Casemix, management, and mortality of patients receiving emergency neurosurgery for traumatic brain injury in the Global Neurotrauma Outcomes Study: a prospective observational cohort study

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Summary

Background Traumatic brain injury (TBI) is increasingly recognised as being responsible for a substantial proportion of the global burden of disease. Neurosurgical interventions are an important aspect of care for patients with TBI, but there is little epidemiological data available on this patient population. We aimed to characterise differences in casemix, management, and mortality of patients receiving emergency neurosurgery for TBI across different levels of human development.

Methods We did a prospective observational cohort study of consecutive patients with TBI undergoing emergency neurosurgery, in a convenience sample of hospitals identified by open invitation, through international and regional scientific societies and meetings, individual contacts, and social media. Patients receiving emergency neurosurgery for TBI in each hospital's 30-day study period were all eligible for inclusion, with the exception of patients undergoing insertion of an intracranial pressure monitor only, ventriculostomy placement only, or a procedure for drainage of a chronic subdural haematoma. The primary outcome was mortality at 14 days postoperatively (or last point of observation if the patient was discharged before this time point). Countries were stratified according to their Human Development Index (HDI)—a composite of life expectancy, education, and income measures—into very high HDI, high HDI, medium HDI, and low HDI tiers. Mixed effects logistic regression was used to examine the effect of HDI on mortality while accounting for and quantifying between-hospital and between-country variation.

Findings Our study included 1635 records from 159 hospitals in 57 countries, collected between Nov 1, 2018, and Jan 31, 2020. 328 (20%) records were from countries in the very high HDI tier, 539 (33%) from countries in the high HDI tier, 614 (38%) from countries in the medium HDI tier, and 154 (9%) from countries in the low HDI tier. The median age was 35 years (IQR 24–51), with the oldest patients in the very high HDI tier (median 54 years, IQR 34–69) and the youngest in the low HDI tier (median 28 years, IQR 20–38). The most common procedures were elevation of a depressed skull fracture in the low HDI tier (69 [45%]), evacuation of a supratentorial extradural haematoma in the medium HDI tier (189 [31%]) and high HDI tier (173 [32%]), and evacuation of a supratentorial acute subdural haematoma in the very high HDI tier (155 [47%]). Median time from injury to surgery was 13 h (IQR 6–32). Overall mortality was 18% (299 of 1635). After adjustment for casemix, the odds of mortality were greater in the medium HDI tier (odds ratio [OR] 2·84, 95% CI 1·55–5·2) and high HDI tier (2·26, 1·23–4·15), but not the low HDI tier (1·66, 0·61–4·46), relative to the very high HDI tier. There was significant between-hospital variation in mortality (median OR 2·04, 95% CI 1·17–2·49).

Interpretation Patients receiving emergency neurosurgery for TBI differed considerably in their admission characteristics and management across human development settings. Level of human development was associated with mortality. Substantial opportunities to improve care globally were identified, including reducing delays to surgery. Between-hospital variation in mortality suggests changes at an institutional level could influence outcome and comparative effectiveness research could identify best practices.

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Introduction

The Global Burden of Disease study estimated that in 2016 over 27 million new cases of traumatic brain injury (TBI) occurred worldwide.[1] A substantial number of patients with TBI require emergency neurosurgery, especially those with severe injuries—for example, in a

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See **Online** for appendix

Research in context

Evidence before this study

We searched PubMed for all articles in English published from inception to Nov 6, 2021, with the search terms "head injury" or "traumatic brain injury" as well as "surgery" and "mortality". The inclusion and exclusion criteria for the search are available in the appendix (p 4). We found no studies comparing casemix, management, or outcomes following emergency neurosurgery for traumatic brain injury (TBI) across human development settings. A small number (11) of predominantly small, single-centre studies reported mortality following any neurosurgical intervention for TBI, but comparison of casemix, management, and outcomes was not possible due to substantial heterogeneity.

Added value of the study

For the first time, the Global Neurotrauma Outcomes Study has captured the landscape of emergency neurosurgery for TBI worldwide. There were significant differences in casemix, management, and outcomes of TBI across levels of human development. Patients in the low human development index (HDI) tier were often young (median age 28 years) and had a mild TBI with a depressed skull fracture due to an assault; in the medium HDI (median age 32 years) and high HDI tiers (median age 35 years), patients were also young but most frequently had a moderate or severe TBI with an extradural haematoma due to a road traffic collision; and in the very high HDI tier, patients were older (median age 54 years) and most often presented with a moderate or severe TBI associated with an acute subdural haematoma following a fall. Quality of care was generally less favourable in lower human development settings, including temporal delays to surgery and a lack of access to postoperative intracranial pressure monitoring and intensive care. After adjustment for casemix, the level of human development was associated with mortality. The least favourable outcomes were observed in the medium HDI tier, which is probably because centres in these countries were dealing with a high volume of seriously injured patients without access to the resources required to care for them. Notably, a relatively favourable outcome was observed in the low HDI tier, which we postulate was due to a lower incidence of high-energy brain injuries in the population overall and a higher proportion of seriously injured patients dying pre-hospital. After adjustment for casemix and level of human development, there was still significant between-hospital variation in the outcome.

Implications of all the available evidence

The Global Neurotrauma Outcomes Study has identified significant heterogeneity in the epidemiology of emergency neurosurgery for TBI across human development settings that has several implications. First, it indicates the importance of collecting high-quality, baseline, local epidemiological data before designing clinical trials, implementation science studies, and public health policies to ensure they are successful. Second, significant between-hospital variation in mortality suggest local changes in care could improve outcomes for patients, and that comparative effectiveness research can use this heterogeneity to identify best practices.

large European cohort, 820 (39%) of 2124 of those admitted to the intensive care unit with a TBI received intracranial surgery.[2] The burden is particularly great in low-income and middle-income countries (LMICs), where almost 4·5 million TBI cases are estimated to require operative management every year.[3] Given this need, the World Bank's Disease Control Priorities report[4] includes operative management for TBI as one of the surgical procedures considered essential to be available on an emergency basis to everyone worldwide.[4] There is growing evidence that access to safe treatment for all surgical conditions is severely lacking globally.[5] However, a Commission[6] in *The Lancet Neurology*, published in 2017, highlighted that for patients with TBI specifically, including those undergoing neurosurgical interventions, contemporary epidemiological data are scarce; the Commission recommended better characterisation of this population through large, collaborative, observational studies. As such, we designed and did a prospective observational cohort study to ascertain the differences in casemix, management, and mortality of patients receiving emergency neurosurgery for TBI across different human development settings.

Methods

Participating centres

We did a prospective observational cohort study of patients with TBI; any hospital performing emergency neurosurgery for TBI worldwide was eligible to participate. Recruitment of hospitals was by open invitation, through international and regional scientific societies and meetings, individual contacts, and social media. The study was supported by the World Federation of Neurosurgical Societies, as well as several other continental and regional societies (appendix p 5). Researchers (doctors, medical students, or clinical research staff) were asked to form teams and collect data on all eligible patients in any 30-day period starting between Nov 1, 2018, and Jan 31, 2020. Multiple teams from the same hospital were eligible to participate if they collected data for non-overlapping 30-day periods. Each team was asked to prospectively collect data on all patients at their institution who received emergency neurosurgery for TBI for which the start time was between 0001 h on day 1 and 2359 h on day 30 of their chosen study period—a list of procedures that would render patients eligible for inclusion is provided in the appendix (p 6).

Patients who underwent only insertion of an intracranial pressure monitor, ventriculostomy placement, or a procedure for drainage of a chronic subdural haematoma, or who had previously had emergency neurosurgery for TBI, were not eligible for inclusion.

A UK National Health Service Research Ethics Service considered this study exempt from formal research registration (South East Scotland Research Ethics Service) but, before commencing data entry, each team was required to submit evidence of appropriate local approval of the study. Patients provided written or oral informed consent to participate if required by local regulations.

Data collection and storage

Data were collected using a web-based electronic case report form at the time of admission and operation, then patients were followed up until their death, discharge, or 14 days postoperatively (whichever came first). Each team was also required to complete a questionnaire about their hospital. If two or more teams participated from any given hospital, instructions were given that the questionnaire should be completed again by a second individual independently from the first to facilitate assessment of inter-rater reliability of the questionnaire items. To ensure face validity, the case report form and hospital questionnaire were both designed, through an iterative process, by a multidisciplinary protocol development group of clinicians caring for patients with TBI from a wide variety of human development settings. A brief pilot study was then undertaken in Zambia (appendix p 7), following which final changes were made and the completed versions were approved by the World Federation of Neurosurgical Societies Neurotrauma committee. All data was stored in a secure database hosted by the University of Cambridge (Cambridge, UK).

Outcomes

The primary outcome measure was mortality at 14 days postoperatively (or last point of observation if the patient was discharged before this time point). The secondary outcome measures were length of hospital stay, length of stay in the intensive care unit, surgical site infection, return to theatre, Glasgow Coma Scale (GCS) score at discharge versus admission, and discharge destination.

The protocol, case report form, hospital questionnaire and data dictionary are all publicly available through the Global Neurotrauma Outcomes Study website. These documents were all translated by collaborators into Arabic, Bengali, Chinese, French, Italian, Portuguese, Spanish, Swahili, and Urdu.

Validity of the data was ensured by two mechanisms. Firstly, web-based forms enforced data entry for critical variables. Secondly, after the end of each study period, each team's data validator was contacted with instructions to review the operating theatre logbooks independently for procedures that met the inclusion criteria. For each case that met the inclusion criteria, the procedure performed and the date it was done were noted and submitted to the central study team for comparison with the data submitted by the primary data collectors. The robustness of our methodology for data collection was assessed against the Data Acquisition, Quality and Curation for Observational Research Designs guidelines (appendix pp 10–12).

Statistical analysis

To examine how the casemix, management, and outcomes of patients in the study cohort varied worldwide, countries were stratified according to their 2018 Human Development Index (HDI),[7] the UN's summary measure of socioeconomic development. The HDI is a composite measure of life expectancy, education, and income indices and has been used to stratify nations according to level of development to allow comparison of epidemiological characteristics.[8] The UN categorises countries into four tiers based on their HDI: very high HDI, high HDI, medium HDI, and low HDI countries.

Data are summarised with medians and IQRs or numbers and percentages. Difference in testing between HDI tiers was done with the Kruskal-Wallis test, χ^2 test, or Fisher's exact test. Corrections for multiple comparisons were done only when explicitly stated. Additionally, results were stratified by age group (<18 years, 18–65 years, and >65 years), severity (mild [GCS score 13–15], moderate [GCS score 9–12], and severe [GCS score 3–8]), and surgical procedure. Where appropriate, results were also presented together for patients with moderate and severe TBI (GCS score <13), all patients who had evacuation of a supratentorial extradural haematoma or acute subdural haematoma, and patients with severe TBI who had evacuation of a supratentorial extradural haematoma or acute subdural haematoma. To assess inter-rater reliability of the hospital questionnaire, κ statistics and Pearson's correlation coefficient for categorical and continuous variables, respectively, were used to express the level of agreement between the first and second respondents for each item.

Mortality was analysed using mixed effects logistic regression to account for, and quantify, between-hospital and between-country variation in outcomes. The mixed effects model was built in three stages. First, a model with only hospital and country as random intercepts was constructed. Second, patient-level fixed effects were entered into the model on the basis of their association with risk of mortality in patients with TBI: age,[9–12] severity of TBI by GCS score,[12–14] pupillary reactivity,[12–14] American Society of Anaesthesiologists (ASA) grade,[15] and surgery performed.[16,17] Third, HDI tier (a

For the **Global Neurotrauma Outcomes Study website** see https://www.globalneurotrauma.com country-level fixed effect) was added. Model selection was done using a criterion-based approach by minimising the Akaike Information Criterion.

The between-hospital and between-country variation in mortality for all three models were expressed as the median odds ratio (MOR) with 95% CIs obtained by bootstrapping (500 replicates). The MOR is described in detail elsewhere;[18] briefly, it is derived from the estimated variance (T_2) of the random effects in the mixed effects model and can be interpreted as the ratio of odds of mortality between a typical high-mortality and a typical low-mortality hospital or country. A MOR equal to 1 indicates no between-hospital or between-country variation, whereas a larger MOR indicates substantial differences. Moreover, the MOR can be directly compared with the odds ratios (ORs) of patient and country level characteristics. The statistical significance of patient and country level predictor variables were calculated using the Wald test. Patient-level fixed effects are reported as ORs with 95% CIs. Frequency of missing data was explored, but data were not imputed.

Statistical tests were two-sided, and we considered $p<0·05$ to show a significant difference. All analyses were done using R (version 3.6.3). The study has been registered on ClinicalTrials.gov (NCT04212754) and the Clinical Trials Registry India (CTRI/2019/02/017479) and the study protocol has been published in a peer-reviewed medical journal.[19] The study is reported in accordance with the STROBE guidelines (appendix pp 8–9).[20]

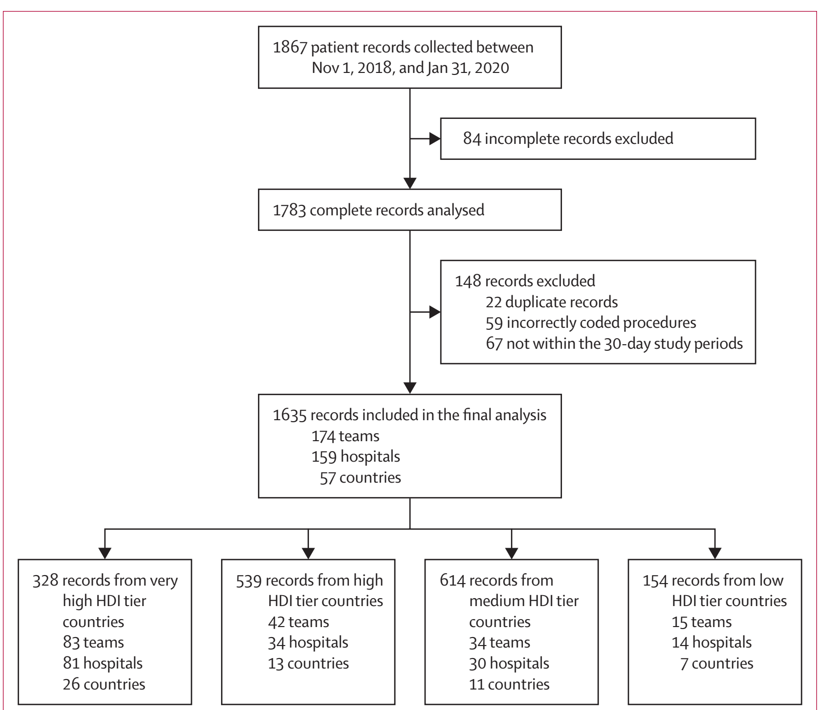


Figure 1: **Patient flow chart**
HDI=human development index.

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.

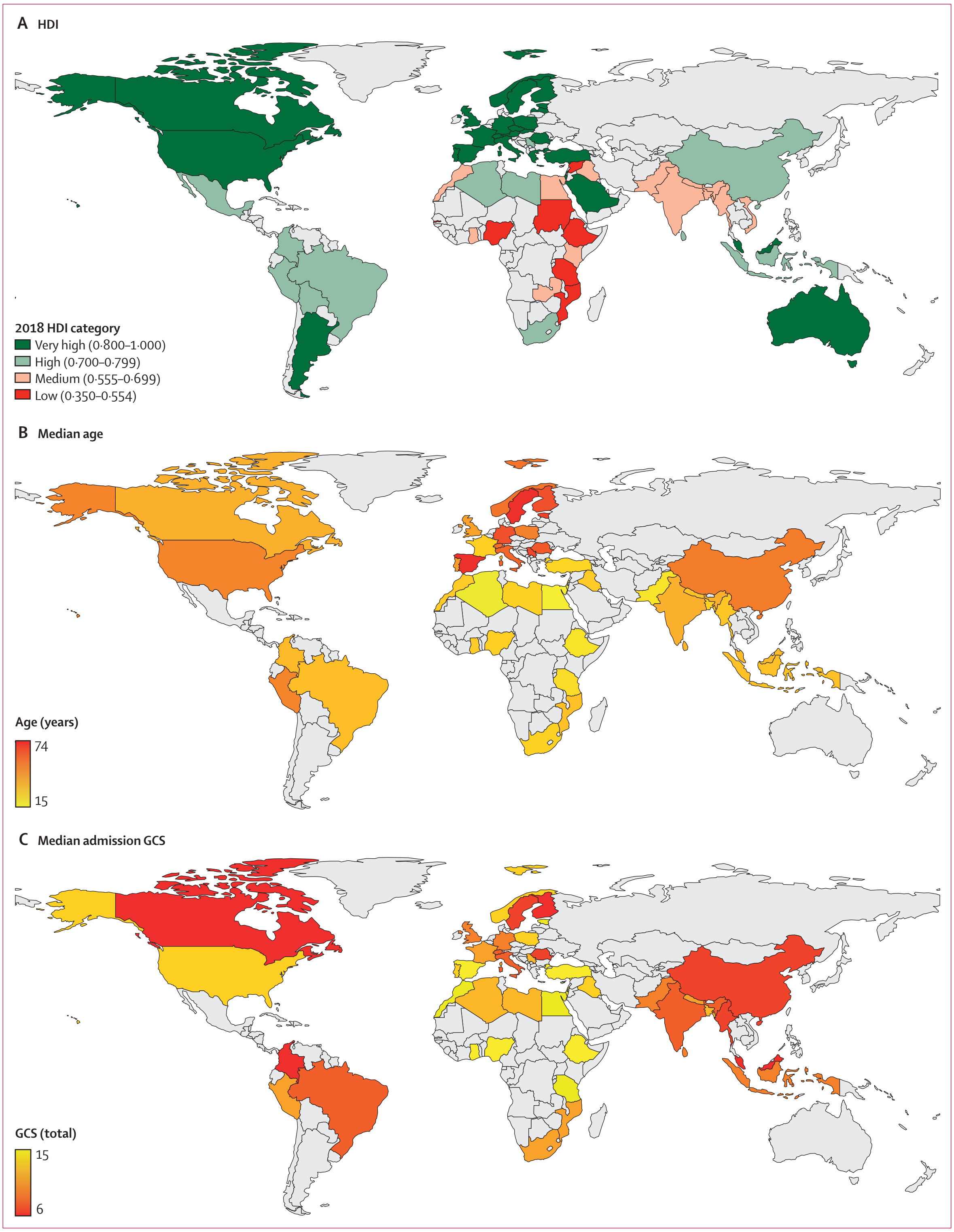
Results

1867 records were submitted for patients receiving surgery between Nov 1, 2018, and Jan 31, 2020. After removing incomplete data, duplicates, and ineligible records (see appendix pp 13–14 for details of excluded records), 1635 records were included in the final analysis, which were spread across all four HDI tiers (figure 1) and all seven World Bank geographical regions—South Asia (555 [34%]), Europe and Central Asia (274 [17%]), sub-Saharan Africa (224 [14%]), Middle East and North Africa (221 [14%]), East Asia and Pacific (181 [11%]), Latin America and the Caribbean (151 [9%]), and North America (29 [2%]).

159 hospitals from 57 countries participated in the study (figure 2A and appendix pp 21–22). Table 1 shows the characteristics of the hospitals according to HDI tier. Hospitals were mostly governmental (132 [86%]) and were in urban areas (147 [96%]). Only one hospital (in the low HDI tier) had no neurosurgeon. The highest median number of neurosurgeons per hospital was observed in the very high HDI tier (median 10, IQR 6–13). In contrast, the highest median number of surgeries for TBI per 30-day period per hospital was observed in the medium HDI hospitals (median 11, IQR 4–19). There were significant differences in the proportion of patients liable for their health-care costs between the HDI tiers, with 12 (86%) of 14 hospitals in the low HDI tier reporting patients were liable for all or some of the costs compared with 17 (22%) of 78 in the very high HDI tier. Onsite CT scanning was available at all times in a smaller proportion of hospitals in the low HDI tier relative to the medium HDI, high HDI, and very high HDI tiers, and intracranial pressure monitoring was always available in a smaller proportion of hospitals in the high HDI, medium HDI, and low HDI tiers relative to the very high HDI tier.

Table 2 lists the characteristics of the study cohort on admission to hospital according to HDI tier. Admission characteristics are presented by age group, severity of injury, and surgical procedure in the appendix (pp 26–61). There were significant differences in the median age at surgery across the HDI tiers with patients in the very high HDI tier being the oldest and those in the low HDI tier being the youngest. 216 (13%) patients were aged younger than 18 years. 974 (60%) of all cases were moderate or severe TBI; the medium HDI tier had the highest proportion of moderate or severe TBI cases (423 [68%]). The most frequent mechanism of injury was assault in low HDI tier countries, road traffic collision in medium HDI tier and high HDI tier countries, and falls in very high HDI tier countries. Age, admission GCS score, and mechanism of injury differed considerably between countries (figure 2B–E). The low HDI tier had the lowest proportion of patients transferred from another hospital.

Median time from injury to start of surgery was 13 h (IQR 6–32) across the cohort, 12 h (5–26) in patients with moderate or severe TBI, 11 h (5–25) in all patients with evacuation of a supratentorial extradural haematoma or acute subdural haematoma, and 8 h (4–17) in patients with severe TBI who had evacuation of a supratentorial



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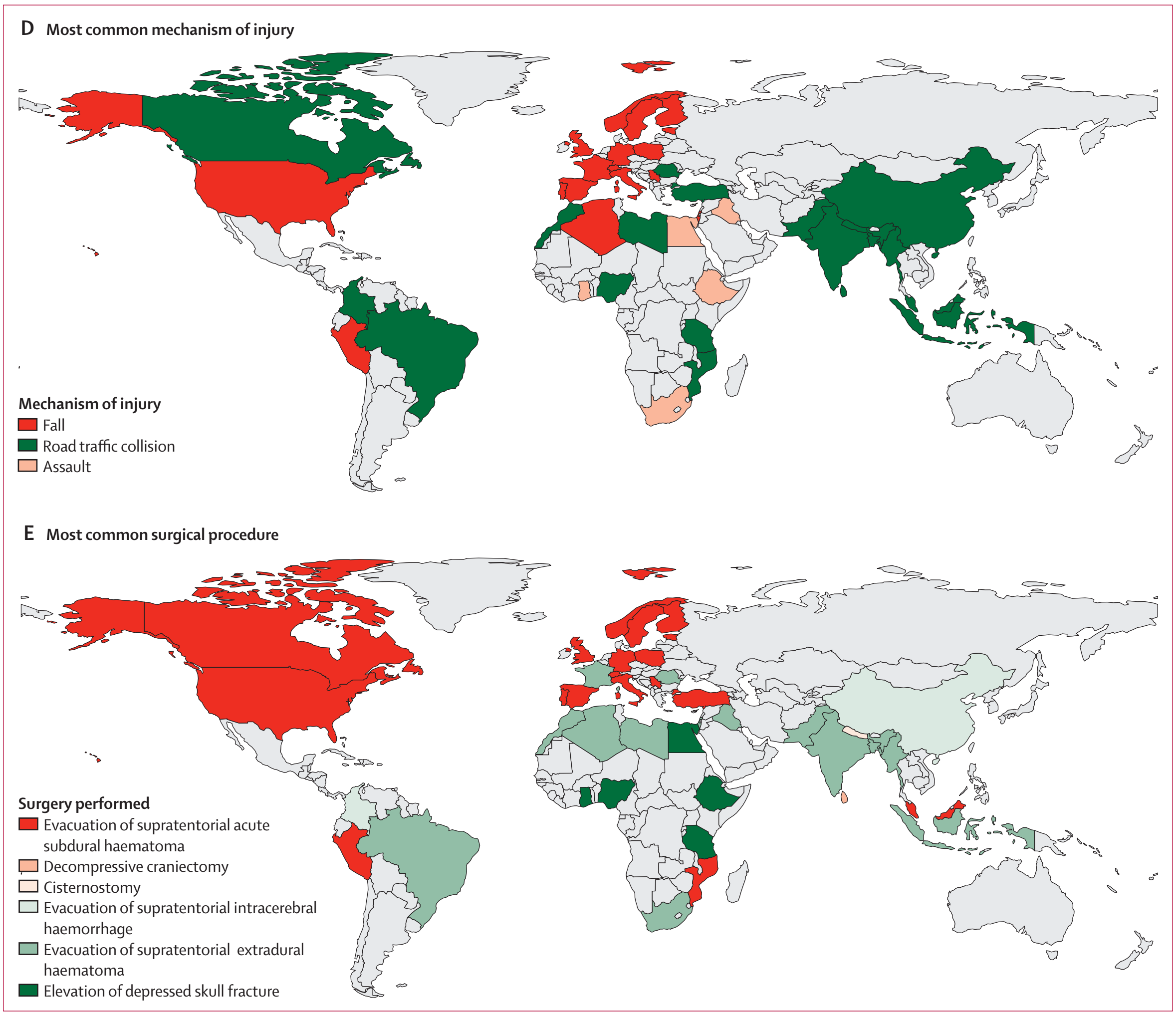

Figure 2: **Between-country variation in casemix**
Between-country variation in casemix according to HDI category (A), age (B), admission GCS score (C), most common mechanism of injury (D), and most common surgical procedure (E). Only countries with five or more patient records are displayed here (except for panel A, which includes all countries contributing to the study). HDI=human development index. GCS=Glasgow Coma Scale.

extradural haematoma or acute subdural haematoma. Time from injury to surgery increased across the HDI tiers from very high to low (appendix p 23). Patients were most frequently brought to the hospital in which the surgery was done in an ambulance with paramedics in the very high HDI tier (258 [79%] of 328) and high HDI tier (347 [64%] of 539), an ambulance without paramedics in the medium HDI tier (291 [47%] of 614), and a private vehicle in the low HDI tier (69 [45%] of 154). A CT scan was done in 1624 (99%) of 1635 patients (appendix p 25).

In over half of all patients, the primary surgical procedure was evacuation of a supratentorial extradural haematoma (489 [30%] of 1635) or acute subdural haematoma (407 [25%] of 1635), and 40% (359 of 896) of these patients had severe TBI. The procedures done differed between countries (figure 2D) and across the HDI tiers (appendix p 25). The most common procedures were elevation of a depressed skull fracture in low HDI countries (69 [45%] of 154), evacuation of a supratentorial extradural haematoma in medium HDI (189 [31%] of 614) and high HDI (173 [32%] of 539) countries, and evacuation of a supratentorial acute subdural haematoma in very high HDI countries (155 [47%] of 328). The most common procedures done in children (aged <18 years; appendix p 28) were evacuation of a supratentorial extradural haematoma (84 [39%] of 216) and elevation of a depressed skull fracture (83 [38%] of 216).The very high HDI tier had the highest proportion of operations in which the most senior surgeon present in the operating theatre was a fully qualified neurosurgeon (251 [77%] of 328) and the medium HDI tier had the lowest proportion (169 [28%] of 614).

18% (112 of 607) of patients with severe TBI had an intracranial pressure monitor in situ at the end of their surgery (appendix p 61). The proportion of patients with severe TBI receiving postoperative intracranial pressure monitoring decreased between very high HDI (68 [47%] of 147), high HDI (40 [22%] of 194), medium HDI (4 [2%] of 236), and low HDI (0 [0%] of 30) tiers. 470 (77%) of 607 patients with severe TBI were admitted to an intensive care unit postoperatively, with the lowest rate in the medium HDI tier (140 [59%] of 236).

Differences in primary and secondary outcome measures are shown in table 3. Mortality was 18% across the cohort, 28% (271 of 974) in patients with moderate and severe TBI, 36% (220 of 607) in patients with severe TBI, and 141 (39% of 359) in patients with severe TBI who had evacuation of a supratentorial extradural haematoma or acute subdural haematoma. The medium HDI tier had the highest mortality for all patients, moderate and severe TBI patients (131 [31%]), severe TBI patients (101 [43%]), and severe TBI patients who had evacuation of a supratentorial extradural haematoma or acute subdural haematoma (62 [47%]). Secondary outcome measures alongside mortality for all relevant subgroups are reported in the appendix (pp 25–61). In the mixed effects models (figure 3), increasing age, moderate or severe TBI, unilateral or bilateral unreactive pupils, ASA grade of 3 or greater, and the primary procedure being evacuation of a supratentorial acute subdural haematoma, decompressive craniectomy for raised intracranial pressure, or evacuation of a supratentorial intracerebral haemorrhage were all significant patient-level predictor variables for mortality in the final model. Mortality was higher in the medium HDI tier (OR 2·84, 95% CI 1·55–5·2) and high HDI tier (2·26, 1·23–4·15), but not the low HDI tier (1·66, 0·61–4·46), relative to the very high HDI tier. There was significant between-hospital variation in mortality (appendix p 64) in the unadjusted model (MOR 1·67, 95% CI 1·15–2·17), after adjustment for patient level characteristics (2·07, 1·29–2·73), and after adjustment for both patient-level characteristics and HDI tier (2·04, 1·17–2·49). Compared with between-hospital variation, the magnitude of between-country variation in mortality was less in the unadjusted model (MOR 1·58, 95% CI 1·00–2·08) as well as after adjustment for patient-level characteristics (1·56, 1·00–2·13). Furthermore, there was negligible between-country variation after adjustment for both patient-level and country-level characteristics (MOR 1·00, 95% CI 1·00–1·57), suggesting that the single country-level variable, HDI, accounted for all or most between-country variation.

Overall, missingness was low (appendix p 65). For variables included in the mixed effects models for mortality, only a single value in a single patient was missing and this record was excluded. In the validation exercise, there was a strong positive correlation between the number of cases identified by each participating team's primary data collectors and their independent validators for all procedures (Pearson's r 0·975, p<0·0001; appendix p 19). Inter-rater reliability for all items of the hospital questionnaire was acceptable (appendix pp 15–16): the level of agreement between respondents was good to very good (κ 0·6–1·0) for all categorical variables and there was a strong, positive correlation for number of

	Very high HDI tier (n=78)	High HDI tier (n=33)	Medium HDI tier (n=28)	Low HDI tier (n=14)	Total (n=153)	p value
Characteristics of hospitals						
Hospital type						0·0040
Government	74 (95%)	29 (88%)	18 (64%)	11 (79%)	132 (86%)	..
Private	3 (4%)	4 (12%)	7 (25%)	1 (7%)	15 (10%)	..
Other	1 (1%)	0 (0%)	3 (11%)	2 (14%)	6 (4%)	..
Location						0·46
Urban	75 (96%)	33 (100%)	26 (93%)	13 (93%)	147 (96%)	..
Rural	3 (4%)	0 (0%)	2 (7%)	1 (7%)	6 (4%)	..
Proportion of health-care costs paid for by patient						0·0005
None	61 (78%)	20 (61%)	7 (25%)	2 (14%)	90 (59%)	..
Some	17 (22%)	11 (33%)	15 (54%)	7 (50%)	50 (33%)	..
All	0 (0%)	2 (6%)	6 (21%)	5 (36%)	13 (8%)	..
Age of patients treated*						0·014
Both adults and children	51 (65%)	25 (76%)	27 (96%)	14 (100%)	117 (76%)	..
Adults only	26 (33%)	8 (24%)	1 (4%)	0 (0%)	35 (23%)	..
Children only	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	..
Availability of resources						
CT availabiity						0·0005
Always available in base hospital	76 (98%)	26 (79%)	24 (86%)	5 (36%)	131 (86%)	..
Always available in base or nearby hospital	1 (1%)	7 (21%)	4 (14%)	6 (43%)	18 (12%)	..
Not always available	1 (1%)	0 (0%)	0 (0%)	3 (21%)	4 (3%)	..
Intracranial pressure monitoring						0·0005
Yes, always available	68 (87%)	12 (36%)	7 (25%)	0 (0%)	87 (57%)	..
Yes, sometimes available	6 (8%)	8 (24%)	10 (36%)	1 (7%)	25 (16%)	..
No, never or rarely available	4 (5%)	11 (33%)	11 (39%)	13 (93%)	39 (25%)	..
No, not considered clinically useful	0 (0%)	2 (6%)	0 (0%)	0 (0%)	2 (1%)	..
Type of ICU						0·0010
Neurosciences ICU	37 (47%)	6 (18%)	17 (61%)	1 (7%)	61 (40%)	..
Other specialty ICU	14 (18%)	5 (15%)	6 (21%)	4 (29%)	29 (19%)	..
General ICU	27 (35%)	22 (67%)	5 (18%)	9 (64%)	63 (41%)	..
Availability of high-speed drill						0·0005
All cases	72 (92%)	16 (48%)	14 (50%)	2 (14%)	104 (68%)	..
Some or most cases	5 (6%)	16 (48%)	13 (46%)	6 (43%)	40 (26%)	..
Never	1 (1%)	1 (3%)	1 (4%)	6 (43%)	9 (6%)	..
Neurosurgeons per hospital	10 (6–13)	7 (5–14)	5 (2–7)	3 (1–5)	8 (4–12)	<0·0001
Surgeries for TBI per 30-day period	3 (2–5)	9 (4–21)	11 (4–19)	4 (2–17)	4 (2–10)	<0·0001

Data are n (%),median (IQR), or p value. 153 (96%) of 159 participating hospitals submitted the provider profiling questionnaire. All data presented here are from the provider profile questionnaire with the exception of the number of surgeries for TBI for each 30-day study period, which was calculated from the main data set. HDI=human development index. ICU=intensive care unit. TBI=traumatic brain injury. *What constitutes an adult or a child was defined by the local participating teams.

Table 1: **Characteristics of the participating hospitals by HDI tier**

	Very high HDI tier (n=328)	High HDI tier (n=539)	Medium HDI tier (n=614)	Low HDI tier (n=154)	Total (n=1635)	p value
Demographic characteristics and pre-injury status						
Median age, years	54 (34–69)	32 (21–47)	35 (25–48)	28 (20–38)	35 (24–51)	<0·0001
<18	27 (8%)	92 (17%)	71 (12%)	26 (17%)	216 (13%)	0·0006
>65	102 (31%)	46 (9%)	25 (4%)	5 (3%)	178 (11%)	<0·001
Sex						0·011
Male	250 (76%)	444 (82%)	492 (80%)	136 (88%)	1322 (81%)	..
Female	78 (24%)	95 (18%)	122 (20%)	18 (12%)	313 (19%)	..
American Society of Anaesthesiologists grade						<0·0001
1	76 (23%)	285 (53%)	264 (43%)	102 (66%)	727 (44%)	..
2	146 (45%)	180 (33%)	174 (28%)	45 (29%)	545 (33%)	..
3+	106 (32%)	74 (14%)	176 (29%)	7 (5%)	363 (22%)	..
Mechanism of injury and clinical presentation						
Road traffic collisions	90 (27%)	235 (44%)	382 (62%)	57 (37%)	764 (47%)	<0·0001
Motorcyclist	29 (9%)	119 (22%)	283 (47%)	15 (10%)	446 (28%)	..
Pedestrian	24 (8%)	55 (10%)	59 (10%)	28 (18%)	166 (10%)	..
Car	25 (8%)	39 (7%)	11 (2%)	12 (8%)	87 (5%)	..
Fall	176 (54%)	132 (24%)	138 (22%)	18 (12%)	464 (28%)	..
From height	68 (22%)	87 (16%)	76 (13%)	11 (7%)	242 (15%)	..
From standing	108 (35%)	45 (8%)	62 (10%)	7 (5%)	222 (14%)	..
Assault	23 (7%)	126 (24%)	58 (10%)	71 (46%)	278 (17%)	..
Other	36 (12%)	60 (11%)	52 (9%)	9 (6%)	157 (10%)	..
Glasgow Coma Scale	10 (5–14)	12 (7–15)	10 (7–13)	14 (10–15)	11 (7–14)	<0·0001
Severity						<0·0001
Mild	130 (40%)	244 (45%)	191 (31%)	96 (62%)	661 (40%)	..
Moderate or severe	198 (61%)	295 (57%)	423 (68%)	58 (37%)	974 (60%)	..
Moderate	51 (16%)	101 (19%)	187 (30%)	28 (18%)	367 (22%)	..
Severe	147 (45%)	194 (36%)	236 (38%)	30 (19%)	607 (38%)	..
Unreactive pupils						0·0001
Neither	228 (70%)	446 (83%)	474 (77%)	135 (88%)	1283 (78%)	..
One	63 (19%)	54 (10%)	81 (13%)	15 (10%)	213 (13%)	..
Both	37 (11%)	39 (7%)	59 (10%)	4 (2%)	139 (9%)	..
Major extracranial injury	76 (23%)	110 (20%)	72 (12%)	18 (12%)	276 (17%)	<0·0001
Hypoxia before surgery						<0·0001
Yes	41 (12%)	29 (5%)	53 (9%)	17 (11%)	140 (9%)	..
No	269 (82%)	456 (84%)	430 (70%)	130 (83%)	1285 (78%)	..
Not measured	18 (5%)	61 (11%)	132 (21%)	10 (6%)	221 (13%)	..
Hypotension before surgery						<0·0001
Yes	73 (22%)	76 (14%)	81 (13%)	32 (20%)	262 (16%)	..
No	255 (78%)	454 (83%)	528 (86%)	125 (80%)	1362 (83%)	..
Not measured	0 (0%)	16 (3%)	6 (1%)	0 (0%)	22 (1%)	..
Inter-hospital transfer	164 (50%)	246 (45%)	165 (27%)	24 (15%)	599 (37%)	<0·0001
No inter-hospital transfer	164 (50%)	239 (55%)	449 (73%)	130 (85%)	982 (62%)	

Data are median (IQR), n (%), or p value. HDI=human development index.

Table 2: **Baseline characteristics of the study cohort by HDI tier**

neurosurgeons reported per hospital (Pearson's r 0·970, p <0·0001).

Discussion

The Global Neurotrauma Outcomes Study is the first worldwide, prospective observational cohort study to assess similarities and differences in the casemix, management, and outcomes of patients receiving emergency neurosurgery for TBI across human development settings. Casemix differed significantly across HDI tiers. The transition of the mechanism of injuries from assaults to road traffic collisions and falls, and of the demographics from young to old, with increasing levels of human development, is consistent with trends in the epidemiology of all injuries and TBI specifically that have been observed previously.[2, 21–25] The proportion of TBI cases that were moderate or severe was highest in the medium HDI tier. We postulate that this is due to these countries having the greatest incidence of high-energy road traffic collisions.[21] The large burden of road traffic collisions in medium HDI countries is thought to be due to the fact that vehicle ownership is higher than in low HDI countries and road safety measures are inferior to those in high HDI and very high HDI countries. Furthermore, improvements in pre-hospital care between the medium HDI and low HDI tiers could mean a higher proportion of seriously injured patients survive to reach the neurosurgical operating theatre in the medium HDI tier, which is consistent with the lowest rates of inter-hospital transfers in the low HDI tier. Relatedly, clinicians in the low HDI tiers might generally be deciding not to operate on patients who are likely to survive with severe disability if there is a paucity of resources for rehabilitation and long-term care available in their region. We also identified differences in the most frequent emergency neurosurgical procedures done for TBI across the HDI tiers. Patients in the low HDI tiers most frequently underwent elevation of a depressed skull fracture, consistent with a high proportion of assaults. Evacuation of a supratentorial extradural haematoma made up the highest proportion of procedures in the medium HDI and high HDI tiers, which might be explained by the number of road traffic collisions in a reasonably young population (including many involving motorcyclists). Patients in the very high HDI tier most commonly had an acute subdural haematoma evacuated, which is to be expected given the proportion of older patients sustaining a fall.

We identified significant deficiencies in quality of care received by patients. Improved pre-hospital care has been associated with a better outcome for patients with TBI,[26] but only a minority of patients in the medium HDI and low HDI tiers were brought to the neurosurgical unit by vehicles manned by trained health-care professionals, which is consistent with other contemporary surveys of the state of emergency medical services in LMICs.[27,28] Relatedly, mortality in patients with severe TBI who had evacuation of a supratentorial extradural haematoma or acute subdural haematoma has long been known to increase dramatically when there is a delay of more than 4 h between the time of injury and surgery,[29–31] but the median time from injury to surgery was 8 h for these patients and, even in the very high HDI tier, the delay was greater than 4 h in approximately half of such cases. Cost-effective, contextually appropriate policies and interventions, such as training lay first responders in pre-hospital trauma care, need to be designed and implemented to reduce the time to surgery and prevent secondary brain injuries due to hypotensive and hypoxic insults in the hyperacute period.[32,33] Moreover, fewer than one in five patients with a severe TBI had an intracranial pressure monitor in situ at the end of surgery despite evidence from observational studies suggesting their use can reduce mortality.[34,35] Finally, one-quarter of patients with severe TBI were not admitted to an intensive care

	Very high HDI tier (n=328)	High HDI tier (n=539)	Medium HDI tier (n=614)	Low HDI tier (n=154)	Total (n=1635)	p value
Mortality*	64 (20%)	86 (16%)	138 (22%)	11 (7%)	299 (18%)	<0·0001
Not yet discharged at 14 days†	138 (52%)	153 (34%)	88 (18%)	21 (15%)	400 (30%)	<0·0001
Length of hospital stay, days	11 (3–13)	6 (3–13)	5 (1–10)	5 (3–11)	6 (2–13)	<0·0001
Length of ICU stay, days	12 (4–13)	9 (3–13)	9 (2–13)	3 (1–12)	10 (3–13)	0·0001
Surgical site infection	6 (2%)	23 (4%)	18 (3%)	4 (3%)	51 (3%)	0·21
Return to operating theatre	33 (10%)	28 (5%)	21 (3%)	4 (3%)	86 (5%)	<0·0001
Reason for return to operating theatre†						0·48
Craniectomy	5 (15%)	4 (14%)	3 (14%)	2 (50%)	14 (16%)	..
Cranioplasty	2 (6%)	3 (11%)	0 (0%)	0 (0%)	5 (6%)	..
Evacuation of contralateral haematoma	4 (12%)	3 (11%)	3 (14%)	0 (0%)	10 (12%)	..
Infection (wound washout)	1 (3%)	4 (14%)	1 (5%)	0 (0%)	6 (7%)	..
Other neurosurgical procedure	7 (21%)	9 (32%)	6 (29%)	0 (0%)	22 (26%)	..
Re-evacuation of ipsilateral haematoma	14 (42%)	5 (18%)	8 (38%)	2 (50%)	29 (34%)	..
GCS score at discharge versus admission						<0·0001
Improvement in GCS score	159 (48%)	242 (45%)	343 (56%)	62 (40%)	806 (49%)	..
No change in GCS score	67 (20%)	164 (30%)	114 (19%)	68 (44%)	413 (25%)	..
Worsening of GCS score or death	102 (31%)	133 (25%)	157 (26%)	24 (16%)	416 (25%)	..
Discharge destination						0·0005
Usual place of residence	76 (60%)	252 (84%)	156 (40%)	116 (95%)	600 (64%)	..
Transfer to another hospital	33 (26%)	42 (14%)	173 (45%)	5 (4%)	253 (27%)	..
Transfer to rehabilitation unit	14 (11%)	5 (2%)	9 (2%)	1 (1%)	29 (3%)	..
Other	3 (2%)	1 (0%)	50 (13%)	0 (0%)	54 (6%)	..

Data are n (%), median (IQR), or p value. All primary and secondary outcome measures were assessed at 14 days post-operatively (or last point of observation if discharged before this time point). Length of hospital stay in days refers to the number of days from admission to discharge in patients who were still admitted to hospital at the 14 day follow-up period; their length of stay was considered as 14 days. Similarly, in patients who were still admitted to ICU at the end of the 14-day follow-up period, their length of ICU stay in days was considered the time from admission to ICU to the end of the follow-up period. GSA=Glasgow Coma Scale. HDI=human development index. ICU=intensive care unit. *Mortality was the only primary outcome, all other fields were secondary outcomes. †Not a planned primary or secondary outcome, but included in this table as additional information to support primary and secondary outcomes.

***Table 3:* Outcomes of the study cohort by HDI tier**

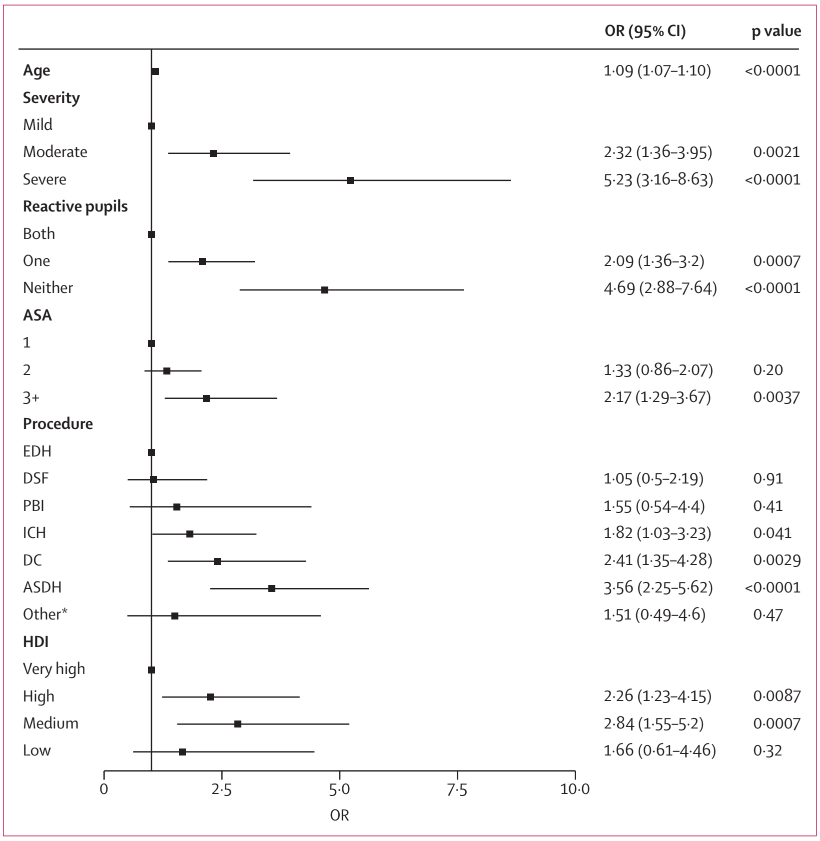

***Figure 3:* Factors associated with mortality in the mixed effects model**
ASA=American Society of Anaesthesiologists grade. ASDH=evacuation of supratentorial acute subdural haematoma. DC=decompressive craniectomy for raised intracranial pressure (no significant haematoma evacuated). DSF=elevation of depressed skull fracture or other operation for depressed skull fracture. EDH=evacuation of supratentorial extradural haematoma. HDI=human development index. ICH=evacuation of supratentorial intracerebral haemorrhage. OR=odds ratio. PBI=surgical debridement of penetrating brain injury. *Surgical procedures with 30 or fewer cases (evacuation of extradural, subdural, or intracerebral posterior fossa haematoma, cisternostomy, and exploratory burr holes) were aggregated into this category.

unit postoperatively, which echoes previous reports of the mismatch between the burden of critical illness and intensive care unit availability globally,[36] particularly in low-resource settings.[37]

The highest unadjusted mortality across the cohort and for all subgroups was observed in the medium HDI tier. After adjustment for casemix, patients in the medium HDI and high HDI tiers had statistically higher odds of mortality relative to the very high HDI tier, with the least favourable odds again in the medium HDI tier, which is consistent with findings from other studies examining a variety of disease processes that survival is associated with socioeconomic status.[25,38–40] The medium HDI tier was characterised by the highest proportion of patients with moderate or severe TBI and these patients were managed without consistent access to effective pre-hospital care, intracranial pressure monitoring, or intensive care unit admission, and it therefore follows that both the unadjusted and adjusted mortality would be highest in this group of patients. Although a lack of access to resources was also found in the low HDI tier, patients in this group typically had mild injuries for which a favourable outcome can be achieved with low-cost interventions—such as elevation of a depressed skull fracture, which almost half of the patients in the low HDI tier had—and the unadjusted mortality was consequently the lowest. Notably, even after adjustment for casemix, there was no statistically significant difference in the odds of mortality for patients in the low HDI tier relative to the very high HDI tier, which we attribute to a bias towards less seriously injured patients being operated on in low HDI tier countries that we were unable to account for with the markers of injury severity in our model.

Between-hospital variation in mortality was significant, consistent with previous reports from North America and Europe.[41,42] Between-hospital variation in mortality in the final model (MOR 2·04) was comparable in magnitude to the increased risk of mortality conferred by having one unreactive pupil (OR 2·17) or a moderate TBI (OR 2·61). Moreover, between-hospital variation was greater than between-country variation, suggesting that outcome is influenced more by hospital characteristics than country of origin, which raises the possibility that changing the structure and processes of care of surgical TBI in individual hospitals might be able to improve mortality. Furthermore, comparative effectiveness research could exploit this heterogeneity to identify best practices and facilitate the design of clinical practice guidelines tailored to the resources available.[43] Such efforts should be mindful that a holistic approach across the entire health system (including prevention, pre-hospital care, surgery, intensive care, and rehabilitation) is likely to be required to truly address the complexity of improving care for TBI, surgical or otherwise, worldwide.[33,44]

The main strength of the study is the geographical and socioeconomic diversity of the patient population, with approximately half being from medium HDI or low HDI countries, and 57% originating from the South Asia, sub-Saharan Africa, or Latin American and Caribbean regions. Moreover, despite limited resources, we showed excellent case ascertainment and completeness of data collection. However, our study has several limitations that should be considered when interpreting the data. First, participation in this study by hospitals was voluntary and, as such, there is a possibility of selection bias. Most hospitals were neurosurgical centres located in urban areas with access to neuro-imaging and thus patients receiving emergency neurosurgery for TBI in rural settings are under-represented. As such, we are unable to draw conclusions about aspects of the surgical management of TBI that are known to take place in such environments, including task-shifting of neurosurgery to general surgeons[45–47] and exploratory burr holes.[46] Second, we did not assess functional outcome in this study. Third, we were unable to evaluate long-term outcomes. Finally, our study did not capture non-operative cases of TBI, and we are, therefore, unable to comment on differences in which patients were selected for neurosurgical intervention between HDI settings.

For the first time, the Global Neurotrauma Outcomes Study has captured significant differences in casemix, management, and mortality of patients who receive emergency neurosurgery for TBI globally, including identifying opportunities to improve management across the cohort and showing that outcome is associated with the level of human development. Considerable between-hospital variation in mortality suggests local changes in care could improve outcomes, and comparative effectiveness research can potentially use this heterogeneity to identify best practices depending on the resources available. Longitudinal studies are being planned to assess long-term outcomes and design contextually appropriate interventions to reduce preventable deaths in this patient population globally.

Contributors

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. DC conceived the idea for the study, wrote the study protocol, designed the case report form and hospital questionnaire, coordinated the data collection and validation, undertook the data analysis, and wrote and revised the manuscript. PH, DC, AJ, and AK are the principal investigators of the study. DC, PH, AJ, and AK verified the data, prepared the draft manuscript, and coordinated its finalisation. DC and AE did the data extraction, statistical analyses, and drafting of tables and figures. All authors reviewed and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

PH is supported by the National Institute for Health Research (Global Neurotrauma Research Group, Senior Investigator Award, Cambridge Biomedical Research Centre, and Brain Injury Medtech Co-operative) and the Royal College of Surgeons of England. All other authors declare no competing interests.

Data sharing

After publication, data will be available to any researcher who provides a methodologically sound study proposal that is approved by the central study team. Proposals can be submitted to the Division of Neurosurgery at the University of Cambridge. Individual patients and hospitals will not be identifiable in any released data and all appropriate information governance protocols will be followed.

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