%) patients were emergently intubated, among which 154 received pre-hospital intubation, and 2502 were intubated in the emergency room before admission to the general ward or ICU (appendix p165 table S3).

Intracranial interventions, including ICP monitoring, external ventricular drainage (EVD), craniotomy and decompressive craniectomy were performed in 1509 (11%), 774 (5·9%), 2679 (20%) and 2170 (17%) patients respectively (appendix p165 table S3), with substantial variation occurring between provinces and centers (appendix p11 figure S9figure 3 C-D and appendix p132 table S1). Overall, only 208 patients (1·6%) received extracranial surgery. Differences in treatments were demonstrated between strata (appendix p165 table S3).

Adjusting for center effects, it was shown that intracranial interventions, including ICP monitoring, EVD, craniotomy, and decompressive craniectomy decreased mortality in patients with severe TBI and absent pupillary light reflex, but not in those with normal pupillary response (appendix p121 figure S109).

Discussion

In this registry study, we present a contemporary picture of TBI in China. We found that, in China, adult patients in the ages 18-65 years old form the major part of the TBI population, that road traffic incidents remain the main cause of TBI and that most patients were in a normal healthy condition before the injury. Substantial differences in treatment and outcome were found between centres and regions. Overall, hospital mortality was 4·8%, which compares favorably to previous studies.[5]

These data indicate that the baseline of TBI in China has remained stable, compared with published cohort data collected from 2004, or from 2008 to 2009.[5,12] The proportion of severe TBI remains around 20%. In the present study, the median age is 48 years. These data indicate that unlike other regions, TBI in China remains a problem primarily of young and middle-aged adults, leading to huge losses in health and labor capacity.[13-15] Nonetheless, 18% of patients admitted to the ICU had been injured at home, illustrating that accidents occurring in daily life at home may lead to a serious head injury, which is in line with the evidence from other studies.[16] We anticipate that the changing demographics (ageing) of the population in China combined with further improvements in road traffic safety will lead to an increase of domestic injuries as cause of TBI in the near future, in particular in the elderly, thus following a trend observed in high income countries.[1]

On presentation to the emergency department, 1257 (9·6%) patients suffered hypoxia leading to a high rate of emergency intubations. Combined with the low rate (1·2%, n = 154) of on-scene intubations, these data indicate that the prehospital management of TBI patients needs further improvement regarding airway maintenance on-site or during transfer. Surgical interventions, including ICP device insertion, decompression, EVD and hematoma removal show clear therapeutic effects in patients with signs of brain herniation. The efficacy shown in this cohort likely reflects the greater severity of injuries, but from a clinical perspective it would be preferable to pre-emptively treat impending brain herniation, rather than to wait for its full development. Demonstrating effectiveness of these interventions in this cohort is of particular relevance given the lack of benefit reported in the overall populations of selected clinical trials.[17-19] Identification of subgroups most likely to benefit from these interventions should be a priority, that can be addressed in comparative effectiveness research.[20,21]

Of all patients admitted to the ICU with severe TBI, 64% did not receive an ICP device, thus implying that in many Chinese centres, clinical and image findings are still showing potential in driving treatments. The number of patients undergoing surgical treatments for extracranial injuries, was low in this cohort, likely reflecting admission policies of participating centres, where patients with more isolated TBI will be admitted to the neuro-intensive care unit, but patients with polytrauma to a general surgical ICU.

The overall mortality of 4·8% and of 19·7% in patients with severe TBI compares favorably to published series from high income countries and was lower than expected from the CRASH basic model.[11,22] The highest number of deaths occurred on the second day. Predictors of early mortality were in line with previous publications.[23-25] A unique finding from this cohort was that injury in higher altitude areas caused more death victims, and patients in areas of higher GDP had higher odds of mortality. Conceptually, these associations may be explained by centre effects, but this is rendered less likely by the random effects analysis which took centre into consideration. These results imply that the health policy to improve the care of TBI should also take into account the multiple geographic and developing levels, especially in China with variable natural, social, and economic status between provinces or regions.

We found substantial differences in case-mix, treatment and outcome across Chinese centres. Variations in injury mechanism and process of care were found between provinces, which is in line with reports from other studies.[8,26-28] Whilst the observed differences between provinces and centres offer potential to evaluate the performance of institute organization and professional behavior, they also indicate the need for initiatives to improve health care policy for TBI to take local aspects into consideration and to tailor head trauma systems to better fit the situation in different areas.

The China TBI registry was modelled on the CENTER-TBI European registry with an identical format for data collection and coding. The intrinsic "twin" studies feature illustrates the benefits of standardized data collection according to a common format, and highlights the relevance of understanding the heterogeneous nature of TBI and its treatments in different continents. Compared to the CENTER-TBI registry in Europe, Chinese patients had higher severity (median GCS 14 in China vs. 15 in Europe for admission stratum; median GCS 10 in China vs. 12 in Europe for ICU stratum) and more patients received craniotomy (8% in China vs. 1.5% in Europe for admission stratum; 42% in China vs. 16% in Europe for ICU stratum).[8] Chinese dataset provides evidence that different approaches may be appropriate for different settings. This supports the potential for comparing different registries and collaborative studies.[29,30]

The main strengths of our study are the large size of the cohort, the prospective recording of patient data and the multicentre organization for collecting data in China, covering 2/3 of all provinces, which increases representativeness of the data. The findings of this study provided a unique window to perceive the current profile of TBI in China, and the identical format to the CENTER-TBI registry in Europe permitted determination of similarities and differences between China and Europe. Some limitations should be recognized: *First,* we only analyzed data on patients admitted to 52 hospitals, not a nationwide population-based study. *Second,* data were collected from neuro-intensive care and neurosurgical units, and it should be recognized that patients with major extracranial injuries were underrepresented, as these are generally admitted to a general ICU in China. *Third*, outcome evaluation was limited to outcome on discharge and no information on long term complications and outcome collected. We consider it a priority for future studies in China to attempt to collect longer term outcomes. Despite these limitations, we consider our study to provide a representative picture of the current care for TBI across China, highlighting also differences in structure and processes of care, which provide both challenges and opportunities.

In conclusion, we prospectively collected demographic, clinical, treatment and hospital discharge data in a large cohort of patients with TBI in China. Despite observing substantial differences between centers or regions, mortality on discharge after adjustment for random effects and for case-mix and was better than expected according to the CRASH prognostic model. These data indicate that large scale collaborative studies between China and high income countries on TBI are feasible. The substantial differences between provinces and centres within China indicate the potential for comparative effectiveness research to explore best practices. Prognostic modelling confirmed the relevance of known predictors and identified new predictors including altitude and GDP. Clear therapeutic effects of third tier therapies were demonstrated in the most severely injured patients. Combined together, the results of this study indicate the feasibility of large scale collaborative studies including Chinese centres, inform policymaking for targeted TBI prevention and management, and provide evidence for decision making on clinical scenarios.

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Declaration of interest

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XW, JF, JH, QM, FL, and HL declare no competing interests.

Contributors' statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the concept, design, analysis, writing, or revision of the manuscript. All authors participated in the reported analyses and interpretation of results relevant to their domain of interest. GG, XW, JJ and AIRM prepared the draft manuscript and coordinated its finalization. JH performed the data extraction. XW, QM and JF performed statistical analyses and drafting of tables and figures. FL and HL revised the manuscript and gave support in statistical analyses and figures drafting. All authors approved the final manuscript.

Ethics statement

The China CENTER-TBI registry has been conducted in accordance with all relevant laws of the People's Republic of China, including but not limited to, the relevant privacy and data protection laws and regulations (the "Privacy Law"), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) ("ICH GCP") and the World Medical Association Declaration of

Helsinki entitled “Ethical Principles for Medical Research Involving Human Subjects”. Ethical approval was obtained for all recruiting sites.

Data sharing statement:

Researchers who submit a methodologically sound study proposal that is approved by the management committee can have access to the study protocol, individual participant data, data dictionary, analytic code and analysis scripts. Proposals may be submitted online https://www.center-tbi.eu/data. A Data Access Agreement is required, and all access must comply with regulatory restrictions imposed on the original study.

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Figures and legends

Figure 1: Study population and selection process

Severe TBI patients: GCS 3-8, mild to moderate TBI patients: GCS 9-15.

Figure 2: Survival analysis and death causes

(A) Number of deaths on every single day after admission; (B) Kaplan-Meier curve for crude survival with 95% CI in the overall population within 90 days, showing that 30-day survival rate was 94.5% and 90-day survival rate was 91.4%; (C) Density plot of each death cause overwith time, in which the area under each death causes curve is 1, showing the time distribution of each death causes.

Figure 2: Variation in injury mechanisms in 22 provinces in China

Centres were grouped according to the provinces, and patients of centres in the same province were clustered for analysis.

Figure 33: Variations in process of care for severe TBI patients between provinces

(A) The log odds of discharge mortality per province compared with the overall average, showing the variations in mortality rate across China.; (B) The percentage of severe TBI patients referred from another hospital, per province, showing the variations in percentage of secondary referral across China; (C) The log odds of ICP monitoring per province compared with the overall average, showing the variations in ICP monitoring rate across China; (D) The log odds of external ventricular drainage (EVD) per province compared with the overall average, showing the variations in EVD rate across China; (E) The log odds of craniotomy per province compared with the overall average, showing the variations in craniotomy rate across China; (F) The log odds of decompression craniectomy (DC) per province compared with the overall average, showing the variations in DC rate across China. The interventions and Themortality analyses were adjusted for baseline characteristics, clinical severity and CT result, and may reflect true differences in mortalitypolicy.

Figure 44: Odds of mortality between centres

(A) Variation of mortality between centres in all TBI patients. (B) Variation of mortality between centres in severe TBI patients. The estimates are the (adjusted) log odds ratios for each centre for mortality, compared to the average centre. For example, a log odds of 1 means an exp(1)=2.7 times higher odds of mortality in that centre compared to the average centre. It is demonstrated that odds of mortality varied significantly between centres. Purple ones had odds of mortality significantly below average and green above average. Size of the diamond reflected the number of patients recruited in each centre.

Figure 5: Predictors for mortality in TBI patients

Multivariable mixed effect Cox regression showed that age, GCS, ISS, pupillary reflex, hypoxia, systemic hypotension, compressed basal cistern, midline shift > 5mm, altitude > 500 meters, and GDP per capita were significantly associated with mortality in TBI patients.

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2nd, May, 2020

Dear Dr. Wulff:

Enclosed please find the revised paper entitled "*Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective, multicentre, longitudinal, observational study*" (THELANCETNEUROLOGY-D-19-01039R4).

I would like to appreciate you and the reviewers for all the efforts devoted to the paper in the past months.

We have now replied all the editorial concerns and questions on the following pages in "Point by point responses".

Because the corresponding author has multiple affiliations, we now detailed in the text.

One clean copy of the revised manuscript together with an edit-tracking copy which highlighted the changes were uploaded.

I am looking forward to hearing from you soon.

Thank you.

Best wishes,

Ji-yao Jiang

Professor and chairman

Department of Neurosurgery, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, People's Republic of China.

E-mail: jiyaojiang@126.com

Point by Point Response to Editor:

Editorial points to be addressed:

1. Abstract:

a) Based on the outcome section in the main text "The primary outcome was survival at discharge. In case of in-hospital death, time and cause of death were recorded. The secondary outcomes included: transferals, and emergency interventions."

b) Please only report the primary outcome (ie, survival at discharge) in the abstract. Remove all other analyses and outcomes.
Reply: The secondary outcomes including transferals and emergency interventions were removed from the abstract section in an earlier version. Please specify any amendment if necessary.

c) The interpretation needs to be amended as secondary outcomes will need to be removed from here.
Reply: The secondary outcomes including transferals and emergency interventions were not reported in the interpretation section. Please specify any amendment if necessary.

d) Move figure S7 (ie, the Kaplan-Meier curve) from the appendix to the main text as this was the primary outcome. Ensure that this figure is editable. Please add 95% CI to all time-to-event data and other data derived from Kaplan-Meier analyses. Please include number at risk (and, if available, number censored) in each group for each time point on any Kaplan-Meier curves. X axis should start at 0.
Reply: Figure S7 was moved to the main text (Current Figure 2), with each individual part uploaded as eps file and a combined version was also uploaded. Part C contains transparency in layers which causes error in exporting as eps in R. Now it is first exported as pdf then converted to eps, and please inform us if you fail to edit it. 95% CI was added to the K-M plot and number at risk was reported. The current X axis starts at 0.

2. There are several other analyses and outcomes reported in the result section of the main text, however, these have not been described in the outcome section (eg, predictors for hospital mortality; variations in hospital mortality between centers and provinces) nor described as secondaty outcomes in the statitistcial analyses section. Please add and ensure that the order of the method section, statistical analyses and result section has the following order: primary outcome, secondary outcomes, and finally any post-hoc or sensitivity analyses. This is not clear yet throughout the manuscript.
Reply: Predictors and variations for primary outcome are now described in the outcome section and in the statistical analyses. The Methods and Results sections

are now in the order above. The methods and results for secondary outcomes including transferals and emergency interventions were described after primary outcome.

3. „In 8351 patients with GCS <= 14“ – does it mean all TBI patients? Why not “mild to moderate TBI GCS of 15 or less”? Please clarify and adjust text if needed
Reply: The observed mortality of this study was compared with the predicted mortality by CRASH model, which only fits for patients with Glasgow coma score (GCS) of 14 or less, so we selected patients who met the CRASH model criteria before comparing. We now clarify this in the Methods section.

4. Table 1:
a) Please add row for females
Reply: We made adjustments accordingly.

b) Please add subheadings to guide the reader (eg, Demographic characteristics, Pre-injury health status and medical history, Cause of injury, Clinical presentation or whatever might be appropriate). This will help to compare it wit the European TBI Center study
Reply: We made adjustments accordingly.

5. Some work is needed on the figures: only main results should be illustrated in the main text, all other plots need to be moved to the appendix
Reply: Figure 2, which describes the injury mechanisms rather the primary outcome, is now moved to the appendix (Current Figure S3). Please let us know if there is any other figure that you think should be removed from the main text.

6. Figure 2 and 4 are not editable. Please submit editable figures
Reply: All the figures uploaded are now editable. Current Figure 2 (Original Figure S7) is composed of 3 individual parts, and each part was uploaded as eps file. Part C contains transparency in layers which causes error in exporting as eps in R. Now it is first exported as pdf then converted to eps, and please inform us if you fail to edit it.

7. Figure 4: there are no centres mentioned in the graph – please provide.
Reply: All the centre ID were provided in the graph now.

8. Figure 3: please only keep Figure 3 A and move all other graphs to the appendix; please rewrite the figure title to reflect the context better
Reply: We have made adjustment accordingly.

9. Figure 5: Table 1:
a) Please add row for females
Reply: In Cox regression, female was chosen as reference, and was explained in the graph.

In summary, the signed statements we require are:
* Authors' contribution and signatures
* Signed conflict of interest statements for ALL authors
Reply: We have uploaded the signatures and statements for all authors.

Please also check whether you need to provide the following:
* Signed copyright permissions for previously published material
Reply: Not applicable.

* Signed consent from individuals cited in the Acknowledgements
Reply: We have uploaded Signed consent from all individuals cited in the Acknowledgements.

* Signed consent for use of cited personal communications
Reply: Not applicable.

* Signed patient's consent and permission to publish (if not already submitted)
Reply: Not applicable.

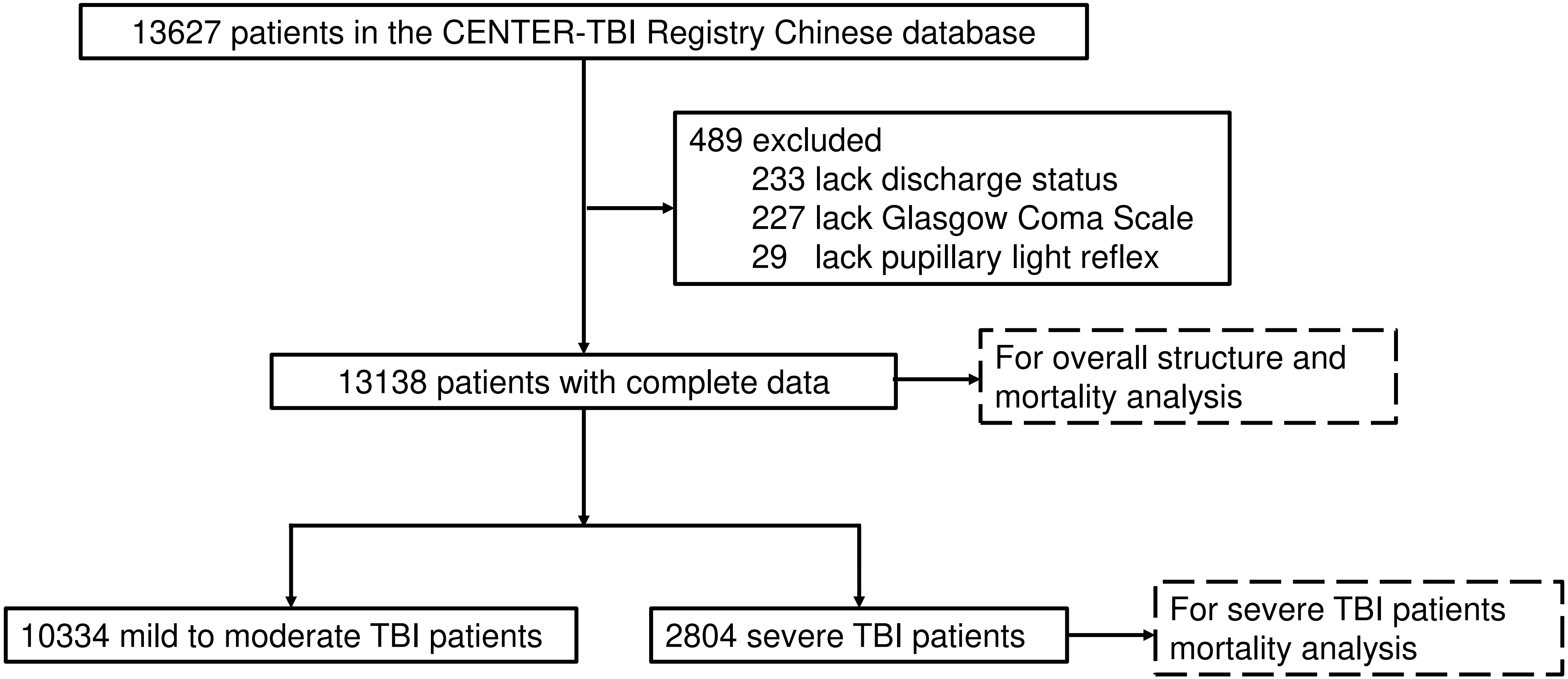
13627 patients in the CENTER-TBI Registry Chinese database
489 excluded
233 lack discharge status
227 lack Glasgow Coma Scale
29 lack pupillary light reflex
13138 patients with complete data
For overall structure and mortality analysis
10334 mild to moderate TBI patients
2804 severe TBI patients
For severe TBI patients mortality analysis

Figure 2 A

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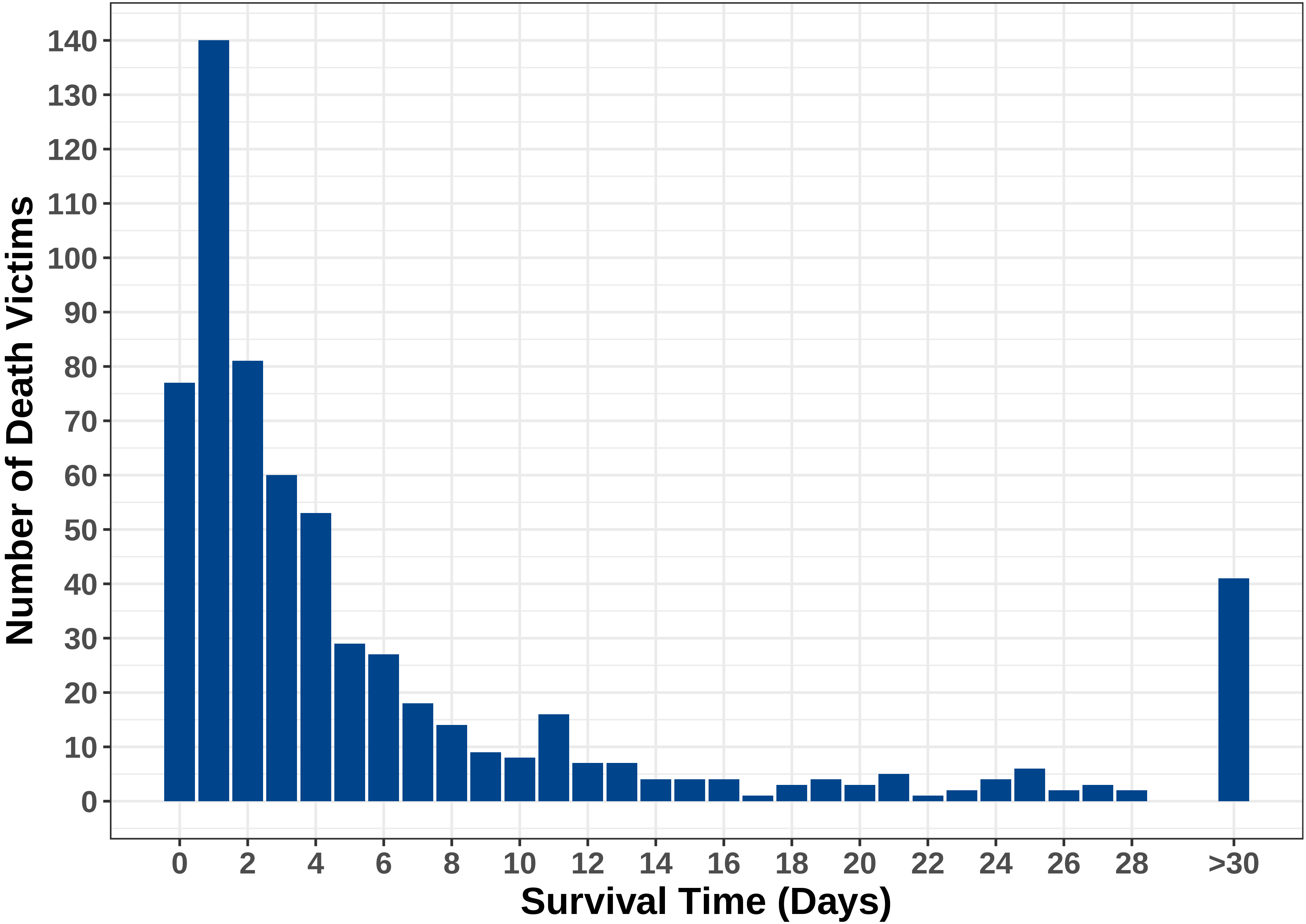
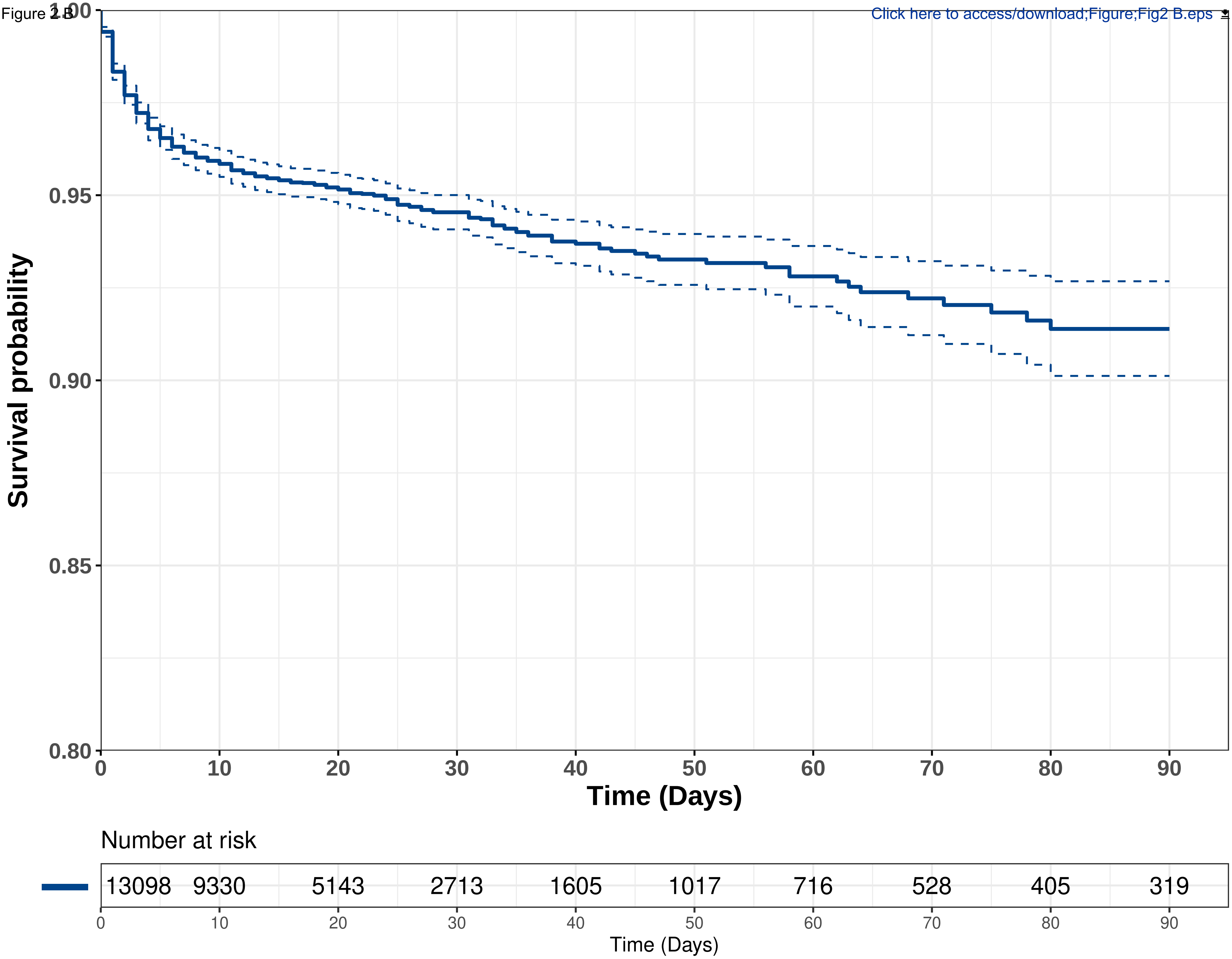


Figure 2.B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Time (Days)

Figure 2 C

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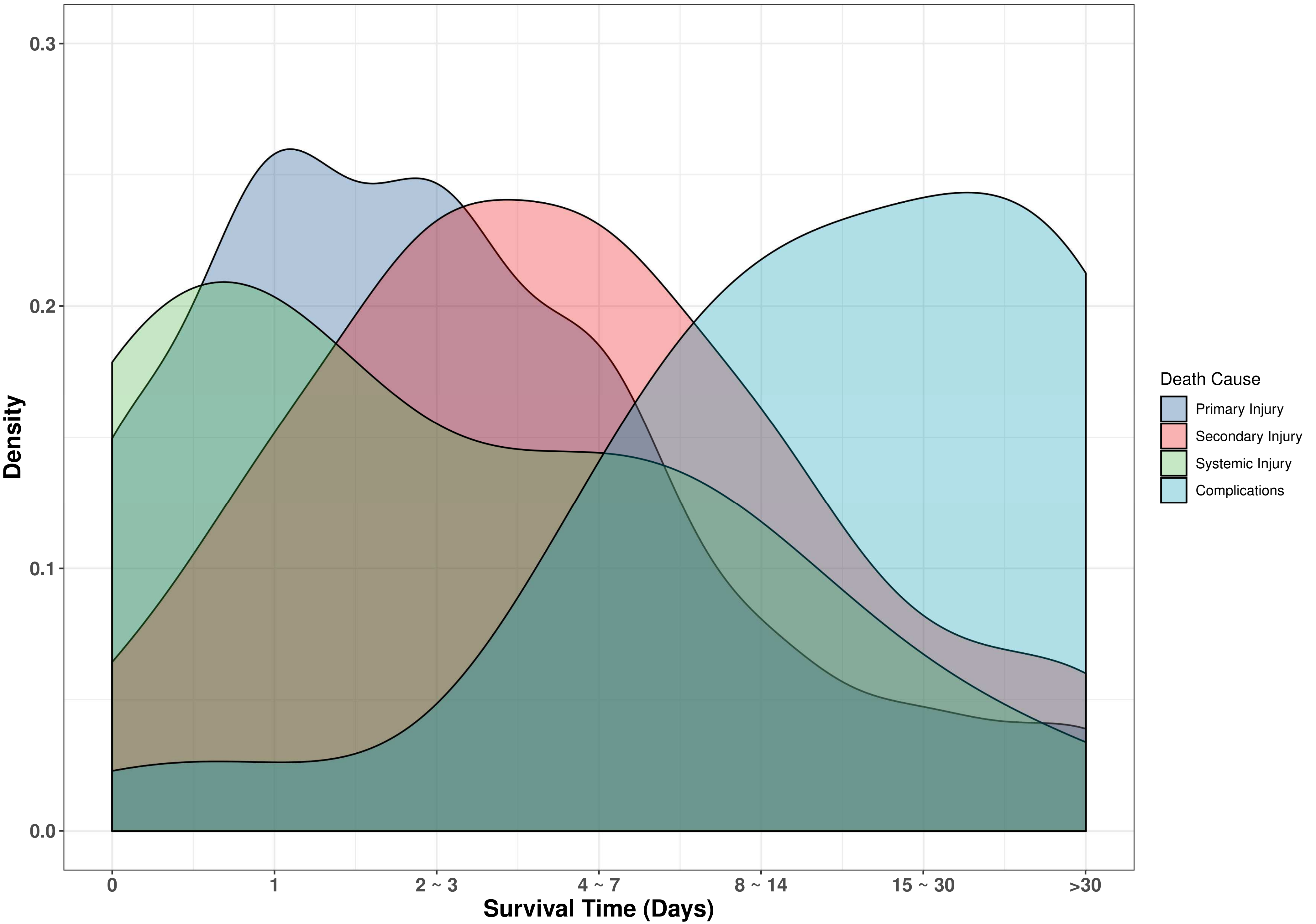

Figure 2 C editable PDF format

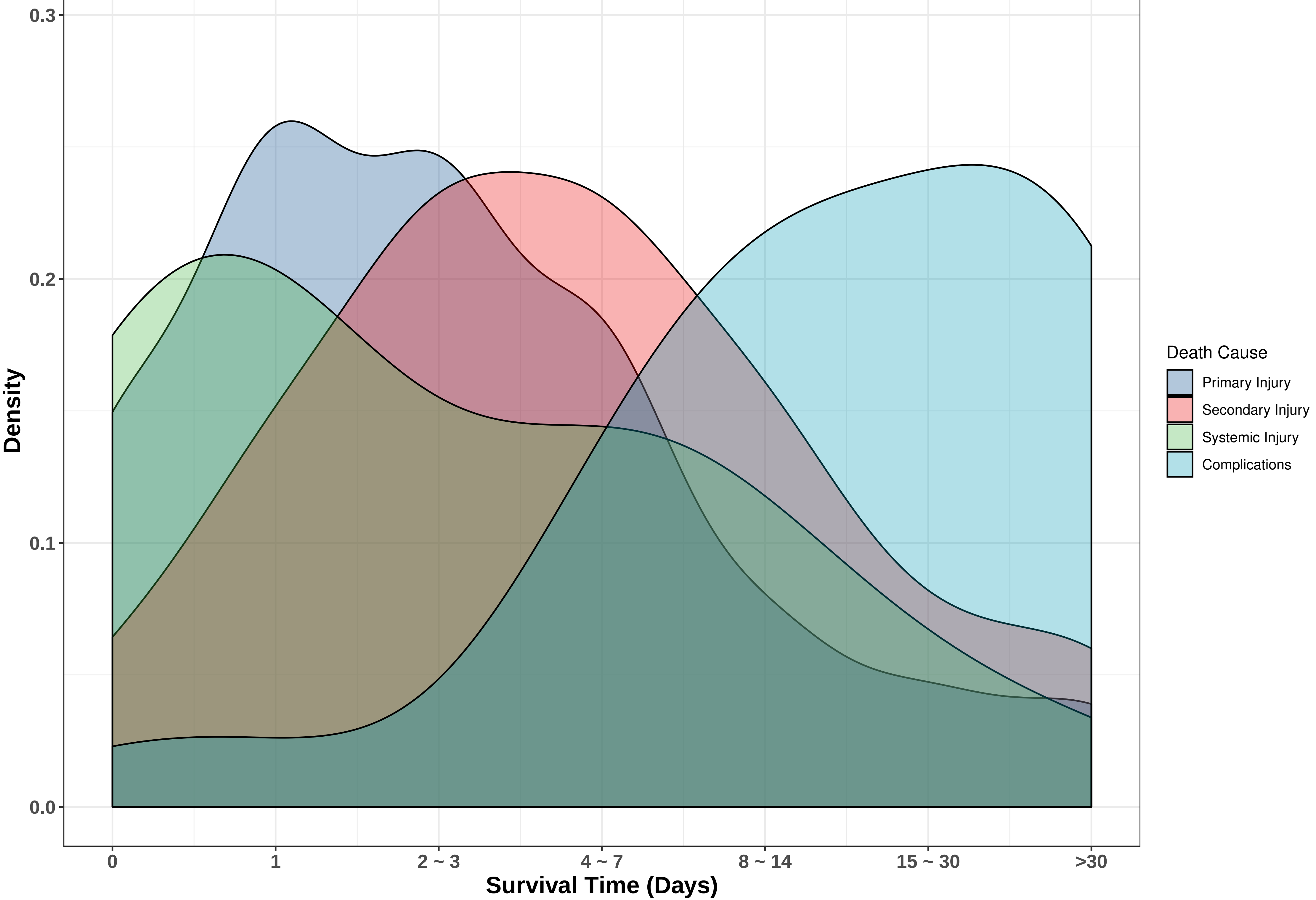

Figure 2 Combined

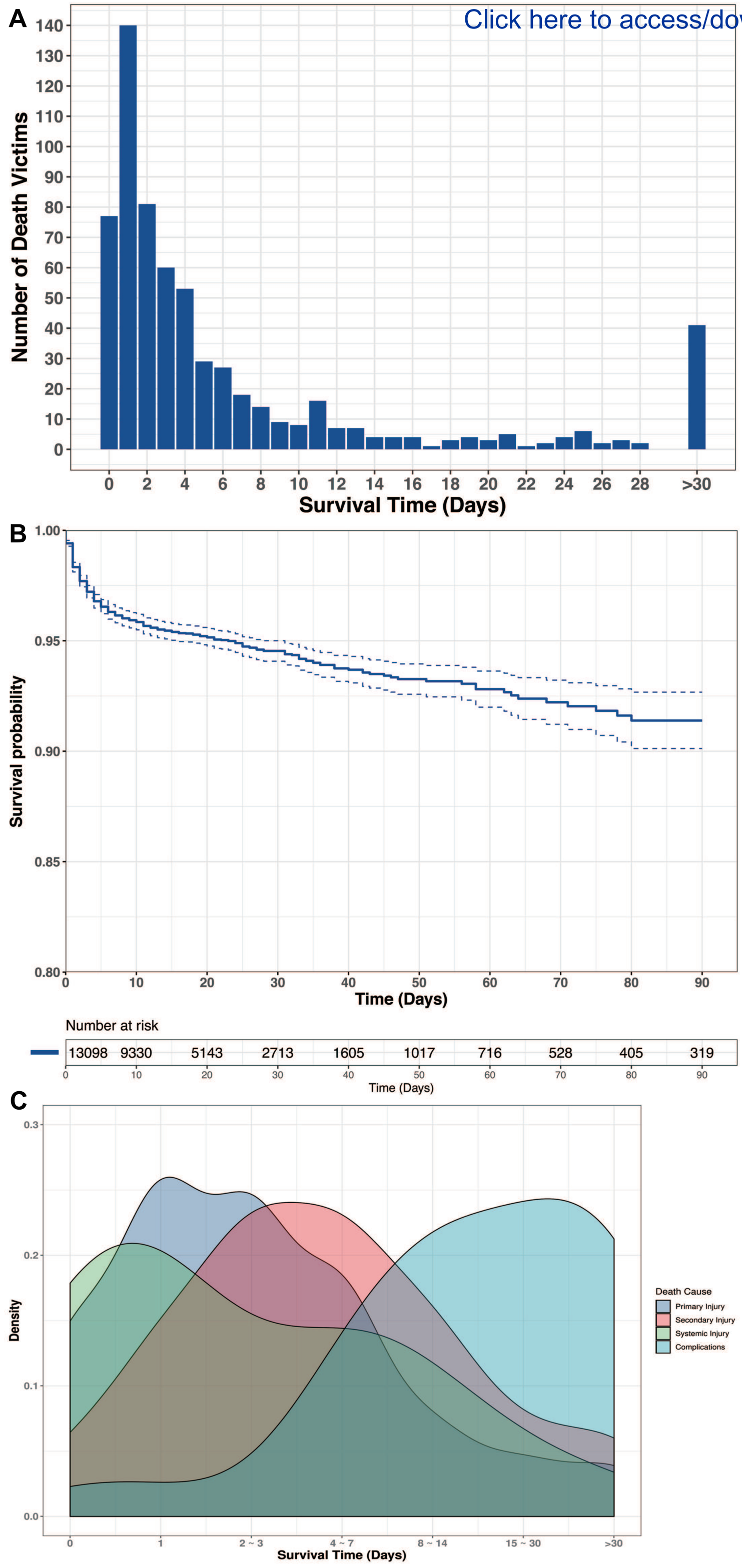

Figure 3

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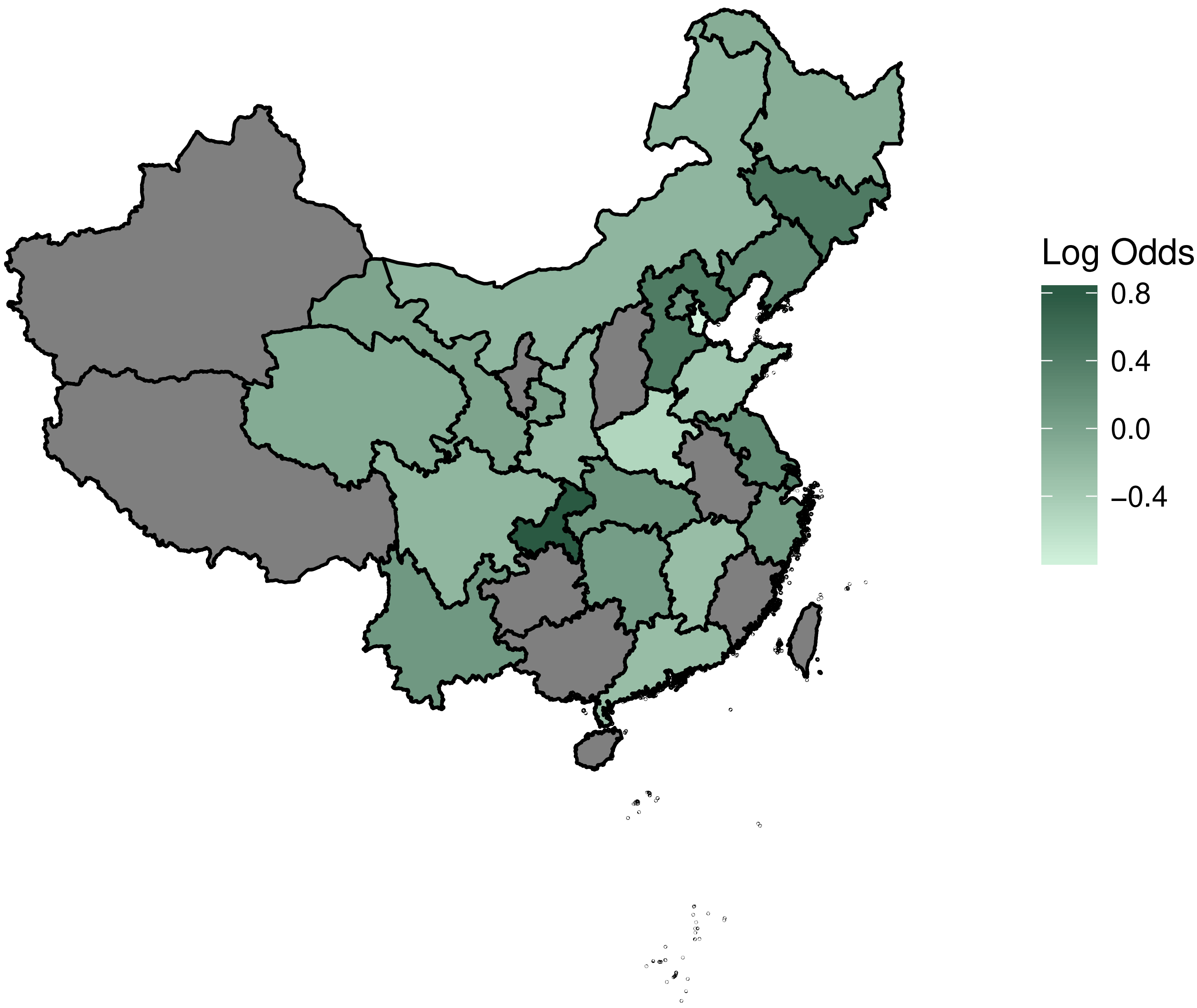

Figure 4

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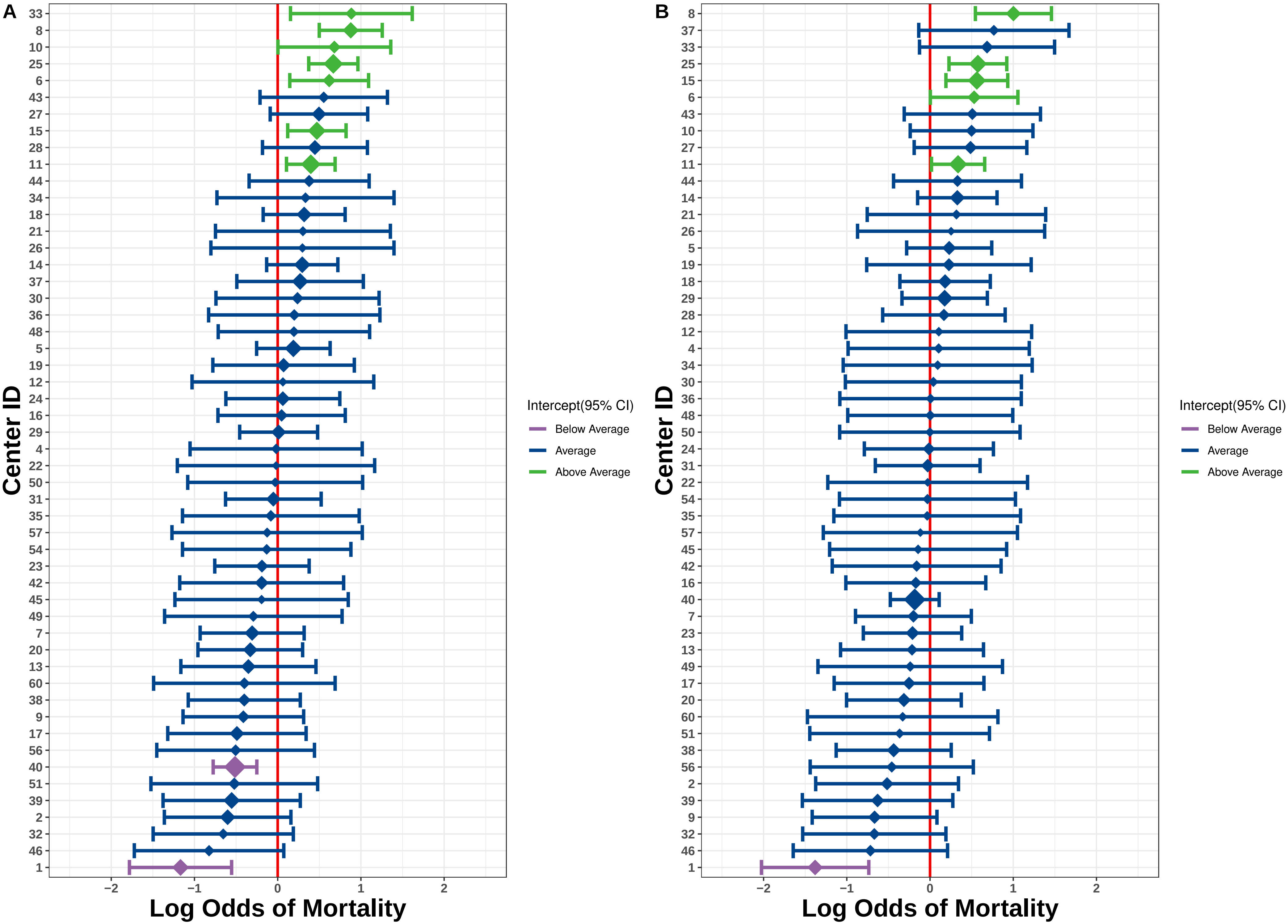
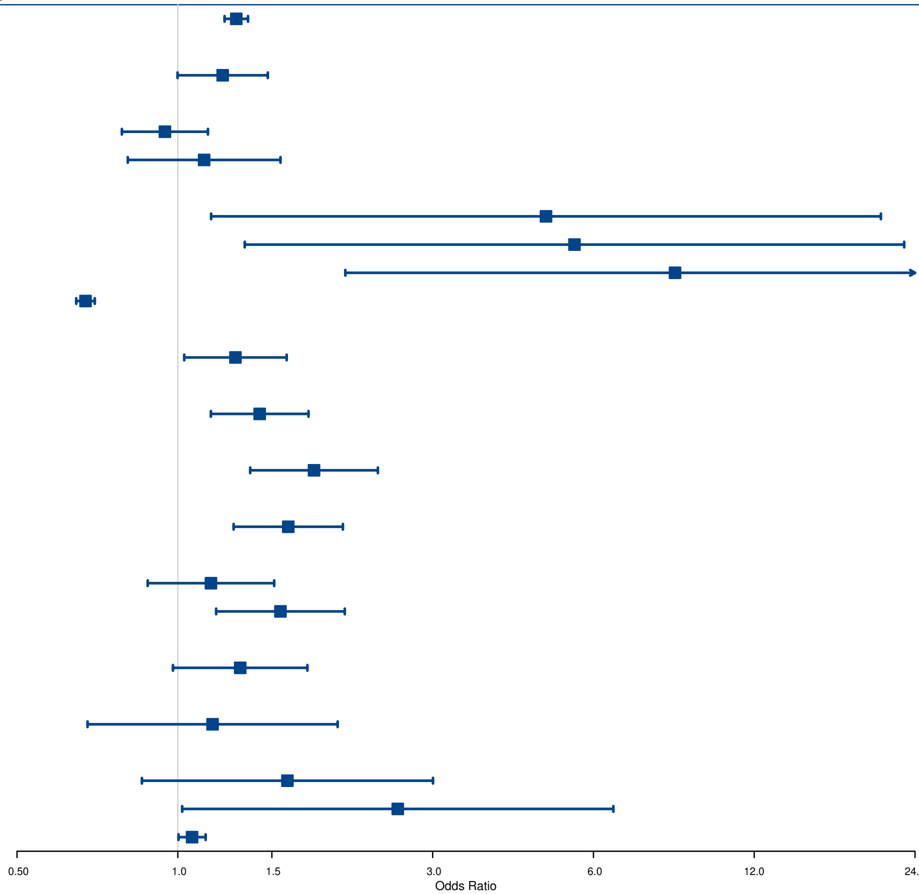


Figure 5

	Coefficient	Standard Error	Hazard Ratio	z value	p value
Age	0.25	0.03	1.29	9.79	<0.0001
Gender (Ref.Female)					
Male	0.19	0.10	1.21	1.95	0.051
Injury Mechanism (Ref. Road Traffic Accident)					
Incidental Fall	−0.06	0.09	0.95	−0.59	0.56
Others	0.11	0.17	1.12	0.68	0.50
Injury Severy Score (Ref. Mild to Moderate (1−8))					
Serious (9−15)	1.59	0.74	4.89	2.16	0.031
Severe (16−24)	1.71	0.73	5.53	2.36	0.018
Critical (25−75)	2.14	0.73	8.53	2.96	0.0031
GCS Score	−0.40	0.02	0.67	−19.49	<0.0001
Pupillary Reflex(Ref.Both Present)					
One or Both Abscent	0.25	0.11	1.28	2.21	0.027
SpO2(Ref.>95%)					
<=95%	0.35	0.11	1.42	3.29	0.0010
Systolic BP(Ref.>90mmHg)					
<=90mmHg	0.59	0.14	1.80	4.18	<0.0001
Basal Cistern(Ref. Present)					
Compressed	0.48	0.12	1.61	3.96	<0.0001
Midline Shift(Ref.No Shift)					
Shift 0−4mm	0.14	0.14	1.15	1.03	0.30
Shift >=5mm	0.44	0.14	1.56	3.13	0.0018
tSAH(Ref. No tSAH)					
With tSAH	0.27	0.15	1.31	1.82	0.069
Intracranial Lesion(Ref. No Intracranial Lesion)					
With Intracranial Lesion	0.15	0.28	1.16	0.55	0.59
Altitude(Ref.<=100m)					
>100m&<=500m	0.47	0.32	1.60	1.48	0.14
>500m	0.95	0.47	2.58	2	0.045
GDP	0.06	0.03	1.06	2.06	0.039



Table

Table 1: Characteristics of 13138 patients enrolled in the China CENTER-TBI registry

Variable	**Overall*** (n = 13138)	**Admission** (n = 8317)	**ICU** (n = 4747)
Demographic characteristics			
Age (median, (IQR))	48 (33-61)	48 (31-61)	50 (35-61)
>65	2217 (17%)	1383 (16·6%)	826 (17.4%)
Sex			
Male	9782 (74%)	6068 (73%)	3661 (77%)
Female	3356 (26%)	2249 (27%)	1086 (23%)
Cause of injury			
Injury characteristics			
Road traffic accident	6548 (50%)	3871 (47%)	2635 (56%)
Incidental fall	4363 (33%)	2833 (34%)	1513 (32%)
ground level fall	*2321 (18%)*	*1635 (20%)*	*677 (14%)*
fall from height	*2042 (16%)*	*1198 (14%)*	*836 (18%)*
Others (e.g. violence, suicide)	1714 (13%)	1215 (15%)	484 (10%)
Unknown	513 (3·9%)	398 (4·8%)	115 (2·4%)
Injury place			
Street/highway	7287 (55%)	4361 (52%)	2890 (61%)
Home	2912 (22%)	2044 (25%)	850 (18%)
Work/school	1056 (8·0%)	533 (6·4%)	519 (11%)
Sport	105 (0·8%)	74 (0·9%)	30 (0·6%)
Public location (e.g. bar, station, nightclub)	1702 (13%)	1248 (15%)	440 (9·3%)
Others	72 (0·5%)	56 (0·7%)	16 (0·3%)
Unknown	4 (0·0%)	1 (0·0%)	2 (0·0%)
Pre-injury health status			
Pre-injury ASA-PS classification			
ASA Ⅰ	10320 (79%)	6617 (80%)	3640 (77%)
ASA Ⅱ	2219 (17%)	1395 (17%)	813 (17%)
ASA Ⅲ	474 (3·6%)	266 (3·2%)	208 (4·4%)
ASA Ⅳ	78 (0·6%)	28 (0·3%)	50 (1·1%)
Unknown	47 (0·4%)	11 (0·1%)	36 (0·8%)
Clinical presentation			
GCS sum score (median, (IQR))	13 (9-15)	14 (12-15)	10 (6-13)
Mild (13-15)	7404 (56%)	5835 (70%)	1518 (32%)
Moderate (9-12)	2930 (22%)	1704 (20%)	1214 (26%)
Severe (3-8)	2804 (21%)	778 (9·4%)	2015 (42%)
ISS score (median, (IQR))	16 (10-25)	13 (9-19)	22 (16-29)
Mild to Moderate (1-8)	886 (6·7%)	808 (9·7%)	63 (1·3%)
Serious (9-15)	4387 (33%)	3947 (47%)	415 (8·7%)
Severe (16-24)	4302 (33%)	2217 (27%)	2068 (44%)
Critical (25-75)	3563 (27%)	1345 (16%)	2201 (46%)
Major extracranial injury	3646 (28%)	1802 (22%)	1831 (39%)

Pupillary light reflex			
One or both absent	1365 (10%)	353 (4·2%)	1006 (21%)
Systemic hypotension	279 (2·1%)	120 (1·4%)	157 (3·3%)
Hypoxia	1257 (9·6%)	479 (5·8%)	776 (16%)

ASA-PS = The American Society of Anesthesiologists (ASA) physical status classification system, GCS = Glasgow Coma Scale, ISS = Injury Severity Score; Major extracranial injury: any AIS non-head >= 3; Systemic hypotension: systolic blood pressure <= 90mmHg; Hypoxia: SpO_2 <= 95%. *74 patients lack stratum information

1. Supplementary Methods

Procedures for database quality control:

(1) Research training:

1) The kick-off meeting of CENTER-TBI China Registry was held in 2014, Kunming, China to make sure that all participants understand the purpose and procedure of this trial. Professor Andrew Maas, the leader of CENTER-TBI project and Professor Mike Jarrett, the director of the database, were also invited to the meeting, which ensured that all centres followed the same study protocol as European Registry.

2) During the meeting, the purpose and procedure of the trial was introduced, and the Chinese version of CRF was distributed to each centre, which was translated directly from the English version of CENTER-TBI Registry CRF by two experienced specialists of neurosurgery.

3) Besides, all centres were trained to fill in the eCRFs by the director of the database at the kick-off meeting.

(2) Data Collection:

1) Clinical data was prospectively collected by one or more dedicated physicians in each centre according to patient medical records. These physicians had received dedicated training. All data is in accordance with the medical records preserved in archives of each centre, which guarantees that all data is traceable.

2) Chinese version of CRF was applied for data collection, which was translated directly from the English version of CENTER-TBI Registry CRF by two experienced specialists of neurosurgery, to guarantee that all participants can understand the CRF well.

3) The e-CRF had built-in data checks to detect errors and alert researchers to these.

4) The CENTER-TBI China Registry has a data monitoring committee to oversee the study and specific central inspectors for data monitoring, who would check all the uploaded data on a continuous basis for data verification and progress report.

5) Professor Andrew Maas, the leader of CENTER-TBI study in Europe, was invited to research meetings annually from 2014 to 2017 for China and European datasets quality assessment and comparison.

(3) Data Storage:

1) Prior to upload to the study database, acquired data was stored locally. All patients were allocated a random Global Unique Personal Identification number (GUPI), which was linked

locally to hospital identifiers. Uploaded data was de-identified prior to upload. All data was kept confidential and anonymized beyond the initial stage of correlation for analysis.

2) All de-identified electronic study data in the CENTER-TBI database was stored securely in the European data space under supervision of Karolinska Institute International Neuroinformatics Coordinating Facility (KI-INCF) for the duration of subject enrollment and follow-up and for a period afterwards for data analysis and preparation of publications.

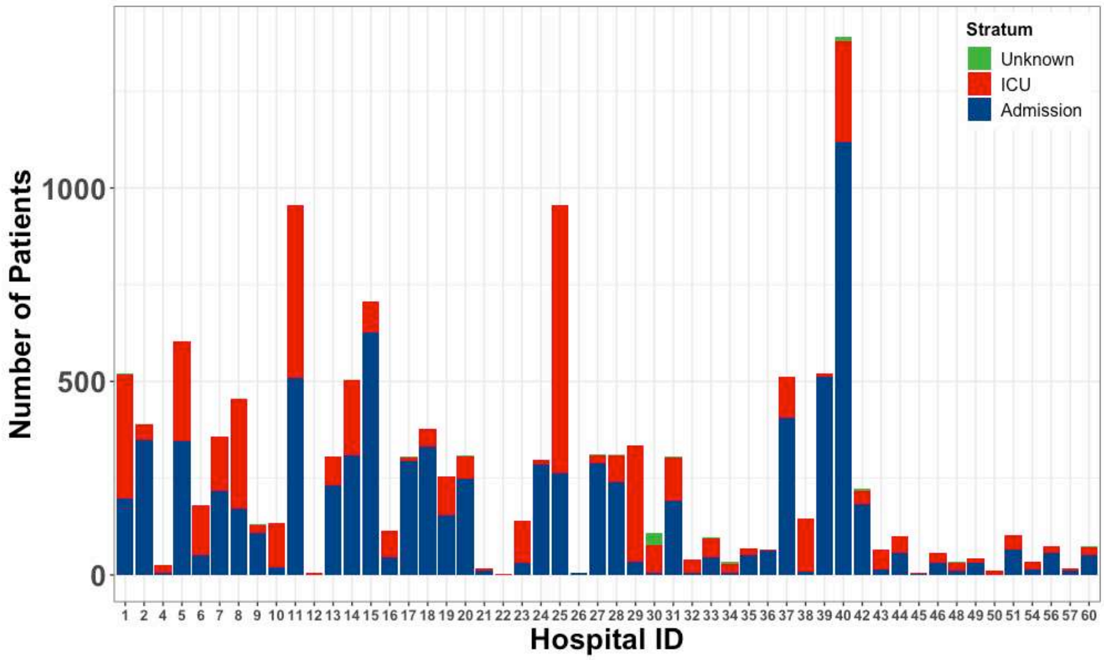
(4) Data Management:

1) Clinical data was entered into eCRFs and managed by the QuesGen data management platform, which was developed in collaboration with KI-INCF. Data collection is based upon the CDEs. As data are entered into each form, the system will run data validation checks that include conditionally required data, validation across fields, and validation requirements based on subject type. If any validation check fails, the user is alerted immediately that the data do not meet quality assurance (QA) criteria and the issue can be addressed and corrected at that point.

2) Together with QuesGen Systems, KI-INCF ensured that data standards are established for the data model (eg, conformity of field formats, field codes, and names to ensure consistency across all datasets). Any approved changes were fully documented with dataset updates to maintain data quality and accuracy. KI-INCF was responsible for importing cleaned datasets to other analytic platforms.

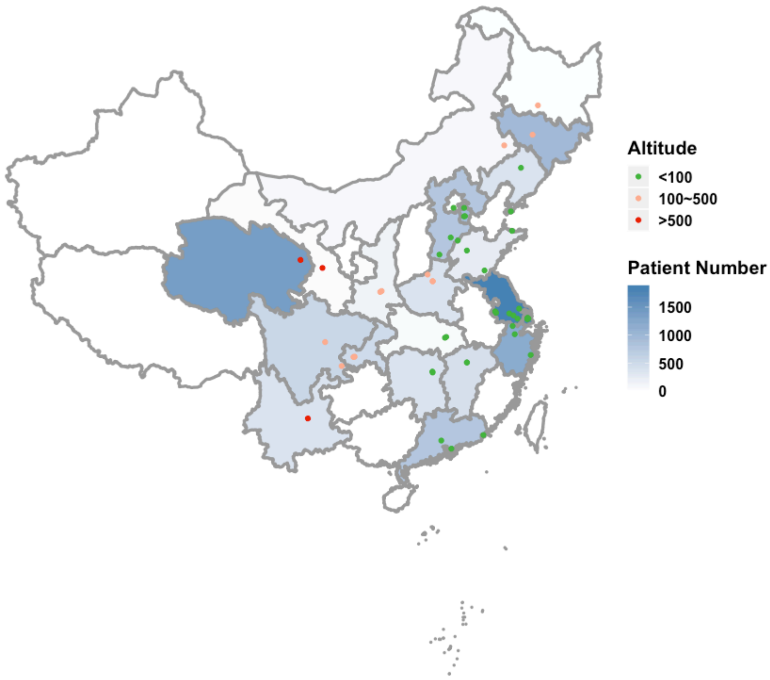
2. Supplementary Figures

Appendix Figure S1: Number of patients enrolled per centre differentiated by stratum



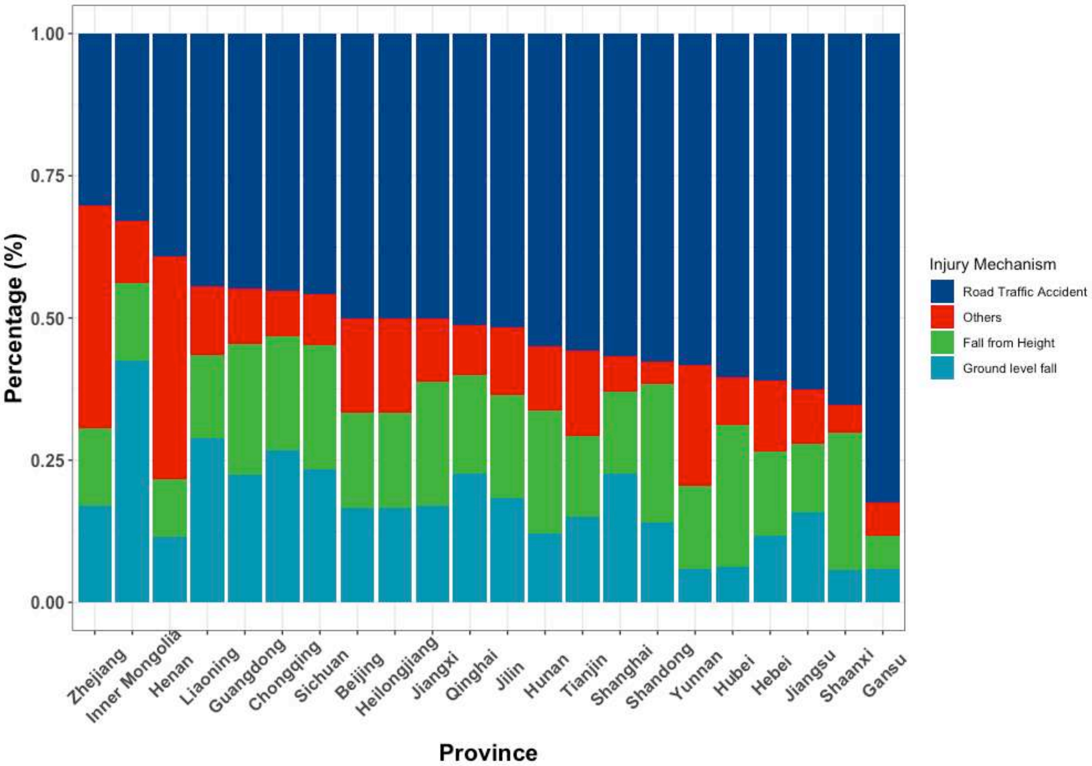
Patients were recruited in 52 participating hospitals across China. The median enrolment by centre was 137 patients. 63% patients recruited were in the admission stratum and 36% in the ICU stratum.

Appendix Figure S2: Centres participating in study



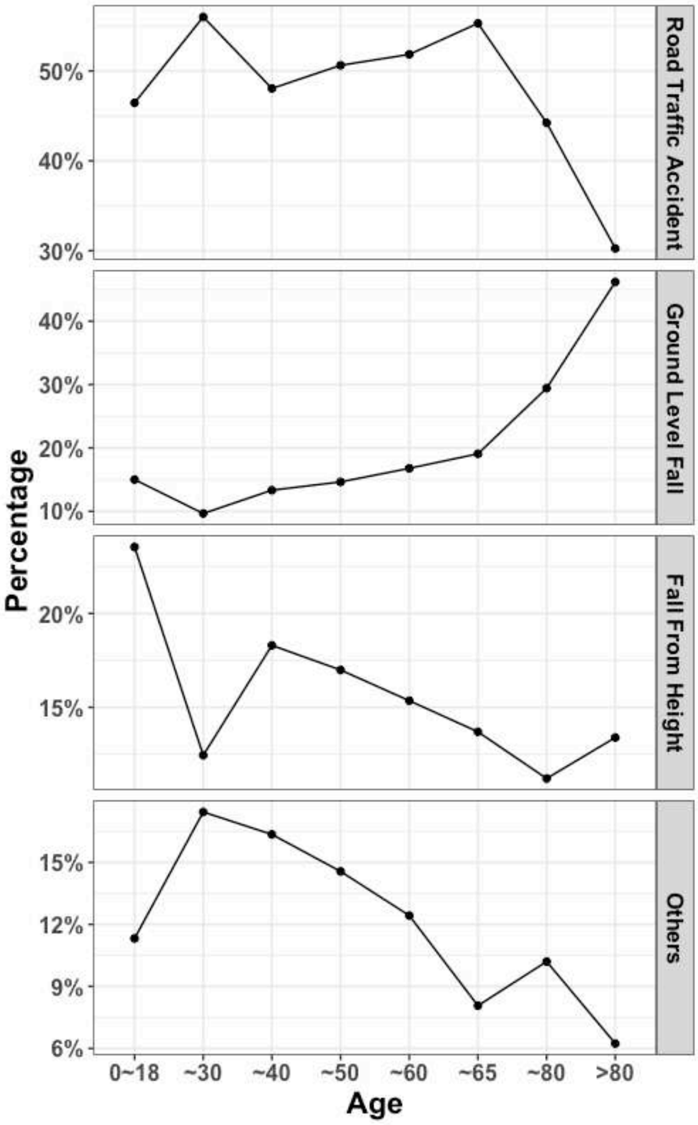
13138 patients were recruited in 52 participating hospitals from 22 provinces of China. Each dot demonstrates one of the 52 centres, with color representing altitude level. Number of patients recruited in each province were represented by color of the province.

Appendix Figure S3: Variation in injury mechanisms in 22 provinces in China



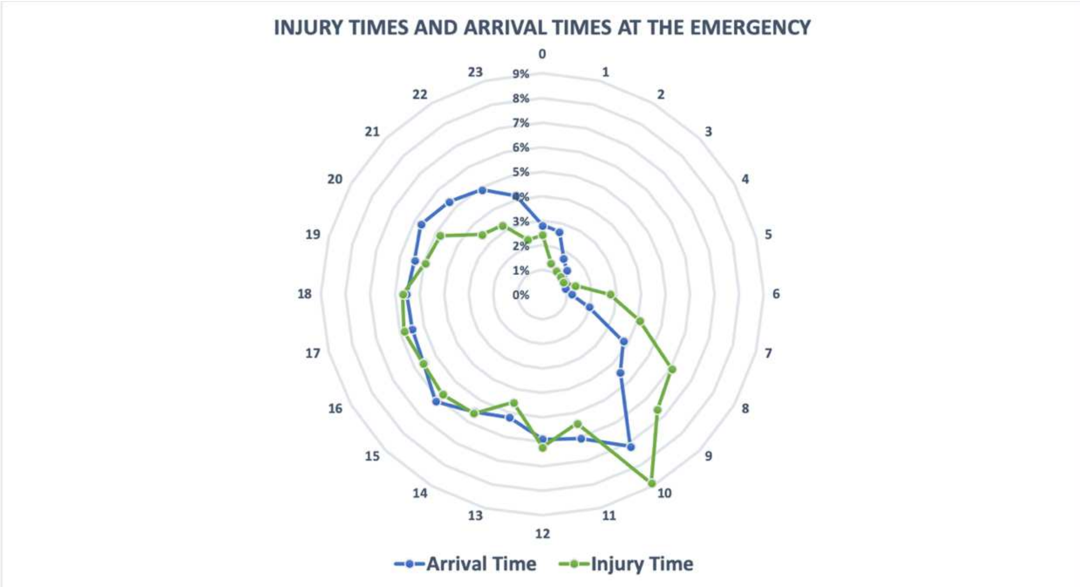
Centres were grouped according to the provinces, and patients of centres in the same province were clustered for analysis.

Appendix Figure S4: Differences in injury mechanisms among different ages



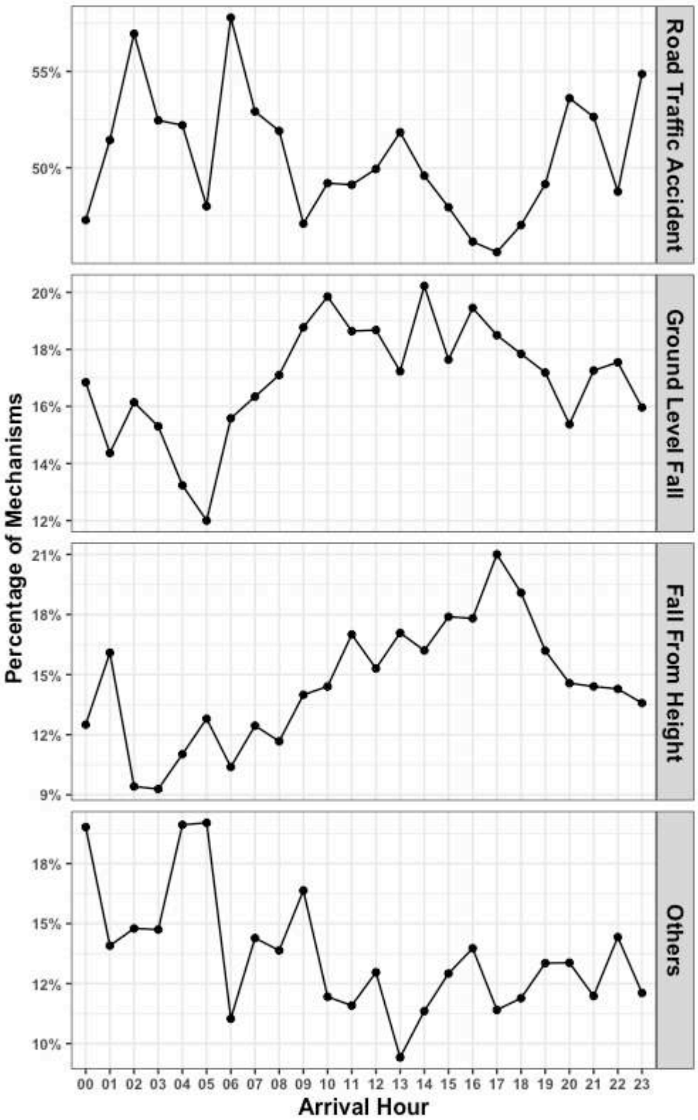
Injury mechanisms differed by age. Traffic incidents occurred more often in patients 18-65 years of age and decreased dramatically at higher ages. Ground level falls increased with age. Other injury mechanisms, mostly violence and suicide, peaked at 18-30 years of age.

Appendix Figure S5: Time distribution of injury and patient arrival



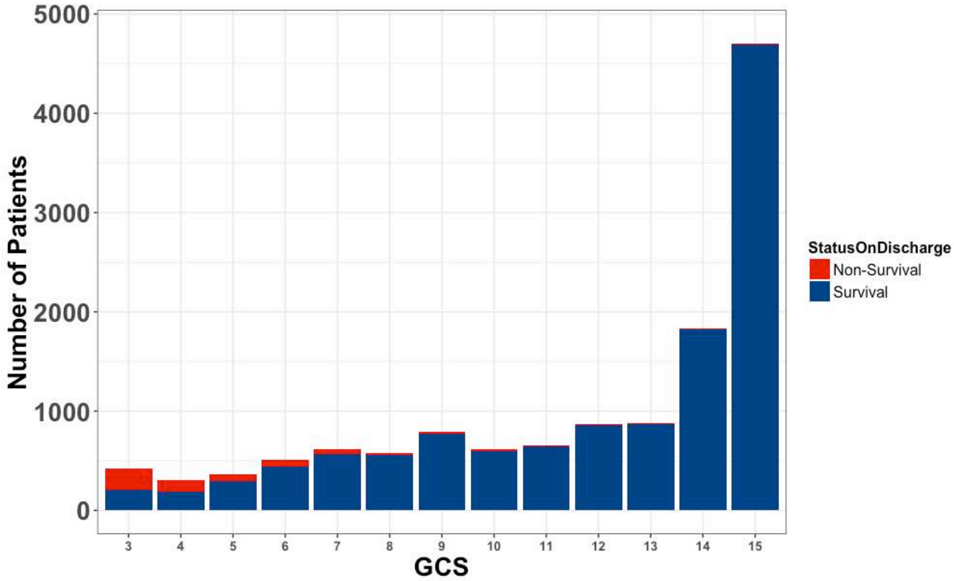
TBI was most commonly seen between 9 am and 11 pm and peaked at 10 am, and patient arrival time showed similar trend in terms of time distribution.

Appendix Figure S6: Time distribution of different injury mechanisms



The causes of injury varied at different patient arrival time. Although road traffic incidents were the leading cause throughout the whole day, their proportion was relatively low in the daytime. Conversely, the percentage of accidental falls, including ground level fall and fall from height, increased from 9 am to 7 pm.

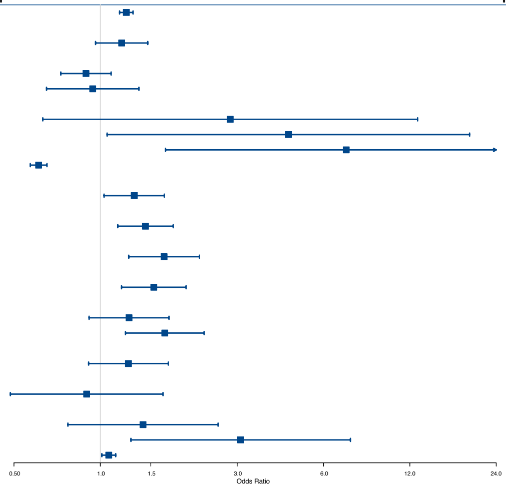
Appendix Figure S7: Number of patients for each GCS sum score, differentiated by discharge status



Median GCS was 13, and 2804 (21%), 2930 (22%) and 7404 (56%) respectively were classified as severe (GCS 3-8), moderate (GCS 9-12) and mild TBI (GCS 13-15).

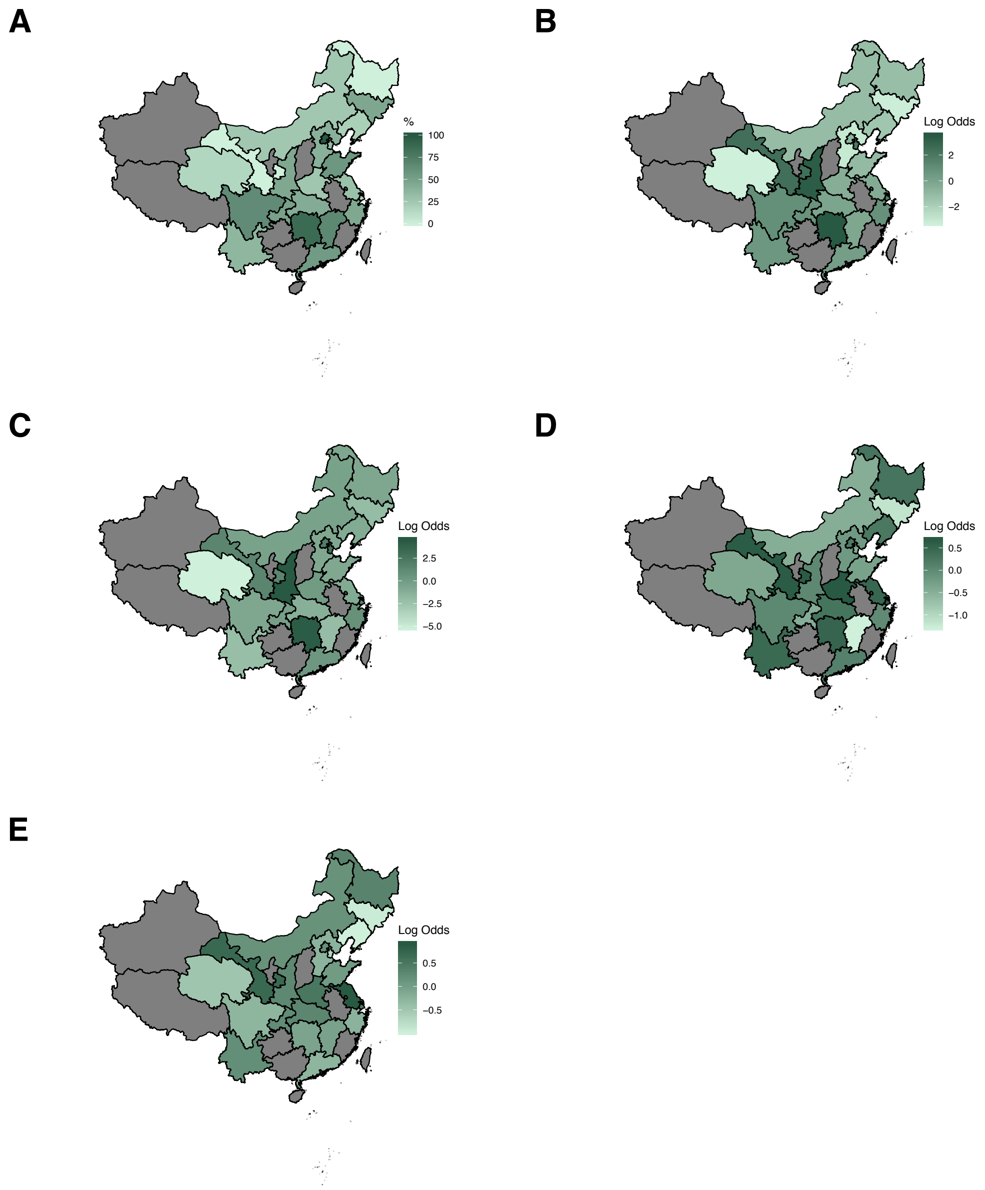
Appendix Figure S8: Predictors for mortality in severe TBI patients

	Coefficient	Standard Error	Hazard Ratio	z value	p value
Age	0.21	0.03	1.23	7.57	<0.0001
Gender (Ref.Female)					
Male	0.17	0.11	1.19	1.60	0.11
Injury Mechanism (Ref. Road Traffic Accident)					
Incidental Fall	−0.12	0.10	0.89	−1.12	0.26
Others	−0.06	0.19	0.94	−0.32	0.75
Injury Severy Score (Ref. Mild to Moderate (1−8))					
Serious (9−15)	1.04	0.77	2.84	1.36	0.17
Severe (16−24)	1.51	0.74	4.52	2.03	0.042
Critical (25−75)	1.97	0.74	7.20	2.67	0.0076
GCS Score	−0.50	0.03	0.61	−14.49	<0.0001
Pupillary Reflex(Ref.Both Present)					
One or Both Abscent	0.27	0.12	1.31	2.20	0.028
SpO2(Ref.>95%)					
<=95%	0.36	0.11	1.44	3.20	0.0014
Systolic BP(Ref.>90mmHg)					
<=90mmHg	0.51	0.14	1.67	3.54	0.00040
Basal Cistern(Ref. Present)					
Compressed	0.43	0.13	1.54	3.25	0.0012
Midline Shift(Ref.No Shift)					
Shift 0−4mm	0.23	0.16	1.26	1.41	0.16
Shift >=5mm	0.52	0.16	1.68	3.21	0.0013
tSAH(Ref. No tSAH)					
With tSAH	0.23	0.16	1.25	1.39	0.17
Intracranial Lesion(Ref. No Intracranial Lesion)					
With Intracranial Lesion	−0.11	0.31	0.90	−0.35	0.73
Altitude(Ref.<=100m)					
>100m&<=500m	0.34	0.31	1.41	1.11	0.27
>500m	1.13	0.45	3.09	2.51	0.012
GDP	0.07	0.03	1.07	2.40	0.017



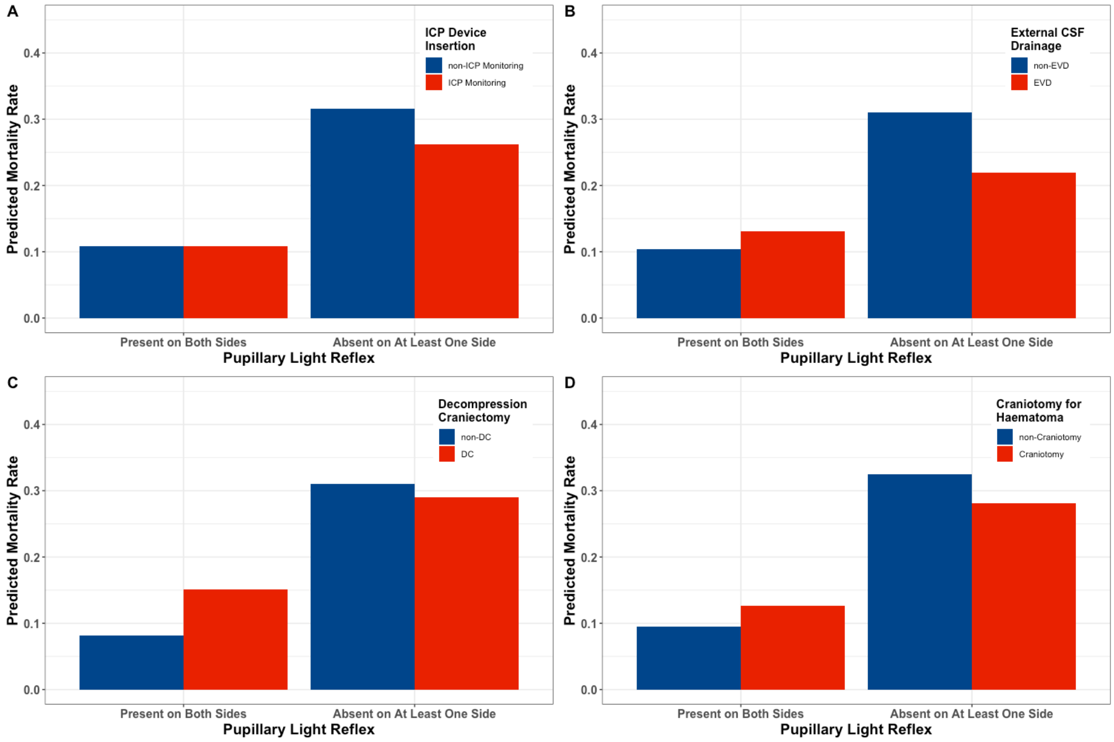
Multivariable analysis in severe TBI patients showed that the mortality predictors for severe cases included age, GCS, ISS, pupillary reflex, hypoxia, systemic hypotension, compressed basal cistern, midline shift >5mm, altitude > 500 meters, and GDP per capita of region.

Appendix Figure S9: Variations in process of care for severe TBI patients between provinces



(A) The percentage of severe TBI patients referred from another hospital, per province, showing the variations in percentage of secondary referral across China; (B) The log odds of ICP monitoring per province compared with the overall average, showing the variations in ICP monitoring rate across China; (C) The log odds of external ventricular drainage (EVD) per province compared with the overall average, showing the variations in EVD rate across China; (D) The log odds of craniotomy per province compared with the overall average, showing the variations in craniotomy rate across China; (E) The log odds of decompression craniectomy (DC) per province compared with the overall average, showing the variations in DC rate across China. The interventions analyses were adjusted for baseline characteristics, clinical severity and CT result, and may reflect true differences in policy.

Appendix Figure S10: Mortality rate of different treatments adjusted for center effects



Intracranial intervention including ICP monitoring, EVD, craniotomy, and decompression craniectomy decreased mortality of severe TBI patients with abnormal pupil reflex, adjusting for center effects, but failed to show efficacy in light reflex normal group.

3. Supplementary Tables

Appendix Table S1: Between-centre differences in China CENTER-TBI Registry

	Variation Within China MOR (95%CI)
ICP Device Insertion	7·64 (4·77 – 12·98)
External Ventricular Drainage	9·37 (4·77 – 18·63)
Craniotomy	2·46 (1·90 – 3·17)
Decompression Craniectomy	2·16 (1·74 – 2·70)
Overall Mortality	2·00 (1·55 – 2·42)
Severe Mortality	2·15 (1·62 – 2·71)

Mortality and interventions were adjusted for age, gender, injury characteristics, clinical severity, vital signs and radiological findings. MOR: median odds ratio.

Appendix Table S2: Univariate analysis of predictors for hospital mortality in all 13138 patients

Variable	Survival(n = 12501)	Dead(n = 637)	P value*
Age (median, (IQR))	48 (32-61)	54 (44-68)	<0·0001
Male sex	9286 (74%)	496 (78%)	0·048
Injury Characteristics			
Road traffic accident	6168 (49%)	380 (60%)	<0·0001
Incidental fall	4186 (33%)	177 (28%)	
ground level fall	2248 (18%)	73 (11%)	
fall from height	1938 (16%)	104 (16%)	
Others (e.g. violence, suicide)	1655 (13%)	59 (9·3%)	
Unknown	492 (3·9%)	21 (3·3%)	
GCS Sum Score	14 (10-15)	4 (3-7)	<0·0001
ISS Score (median, (IQR))			
Mild to Moderate (1-8)	884 (7·1%)	2 (0·3%)	<0·0001
Serious (9-15)	4354 (35%)	33 (5·2%)	
Severe (16-24)	4146 (33%)	156 (24%)	
Critical (25-75)	3117 (25%)	446 (70%)	
Pupillary light reflex			
One or both absent	982 (7·9%)	383 (60%)	<0·0001
Systemic hypotension	212 (1·7%)	67 (11%)	<0·0001
Hypoxia	1058 (8·5%)	199 (31%)	<0·0001
Compressed basal cistern	2970 (24%)	468 (73%)	<0·0001
Midline shift			
No shift	7679 (61%)	109 (17%)	<0·0001
Shift 0-4mm	3406 (27%)	172 (27%)	
Shift ≥5mm	1133 (9·1%)	345 (54%)	
Unknown	283 (2·3%)	11 (1·7%)	
tSAH	8244 (66%)	572 (90%)	<0·0001
Intracranial lesion	9879 (79%)	621 (97%)	<0·0001
Altitude			
≤100	8370 (67%)	385 (60%)	<0·0001
>100 & ≤500	2414 (19%)	165 (26%)	
>500	1717 (14%)	87 (14%)	
GDP per capita			
<10000	6014 (48%)	353 (55%)	<0·0001
10000-15000	2176 (17%)	64 (10%)	
>15000	4311 (34%)	220 (35%)	

ASA-PS = The American Society of Anesthesiologists (ASA) physical status classification system, GCS = Glasgow Coma Scale, ISS = Injury Severity Score, tSAH = Traumatic Subarachnoid Hemorrha, GDP = Gross Domestic Product; Major extracranial injury: any AIS non-head >= 3; Systemic hypotension: systolic blood pressure <= 90mmHg; Hypoxia: SpO2 <= 95%. Potential predictors of death in all 13138 patients were age, gender, clinical severity, radiological findings, vital signs, and hospital-related variables including altitude and economic level.

* p-values from Mann-Whitney and chi-square statistics for continuous and categorical characteristics respectively.

Appendix Table S3: Characteristics of care pathways

Variable	Overall* (n = 13138)	Admission (n = 8317)	ICU (n = 4747)
Referral			
Primary referral	9249 (70%)	6144 (74%)	3053 (64%)
Secondary referral	3882 (30%)	2173 (26%)	1691 (36%)
Unknown	7 (0·0%)	0 (0·0%)	3 (0·1%)
Emergency Intubation	2656 (20%)	855 (10%)	1791 (38%)
Pre-hospital Intubation	154 (1·2%)	25 (0·3%)	129 (2·7%)
Intubation at Emergency Department	2502 (19%)	830 (10%)	1662 (35%)
ICP Sensor Insertion	1509 (11%)	172 (2·1%)	1334 (28%)
ICP Sensor Insertion in severe patients	780 (28%)	55 (7·1%)	725 (36%)
External Ventricular Drainage	774 (5·9%)	83 (1·0%)	690 (15%)
External Ventricular Drainage in severe patients	368 (13%)	23 (3·0%)	345 (17%)
Craniotomy for Haematoma	2679 (20%)	662 (8·0%)	2015 (42%)
Craniotomy for Haematoma in severe patients	1399 (50%)	253 (33%)	1145 (57%)
Decompression Craniectomy	2170 (17%)	416 (5·0%)	1751 (37%)
Decompression Craniectomy in severe patients	1354 (48%)	199 (26%)	1153 (57%)
Extracranial Surgery	208 (1·6%)	79 (0·9%)	127 (2·7%)

Extracranial Surgery: limb fixation, thoracotomy, laparotomy and extraperitoneal pelvic packing. *74 patients lack stratum information.

4. Appendix List of Group Contributors: The China CENTER-TBI Registry Participants

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STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist

A checklist of items that should be included in reports of observational studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study Design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	N/A
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	N/A
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	N/A
		Case-control study—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study Size	10	Explain how the study size was arrived at	5
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	5-6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	N/A
		Case-control study—If applicable, explain how matching of cases and controls was addressed	N/A
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	8 & Fig1
		(c) Consider use of a flow diagram	Fig1
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	Table1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A

Section and Item	Item No.	Recommendation	Reported on Page No.
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key Results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Confirmation

We confirm that we are happy to be quoted in the Acknowledgments section of the paper entitled "Clinical characteristics and outcomes in patients with traumatic brain injury in China: a prospective, multicentre, longitudinal, observational study."

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