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Characteristics, management and outcomes of patients with severe traumatic brain injury in Victoria, Australia compared to United Kingdom and Europe: A comparison between two harmonised prospective cohort studies

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ABSTRACT

Objective: : The aim of this manuscript is to compare characteristics, management, and outcomes of patients with severe Traumatic Brain Injury (TBI) between Australia, the United Kingdom (UK) and Europe.

Methods: : We enrolled patients with severe TBI in Victoria, Australia (OzENTER-TBI), in the UK and Europe (CENTER-TBI) from 2015 to 2017. Main outcome measures were mortality and unfavourable outcome (Glasgow Outcome Scale Extended <5) 6 months after injury. Expected outcomes were compared according to the IMPACT-CT prognostic model, with observed to expected (O/E) ratios and 95% confidence intervals.

Results: : We included 107 patients from Australia, 171 from UK, and 596 from Europe. Compared to the UK and Europe, patients in Australia were younger (median 32 vs 44 vs 44 years), a larger proportion had secondary brain insults including hypotension (30% vs 17% vs 21%) and a larger proportion received ICP monitoring (75% vs 74% vs 58%). Hospital length of stay was shorter in Australia than in the UK (median: 17 vs 23 vs 16 days), and a higher proportion of patients were discharged to a rehabilitation unit in Australia than in the UK and Europe (64% vs 26% vs 28%). Mortality overall was lower than expected (27% vs 35%, O/E ratio 0.77 [95% CI: 0.64 – 0.87]. O/E ratios were comparable between regions for mortality in Australia 0.86 [95% CI: 0.49–1.23] vs UK 0.82 [0.51–1.15] vs Europe 0.76 [0.60–0.87]). Unfavourable outcome rates overall were in line with historic expectations (O/E ratio 1.32 [0.96-1.68] vs 1.13 [0.84-1.42] vs 0.96 [0.85-1.09]).

Conclusions: : There are major differences in case-mix between Australia, UK, and Europe; Australian patients are younger and have a higher rate of secondary brain insults. Despite some differences in management and discharge policies, mortality was less than expected overall, and did not differ between regions. Functional outcomes were similar between regions, but worse than expected, emphasizing the need to improve treatment for patients with severe TBI.

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Introduction

Traumatic Brain Injury (TBI) is a leading cause of death and long-term disability, particularly in young adults. Sixty-nine million individuals worldwide are estimated to sustain a TBI each year.(1) In Australia, TBI accounts for over 1000 Intensive Care Unit (ICU) admissions per year.(2) Half of severe TBI patients will be severely disabled or dead within six months of the injury, with lifetime costs largely due to disabled survivors of an estimated annual hospital costs of €33 billion of indirect and direct costs in Europe.(3, 4) For Australia, the lifetime cost for each severe TBI was estimated at $4,8 million.(5, 6)

Although recent randomised trials of alternative current therapies have provided guidance for clinicians (SAFE-TBI, DECRA, RESCUEicp, POLAR), trials of new therapies have been generally discouraging or require further investigations to resolve uncertainty.(7-11) Guideline recommendations for TBI care are often weak, leaving opportunity for individual treatment preferences and resource availability, resulting in variation of care. Comparative effectiveness research subsequently has been embraced internationally, and uses practice variation to measure benefits and risks of systems of care and interventions in ordinary settings and broader populations, reflecting daily clinical practice.(12)

An earlier study that compared outcomes following major trauma involving serious head injury managed in Victoria, Australia and the UK concluded that the absence of an organized trauma system in the UK at that time was associated with increased risk-adjusted mortality compared to management in the inclusive trauma system of Victoria, Australia over these years.(13) However, contemporary global comparisons of patients with severe TBI have been few, are largely limited to North America and Europe, and are hampered by different times, settings and populations. Improved understanding of the benefits and limitations of different approaches to care for TBI patients requires comparisons across trauma care systems, using comparable methods of data collection and comparable time periods. Practice variation in the management of TBI patients admitted to the ICU might then offer opportunities for identification of best practices using comparative effectiveness research.

This study compared demographics, treatment characteristics and outcomes in two prospective harmonised cohorts of severe TBI patients in the state of Victoria Australia (population 6 million; OzENTER), with UK and Europe (CENTER-TBI).

Methods

Study population

Data came from the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) Core Study and the OzENTER-TBI (Australia-Europe NeuroTrauma Effectiveness Research in Traumatic Brain Injury) Study. Both studies were longitudinal cohort studies with harmonised data points and outcome assessments. The OzENTER-TBI Study was conducted in the two designated adult major trauma centres in Victoria, Australia at different intervals between February 2015 to March 2017. These centres receive 85% of adults with severe TBI from a state population of 6 million. The CENTER-TBI Core study included TBI patients that were admitted to the ICU across 54 centres in the European Union, the United Kingdom (UK) and Israel between 2015 and 2017. Patients or family were given the opportunity to opt-out of data collection in the OzENTER-TBI Study. Ethics approval in the OzENTER-TBI study was granted by Human Research Ethics Committees of the local university, along with the two participating adult major trauma centres. The CENTER-TBI Core study was approved by the medical ethics committees of all participating centres and consent was obtained according to local regulations. More detailed information about the CENTER-TBI Core Study can be found in the study protocol and the publication of the main results.(14-16) Patients of any age were included if they underwent a CT-scan of the brain and were admitted to the ICU within 24 hours of injury. Patients with a pre-existing neurological disorder that would otherwise confound outcome assessment were excluded. For the purpose of the current study, we included all patients with severe TBI, which was defined as a Glasgow Coma Scale (GCS) score of 3-8 at baseline that were admitted to the ICU.

Data collection

Detailed information on demographics, injury characteristics, and clinical characteristics was collected. Clinical data was collected on a daily basis: at ICU admission, during ICU stay (days 1-7, day 10, day 14, day 21, and day 28), and at ICU discharge. Data collection was undertaken by trained Research Coordinators and entered into an online Case Report Form. CT scans were obtained in all patients upon presentation and centrally reviewed. Follow up CT scans were acquired as clinically indicated. All patients were treated according to local protocol.

Outcome assessment

The eight-point Glasgow Outcome Scale Extended (GOSE; overall effect of injury) was collected at 6 months after injury. The GOSE was measured by either a postal questionnaire or a structured (telephone) interview by a trained assessor.(17) The categories 'vegetative state (GOSE 2)' and 'lower severe disability (GOSE 3)' were combined resulting in a seven-point ordinal scale. Unfavourable outcome was defined as a GOSE$<$5, and Favourable outcome as a GOSE $>$4.

Statistical analysis

Patients were stratified into three groups: patients that were admitted to a study centre in 1) Australia (OzENTER-TBI Study), 2) the United Kingdom (CENTER-TBI Study), 3) Europe (CENTER-TBI Study). Countries that included less than 50 severe TBI patients were omitted from analysis.

Baseline characteristics were presented as median values with interquartile ranges (IQR) for continuous variables and as frequencies and percentages for categorical variables. ANOVA was used for comparison of continuous variables across strata. The χ^2 test was used for comparison of categorical variables.

The IMPACT CT model was used to calculate the expected mortality and expected proportion of patients with unfavourable outcome at 6 months in patients with severe TBI.(18) The IMPACT CT (International Mission for Prognosis and Analysis of Clinical Trials in TBI Computed Tomography) model was developed for predicting 6 month outcome in adult patients with moderate to severe head injury using their key covariates. The model was developed and validated in collaboration with the CRASH trial collaborations both including large numbers of individual patient data. The model discriminates well; and has been validated for the purpose of classification and characterization of large cohorts of patients.(19) Observed to expected (O/E) ratios were calculated with 95% confidence intervals. We performed a sensitivity analysis of the outcome comparison after multiple imputation, with use of the mice package in R. All statistical analyses were performed in R (version 3.5.1) and RStudio (version 1.0.136). CENTER-TBI data

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was accessed using a bespoke data management tool, 'Neurobot' (http://neurobot.incf.org, RRID: SCR_01700), vs 2.0 (data freeze: June 2019).

Results

In total, 198 patients were included in the OzENTER-TBI Study and 2138 patients were included in the CENTER-TBI ICU Core Study. After excluding patients with missing GCS at baseline (n= 133), patients with no severe GCS (n= 1135), and patients that were included in countries that included less than 50 patients (n= 194), 874 patients were included in this study.(Fig. 1) These patients were from three regions: Victoria, Australia (2 MTCs, n=107), UK (8 MTCs, n=171), and Europe (28 MTCs, n=596, *The Netherlands, Italy, Spain, Belgium, Norway, France each of which had > 50 patients enrolled and were included*).

Patients with severe TBI in Victoria, Australia, compared to those in the UK and Europe, were younger (median: 32 (IQR: 23-48) vs 44 years (IQR: 27-56) and 44 years (IQR: 26 – 62), p:0.003), a higher proportion was injured due to a road traffic incident (60% vs 51% vs 55%, p<0.001), and a lower proportion due to a fall (21% vs 31% vs 34%). Although a higher proportion of patients in Victoria, Australia and Europe than the UK, were transported direct to the trauma centre from the accident scene (90% vs 89% vs 66%) the transport times (from scene to trauma centre) for primary referrals were similar (median: 97 (IQR: 64-151) vs 105 (IQR: 80 – 127) minutes) in Victoria, Australia and the UK, but shorter in Europe (median: 73 (IQR: 54-100) minutes). In Australia, UK and Europe, two thirds of severe TBI patients were intubated before hospital arrival (67% vs 60% vs 70%). However ICP monitors (75% vs 74% vs 58%, p<0.001), and intensive therapies (74% vs 71% vs 54%, p<0.001) were used in a higher proportion of patients in Australia and UK than Europe. Patients' brain injury severities expressed as GCS scores, and pupil reactivities were similar in all regions, but CT scans reported epidural hematomas in a higher proportion of patients in Australia (p=0.004), and contusions in a lower proportion of patients in Europe (p=0.02).

More patients in Victoria, Australia had secondary brain insults recorded in the prehospital and emergency room phases of care. In Australia compared to UK/Europe, hypotension was recorded in 30% vs 17% / 21% (p=0.03), and hypoxia in 28% vs 19% / 22%. (p=0.23) Major extracranial injuries were observed in a lower proportion of patients in Australia than in the UK and Europe (59% vs 61% vs 68%, p=0.08), but thorax/chest injuries were observed in a higher proportion of patients in Australia. (Table 1, Table 2)

Both extracranial surgeries and cranial surgeries were performed in more patients in Australia than in the UK and Europe (43% vs 20% vs 36%, p<0.001 and 68% vs 50% vs 42%, p<0.001), but most acute management medical practices were equivalent. Two interventions for refractory intracranial hypertension were used in a lower proportion of patients in Australia than the UK and Europe. These were *intensive hypocapnia* (1.1% vs 8.5% vs 6.7%) (p=0.06), and *decompressive craniectomy* (14% vs 25% vs 15%) (p=0.01). There were no differences in the proportion of patients with large intracranial hematomas (Marshall classification V/VI; 27% vs 41% vs 34%). (Table 2)

However, despite the many similarities in other factors, ICU length of stay was substantially shorter in Australia than the UK and Europe, (median: 8.8 vs 13 days vs 11 days, p<0.001), and hospital length of stay was shorter in Australia than in the UK, but similar to Europe (median 17 vs 23 vs 16 days, p<0.001). In Australia although ICU times were shorter, most TBI deaths (19%) occurred in the ICU, and a further 3% occurred after ICU. In the UK, ICU mortality was 16%, with another 5% occurring later. In Europe,

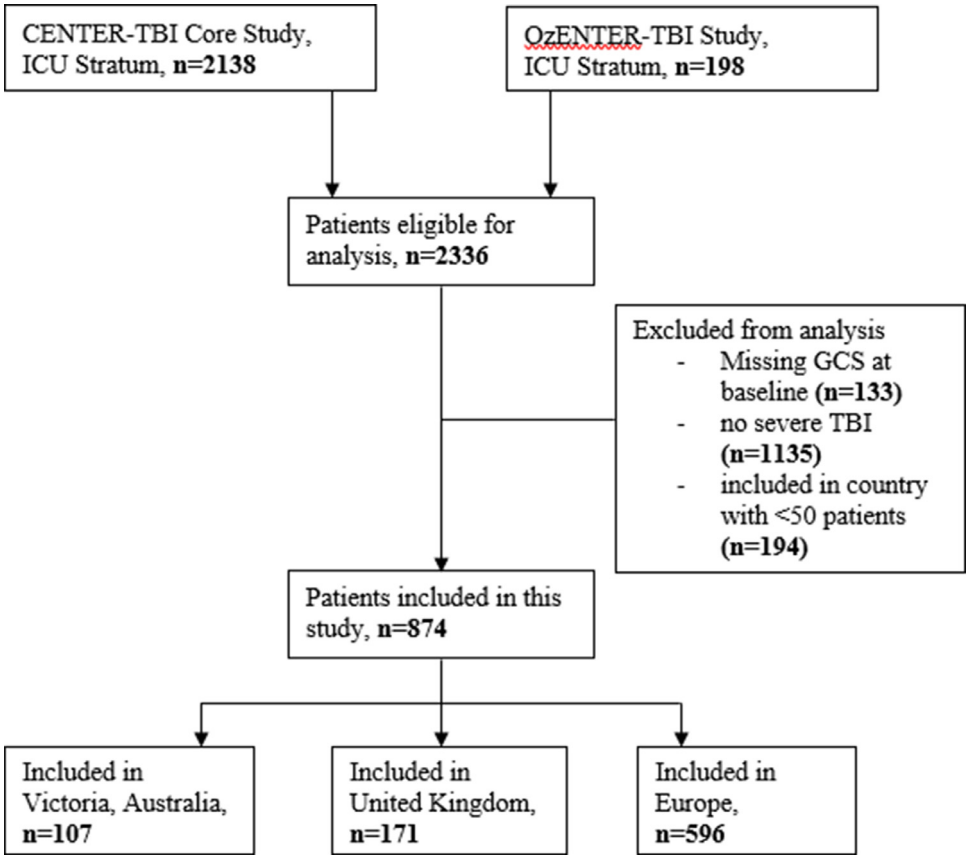

Fig. 1. Flowchart of included patients from the CENTER-TBI and OzENTER-TBI studies

Table 1
Baseline characteristics of patients with severe TBI in Victoria, Australia, the UK and Europe

VariableTotal number of patients	AustraliaN=107	UKN=171	EuropeN=596	p-value
Demographic characteristics				
Age (median (IQR))	32 (23 – 48)	44 (27 – 56)	44 (26 – 62)	0.003
>65 years	13 (12%)	26 (15%)	133 (22%)	0.01
Male sex	84 (79%)	128 (75%)	448 (75%)	0.74
Cause of injury				<0.001
Road traffic incident	64 (60%)	82 (51%)	320 (55%)	
Incidental fall	22 (21%)	50 (31%)	194 (34%)	
Suicide Attempt	6 (5.6%)	3 (1.9%)	18 (3.1%)	
Violence/Assault	9 (8.4%)	12 (7.4%)	6 (1.0%)	
Other	6 (5.6%)	15 (9.3%)	41 (7.1%)	
Missing	-	*9*	*17*	
Clinical presentation				
GCS Motor Score - Baseline				0.05
1/2	51 (49%)	76 (46%)	306 (53%)	
3/4	16 (15%)	44 (27%)	134 (23%)	
5/6	38 (36%)	44 (27%)	143 (25%)	
Missing	*2*	*7*	*13*	
Pupillary Reactivity				0.47
Both pupils reactive	79 (76%)	120 (73%)	403 (70%)	
One pupil unreactive	9 (8.7%)	18 (11%)	53 (9.2%)	
Two pupils unreactive	16 (15%)	27 (16%)	122 (21%)	
Missing	*3*	*6*	*18*	
Hypoxia (prehospital/ER phase)	29 (28%)	28 (19%)	127 (22%)	0.23
Missing	*2*	*21*	*17*	
Hypotension (prehospital/ER phase)	32 (30%)	26 (17%)	120 (21%)	0.03
Missing	*0*	*13*	*19*	
Any major extracranial injury (AIS >=3)	63 (59%)	105 (61%)	405 (68%)	0.08
Spine	17 (16%)	36 (21%)	120 (20%)	0.54
Thorax/Chest	57 (53%)	69 (40%)	262 (44%)	0.10
Abdomen/pelvis	16 (15%)	28 (16%)	121 (20%)	0.28
CT characteristics (central review)				
Epidural Hematoma	28 (29%)	25 (19%)	81 (15%)	0.004
Missing	*10*	*38*	*56*	
Traumatic Subarachnoid Haemorrhage	69 (71%)	105 (80%)	423 (79%)	0.24
Missing	*10*	*39*	*57*	
Contusion	29 (50%)	71 (69%)	204 (51%)	0.02
Missing	*49*	*68*	*194*	
Marshall Classification				0.19
I/II	59 (61%)	61 (46%)	276 (51%)	
III/IV	12 (12%)	18 (14%)	82 (21%)	
V/VI	26 (27%)	54 (41%)	184 (34%)	
Missing	*10*	*38*	*54*	

ANOVA was used for comparison of continuous variables across strata. The χ^2 test was used for comparison of categorical variables. P values relate to how likely differences between groups could occur while no differences between groups exist.

2% of hospital deaths occurred after ICU. In Australia, the median time from ICU admission to death in ICU was 4.1 days [IQR: 1.2 – 8.9] and the median time from ICU admission to decision of withdrawal of treatment was 3.7 days [IQR: 1.3 – 7.8], compared to 7.1 days [IQR: 3.1 – 13] and 8.0 [IQR: 2.5 – 12] in the UK, and 1.7 days [IQR: 0.6 – 6.4] and 1.1 [IQR: 0.3 – 4.6] days in Europe (p=0.01 and p<0.01). Withdrawal of therapy due to very severe brain injury was the primary cause of death in both countries (91% in Australia vs 89% in the UK). In Australia 64% of TBI patients were discharged to a rehabilitation centre compared to 26% in UK and 28% in Europe (P<0.001) where the most common discharge destination was a second hospital.

GOSE at 6 months was available in 776 (89%) patients. The follow-up rate was higher in Victoria (n=99, 93%), compared to UK

Table 2
Management characteristics of patients with severe TBI in Victoria, Australia, the UK and Europe

VariableTotal number of patients	AustraliaN=107	UKN=171	EuropeN=596	p-value
Referral				
Primary referral	96 (90%)	113 (66%)	531 (89%)	<0.001
Time to study centre (median (IQR)) – minutes	97 (64 – 151)	105 (80 – 127)	73 (54 – 100)	0.70
Secondary referral	11 (10%)	58 (34%)	65 (11%)	<0.001
Time to study centre (median (IQR)) – minutes	439 (308 – 512)	325 (239 – 499)	308 (225 – 435)	0.43
Diagnostic and surgical interventions				
Arrived Intubated	71 (67%)	102 (60%)	416 (70%)	0.04
Missing	*1*	-	*2*	
ICP monitor placed	80 (75%)	126 (74%)	343 (58%)	<0.001
Cranial Surgery	72 (68%)	85 (50%)	248 (42%)	<0.001
Missing	*1*	*1*	*1*	
Extracranial Surgery	45 (43%)	35 (20%)	215 (36%)	<0.001
	3	-	2	
Treatment characteristics				
Intensive Monitoring*	79 (74%)	121 (71%)	319 (54%)	<0.001
Mechanical Ventilation for at least 24 hours	104 (97%)	162 (95%)	510 (86%)	<0.001
Invasive Blood Pressure Monitoring	106 (99%)	163 (96%)	545 (92%)	0.01
Missing	-	*1*	*2*	
Hypothermia <35 °C	15 (16%)	24 (15%)	61 (11%)	0.21
Missing	*13*	*6*	*32*	
Mild Hypothermia with a lower limit of 35°C	23 (24%)	48 (29%)	67 (12%)	<0.001
Missing	*13*	*6*	*32*	
Intensive Hypocapnia [PaCO2 < 4.0 kPa (30 mmHg)]	1 (1.1%)	14 (8.5%)	38 (6.7%)	0.06
Missing	*13*	*6*	*32*	
Metabolic Suppression**	23 (24%)	40 (24%)	183 (32%)	0.06
Missing	*13*	*6*	*32*	
Paralysis	54 (57%)	88 (53%)	171 (30%)	<0.001
Missing	*13*	*6*	*32*	
Decompressive craniectomy	13 (14%)	41 (25%)	84 (15%)	0.01
Missing	*13*	*6*	*32*	

ANOVA was used for comparison of continuous variables across strata. The χ^2 test was used for comparison of categorical variables. P values relate to how likely differences between groups could occur while no differences between groups exist.

* A combination of ICP Monitor, Invasive Blood Pressure Monitoring, and Mechanical Ventilation for at least 24 hours

** Metabolic suppression for ICP control with high dose barbiturates or propofol

(n=135, 79%) and similar to Europe (n=542, 91%). Six-month mortalities were 24% vs 30% vs 28%.(Table 3). Overall, six-month mortality was better than predicted (27% vs 35%, observed to expected ratio 0.77 [95% CI: 0.64 – 0.87]), and similar in Victoria, UK and Europe (0.86 [95% CI: 0.49–1.23] vs 0.82 [0.51–1.15] vs 0.76 [0.60–0.87]). In all 3 regions however, unfavourable non-independent functional outcomes measured by GOSE <=4 were similar to predicted (1.32 [0.96-1.86] vs 1.13 [0.84-1.42] vs 0.96 [0.85-1.09]). Unadjusted unfavourable outcomes rates exceeded 50% (63% vs 65% vs 55%). The unadjusted proportion of survivors with severe disability at 6 months was similar in Australia and the UK (51% and 50%), compared to 37% in Europe (Table 3). The observed to expected ratios after multiple imputation were similar to those in complete case analysis. (Supplemental Table 1)

Discussion

Compared to TBI patients in the UK, and Europe, patients in Victoria, Australia were younger, and higher proportions had road traffic incidents compared to falls, secondary insults in the prehospital and emergency phases of care (predominantly hypotension), and epidural hematomas. A lower proportion received intensive hypocapnia and decompressive craniectomy therapies, and the patients treated in Victoria had shorter times to withdrawal of

Table 3
Outcomes among patients with severe TBI in Victoria, Australia, the UK and Europe

Variable	Australia	UK	Europe	P-value
Total number of patients	N=107	N=171	N=596	
Length of Stay				
Hospital Length of Stay, median (IQR) – days*	17 (8.8– 30)	23 (8.1– 54)	16 (1.8 – 33)	<0.001
Hospital Length of stay for all patients who survived to hospital discharge, median (IQR) - days	19 (11 – 32)	30 (12 – 60)	22 (8.6 – 38)	<0.001
ICU Length of stay, median (IQR) – days	8.8 (4.6 – 15)	13 (5.6 – 20)	11 (3.2 – 21)	<0.05
ICU Length of stay for all patients who survived to ICU discharge, median (IQR) – days	9.6 (4.9 – 16)	14 (7.4 – 22)	14 (5.6 – 23)	0.02
Hospital Mortality				
ICU Mortality	20 (19%)	28 (16%)	124 (21%)	0.39
In-hospital Mortality	24 (22%)	36 (21%)	139 (23%)	0.82
Cause of Death (for patients that died in-hospital)				0.21
Head injury/initial injury	20 (83%)	2 (8.3%)	2 (8.3%)	
Head injury/secondary intracranial damage	4 (17%)	8 (32%)	15 (14%)	
Systemic Trauma	1 (4.2%)	-	4 (3.7%)	
Other (including medical complications)	-	2 (8%)	9 (8,4%)	
Missing	-	-	32	
Final Discharge Location				<0.001
Rehab Unit	67 (64%)	42 (26%)	153 (28%)	
Home	7 (6.7%)	33 (20%)	116 (21%)	
Other hospital	6 (5.7%)	46 (28%)	134 (24%)	
Other	1 (1.0%)	5 (3.1%)	15 (2.7%)	
Mortality	24 (23%)	36 (22%)	139 (25%)	
Missing	*2*	*9*	*39*	
6-month Outcome				
6-months mortality	24 (24%)	41 (30%)	154 (28%)	0.58
Missing	*8*	*36*	*54*	
6-month predicted probability of mortality**	29%	34%	36%	
Observed versus expected mortality**	0.86 [0.49 – 1.23]	0.82 [0.51 – 1.15]	0.76 [0.60 – 0.87]	0.72
6-months unfavourable outcome (GOSE<5)	62 (63%)	88 (65%)	297 (55%)	0.05
Missing	*8*	*36*	*54*	
6-month predicted probability of unfavourable outcome **	47%	56%	55%	
Observed versus expected unfavourable outcome **	1.32 [0.96 – 1.68]	1.13 [0.84 – 1.42]	0.96 [0.85 – 1.09]	0.10
6-month GOSE 2-4 vs 5-8	38 (51%)	47 (50%)	143 (37%)	0.01

The χ^2 test was used for comparison of categorical variables. P values relate to how likely differences between groups could occur while no differences between groups exist. The outcome comparisons with the IMPACT CT model were based on patients in whom both information on predicted outcome and observed outcome was available. A chi-squared goodness of fit was applied to the observed versus expected values.

* Length of stay was missing in: 0, 7, 12 patients.

** according to the IMPACT-CT model. ANOVA was used for comparison of continuous variables across strata.

therapy for severe brain injuries, contributing to shorter ICU and hospital times. The proportion discharged to rehabilitation centres in Victoria was greater than UK and Europe but at 6 months after injury, mortality and functional outcomes in all 3 regions were similar, with unfavourable non-independent living being similar to IMPACT predictions.

The younger age of severe TBI patients in Victoria, Australia compared to the UK, likely reflects patient selection within the Victorian Trauma system, which directs adult trauma patients preferentially to two adult trauma centres, but triages patients 65 years old and over with an isolated TBI related to a low fall, to different neurosurgical centres that did not participate in the OzENTER-TBI. A recent Registry study in Victoria of severe TBI patients reported a 85%:15% patient division between the two major trauma centres of our study and the other hospitals with neurological services, and also a median age of severe TBI patients in the whole state of 41.5 years.(14) which is comparable to the UK (44 years), but different to this study (32 years). Selection in Victoria also likely accounts for the lower proportion of falls compared to UK which are more common in the elderly, and the higher rate of road traffic incidents (60% vs 50%). The higher rates of hypotension and hypoxia in Australia may relate to the higher percentage of road traffic incidents in this cohort, with associated greater haemorrhage and thoracic injuries. Our data suggest they are not due to different prehospital intubation rates nor to longer transport times, however they are likely to impact upon patient outcomes. Future research in Australia may optimally be directed towards further improvements in fluid resuscitation and intubation protocols aimed at reducing these secondary insults. (20, 21)

We found large variation between Australia, the UK and Europe in the use of brain-specific treatments including ICP monitoring, metabolic suppression, intensive hypocapnia, and paralysis. Intensive hypocapnia is little used in Australia due to concerns about short duration of action, and possible adverse implications of cerebral vasoconstriction. Several attempts to improve the quality of evidence for ICP monitoring have been performed in the past, which have been complicated by ethical challenges in randomizing patients between ICP monitoring and no ICP monitoring, and result in low evidence recommendations.(22, 23) Recent developments in technology resulted in new monitoring techniques, also known as multimodal monitoring, that can provide the neuro intensivist with information and assist in management decision making.(24, 25) Currently, several collaborations and research efforts are being made to resolve the outstanding questions about the roles and indications for neuro monitoring after TBI and demonstrate unequivocally whether monitor-guided interventions lead to improved outcomes for patients.(26) Another therapeutic option is decompressive craniectomy, which we found to be less common in Australia and Europe than the UK (P=0.01). A current randomised trial is testing decompressive craniectomy after evacuation of intracranial hematomas for brain swelling, but in patients with diffuse severe TBI and combined diffuse and mass lesion TBI, two large randomised trials in 2011 and 2016 found that decompressive craniectomy increased severely disabled survivors at 6 months. At 12 months, neither study showed an increase in patients surviving with a GOSE $\geq$ 5.(7, 8, 27, 28)

ICU and hospital times were 50% shorter for TBI patients in Australia than the UK. Since dying patients consume less hospital time than survivors, timing of death impacts these findings, and in Australia almost all TBI deaths occurred during the first 9 days in ICU. In the UK, ICU stays were longer, yet one third of UK deaths occurred after ICU. It is possible that some of these differences may be because step down care of critically ill patients may have been differentially labelled as ICU or non-ICU care in different hospitals, but such details were unavailable. Since 80% of TBI deaths in both countries were due to such severe head injury that withdrawal of care took place, the unexpected difference in timings of this decision making may be a factor driving reduced hospital times and costs in Australia, compared to the UK.

A higher proportion of patients was discharged to rehabilitation facilities in Victoria than in the comparable countries where a second (less acute) hospital was most common, although this might be explained in part by the younger age of patients in Victoria. However, availability of rehabilitation services in Victoria for road trauma patients who are compensable through the Transport Accident Commission, may be another driver.(29) Lower level RCT evidence and expert opinion suggest that TBI rehabilitation is beneficial in improving the functional outcomes beyond what we would expect from spontaneous recovery.(30, 31) However, the probability of receiving rehabilitation is associated with patients' and regional characteristics. Also, it might be challenging to meet the key success criteria for health and rehabilitation services such as inclusion of and access to and inclusion of well-coordinated multidisciplinary processes incorporating the varying needs of the individuals having sustained a TBI. However, our results may also question the beneficial impact of earlier rehabilitation on long term functional outcomes in severe TBI patients. Therefore, future studies should assess the necessity of more extensive multidimensional and standardized assessment of functional and psychological impairments and corresponding rehabilitation needs.

However despite these differences, after adjusting for predicted outcomes using IMPACT CT, patient outcomes at 6 months in all three regions were very similar: mortality tended to be better than predicted, but independent outcomes were not, indicating that the number of people living with severe disability was increased compared to predicted in all regions. Also, we did not observe any substantial differences in outcome between Victoria, Australia, the UK and Europe, confirming the results of a recent study. (32) Although this could be the result of a homogenous standard of treatment in the three regions, this might also suggest that the differences in therapies may be discordant and urges the need for future studies that study the effect of these therapies in isolation. The IMPACT CT prognostic scheme accounts for only about a third of outcome variance, and outcomes in all three regions may have been affected by unmeasured confounders. This, coupled with the large confidence intervals for our estimates of observed/expected unfavourable outcome in Victoria and the UK may mean that significant differences were missed.

Strengths of this study were the enrollment of patients with severe TBI across three large regions and many countries, and the detailed information on demographics, therapies, and outcomes. Limitations were first that our three cohorts were a small proportion of all patients with TBI in Australia, UK, and Europe, and they were not enrolled consecutively which could introduce selection bias. Second, follow-up data was missing in some patients, adding some uncertainty to the interpretation of the outcome comparisons.

This study highlights regional differences in patient characteristics which need to be considered when interpreting and comparing results from clinical studies on TBI from different regions. This collaboration within the InTBIR initiative will enable future meta-analyses for research questions that require larger numbers. Results from observational studies may give rise to new insights in disease mechanisms and rejuvenate industry interests and investment in TBI.

In conclusion, differences exist in case-mix between Victoria, Australia compared to the UK and Europe, including a younger age and a higher rate of secondary brain insults. Despite some differences in management and discharge policies, mortality and functional outcomes are largely similar. Contemporary mortality is better than expected based on historical data, but independent living outcomes may not have improved. These findings are likely driven by increased survival with disability over time and emphasize the

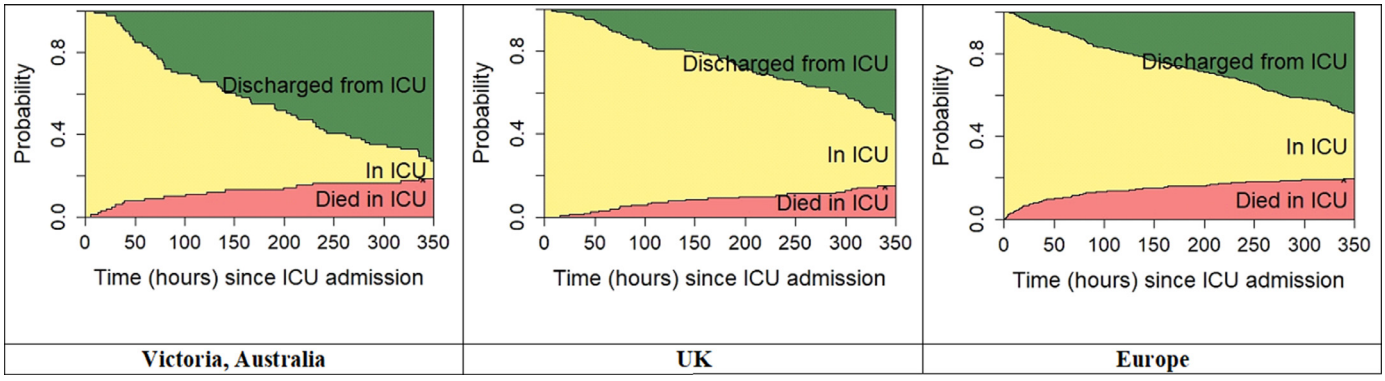

Fig. 2. Probabilities of state of severe TBI patients during the first two weeks after ICU admission. The x-axis represents time from ICU admission in hours, y-axis represents the probability to be in one the following states; discharged from ICU, still in ICU, or died in ICU.

need for further global efforts in order to refine recommendations for severe TBI patients.

Fig. 2

Ethics approval and consent to participate

In each recruiting site ethical approval was given; an overview is available online (https://www.center-tbi.eu/project/ethical-approval).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available via https://www.center-tbi.eu/data on reasonable request.

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Authors' contributions

EW analyzed the data and drafted the tables and Fig.s. EW, and DJC interpreted the data and drafted the manuscript. DJC designed the study protocol and supervised the study. TT, HL, ES, and AM were involved in regular meetings on the manuscript and reviewed the manuscript multiple times. All authors were involved in the design of the CENTER-TBI and the OzENTER-TBI study and reviewed and approved the final version of the manuscript. The lead author that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted.

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OzENTER-TBI

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.injury.2021.04.033.

References

[1] Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg 2018:1–18.
[2] Magee F, Wilson A, Bailey MJ, Pilcher D, Secombe PJ, Young P, et al. Trauma-related admissions to intensive care units in Australia: the influence of Indigenous status on outcomes. Med J Aust 2019;210(11):493–8.
[3] Olesen J, Gustavsson A, Svensson M, Wittchen HU, Jönsson B. The economic cost of brain disorders in Europe. Eur J Neurol 2012;19(1):155–62.
[4] Scholten AC, Haagsma JA, Panneman MJ, van Beeck EF, Polinder S. Traumatic brain injury in the Netherlands: incidence, costs and disability-adjusted life years. PLoS One 2014;9(10):e110905.

[5] Economics A. The economic cost of spinal cord injury and traumatic brain injury in Australia. Report by Access Economics for the Victorian Neurotrauma Initiative Canberra: Access Economics. 2009;31.
[6] Collie A, Keating C, Pezzullo L, Gabbe B, Cooper J, Brown D, et al. Brain and spinal cord injury in Australia–economic cost and burden of disease. Inj Prev 2010;16(Suppl 1):A25–AA6.
[7] Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, D'Urso P, et al. Decompressive Craniectomy in Diffuse Traumatic Brain Injury. N Engl J Med 2011;364(16):1493–502.
[8] Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, et al. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. N Engl J Med 2016;375(12):1119–30.
[9] Nichol A, French C, Little L, Haddad S, Presneill J, Arabi Y, et al. Erythropoietin in traumatic brain injury (EPO-TBI): a double-blind randomised controlled trial. Lancet 2015;386(10012):2499–506.
[10] Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007;357(9):874–84.
[11] Cooper DJ, Nichol AD, Bailey M, Bernard S, Cameron PA, Pili-Floury S, et al. Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients With Severe Traumatic Brain Injury: The POLAR Randomized Clinical Trial. JAMA 2018;320(21):2211–20.
[12] Maas AI, Menon DK, Lingsma HF, Pineda JA, Sandel ME, Manley GT. Re-orientation of clinical research in traumatic brain injury: report of an international workshop on comparative effectiveness research. J Neurotrauma 2012;29(1):32–46.
[13] Gabbe BJ, Biostat GD, Lecky FE, Bouamra O, Woodford M, Jenks T, et al. The effect of an organized trauma system on mortality in major trauma involving serious head injury: a comparison of the United kingdom and victoria, australia. Ann Surg 2011;253(1):138–43.
[14] Burton A. The CENTER-TBI core study: The making-of. Lancet Neurol 2017;16(12):958–9.
[15] Maas AI, Menon DK, Steyerberg EW, Citerio G, Lecky F, Manley GT, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. Neurosurgery 2015;76(1):67–80.
[16] Steyerberg EW, Wiegers E, Sewalt C, Buki A, Citerio G, De Keyser V, et al. Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. The Lancet Neurology 2019;18(10):923–34.
[17] Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the Glasgow Outcome Scale and the extended Glasgow Outcome Scale: guidelines for their use. J Neurotrauma 1998;15(8):573–85.
[18] Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med 2008;5(8):e165 discussion e.
[19] Dijkland SA, Foks KA, Polinder S, Dippel DWJ, Maas AIR, Lingsma HF, et al. Prognosis in Moderate and Severe Traumatic Brain Injury: A Systematic Review of Contemporary Models and Validation Studies. J Neurotrauma 2019;37(1):1–13.
[20] McHugh GS, Engel DC, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, et al. Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. J Neurotrauma 2007;24(2):287–93.
[21] Volpi PC, Robba C, Rota M, Vargiolu A, Citerio G. Trajectories of early secondary insults correlate to outcomes of traumatic brain injury: results from a large, single centre, observational study. BMC Emergency Medicine 2018;18(1):52.
[22] Alali AS, Fowler RA, Mainprize TG, Scales DC, Kiss A, de Mestral C, et al. Intracranial pressure monitoring in severe traumatic brain injury: results from the American College of Surgeons Trauma Quality Improvement Program. J Neurotrauma 2013;30(20):1737–46.
[23] Aries M, Regtien J, Czosnyka M, Donnelly J, Smielewski P. Neuromonitoring of patients with severe traumatic brain injury at the bedside. Critical Care 2015;19(1):1–201.
[24] Roh D, Park S. Brain Multimodality Monitoring: Updated Perspectives. Curr Neurol Neurosci Rep 2016;16(6):56.
[25] Smith M. Multimodality Neuromonitoring in Adult Traumatic Brain Injury: A Narrative Review. Anesthesiology 2018;128(2):401–15.
[26] Lazaridis C. Intracranial Pressure Monitoring in Traumatic Brain Injury: Start Ventricular or Parenchymal? Neurocritical Care 2019;31(1):22–3.
[27] Kolias AG, Scotton WJ, Belli A, King AT, Brennan PM, Bulters DO, et al. Surgical management of acute subdural haematomas: current practice patterns in the United Kingdom and the Republic of Ireland. Br J Neurosurg 2013;27(3):330–3.
[28] Cooper DJ, Rosenfeld JV, Murray L, Arabi YM, Davies AR, Ponsford J, et al. Patient Outcomes at Twelve Months after Early Decompressive Craniectomy for Diffuse Traumatic Brain Injury in the Randomized DECRA Clinical Trial. J Neurotrauma 2020;37(5):810–16.
[29] Gabbe BJ, Sutherland AM, Hart MJ, Cameron PA. Population-based capture of long-term functional and quality of life outcomes after major trauma: the experiences of the Victorian State Trauma Registry. J Trauma 2010;69(3):532–6 discussion 6.
[30] Cicerone KD, Mott T, Azulay J, Sharlow-Galella MA, Ellmo WJ, Paradise S, et al. A randomized controlled trial of holistic neuropsychologic rehabilitation after traumatic brain injury. Arch Phys Med Rehabil 2008;89(12):2239–49.
[31] Formisano R, Azicnuda E, Sefid MK, Zampolini M, Scarponi F, Avesani R. Early rehabilitation: benefits in patients with severe acquired brain injury. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2017;38(1):181–4.
[32] Huijben JA, Wiegers EJA, Lingsma HF, Citerio G, Maas AIR, Menon DK, et al. Changing care pathways and between-center practice variations in intensive care for traumatic brain injury across Europe: a CENTER-TBI analysis. Intensive Care Med 2020.