Fluid balance and outcome in critically ill patients with traumatic brain injury (CENTER-TBI and OzENTER-TBI): a prospective, multicentre, comparative effectiveness study

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Summary

Background Fluid therapy—the administration of fluids to maintain adequate organ tissue perfusion and oxygenation—is essential in patients admitted to the intensive care unit (ICU) with traumatic brain injury. We aimed to quantify the variability in fluid management policies in patients with traumatic brain injury and to study the effect of this variability on patients' outcomes.

Methods We did a prospective, multicentre, comparative effectiveness study of two observational cohorts: CENTER-TBI in Europe and OzENTER-TBI in Australia. Patients from 55 hospitals in 18 countries, aged 16 years or older with traumatic brain injury requiring a head CT, and admitted to the ICU were included in this analysis. We extracted data on demographics, injury, and clinical and treatment characteristics, and calculated the mean daily fluid balance (difference between fluid input and loss) and mean daily fluid input during ICU stay per patient. We analysed the association of fluid balance and input with ICU mortality and functional outcome at 6 months, measured by the Glasgow Outcome Scale Extended (GOSE). Patient-level analyses relied on adjustment for key characteristics per patient, whereas centre-level analyses used the centre as the instrumental variable.

Findings 2125 patients enrolled in CENTER-TBI and OzENTER-TBI between Dec 19, 2014, and Dec 17, 2017, were eligible for inclusion in this analysis. The median age was 50 years (IQR 31 to 66) and 1566 (74%) of patients were male. The median of the mean daily fluid input ranged from 1·48 L (IQR 1·12 to 2·09) to 4·23 L (3·78 to 4·94) across centres. The median of the mean daily fluid balance ranged from –0·85 L (IQR –1·51 to –0·49) to 1·13 L (0·99 to 1·37) across centres. In patient-level analyses, a mean positive daily fluid balance was associated with higher ICU mortality (odds ratio [OR] 1·10 [95% CI 1·07 to 1·12] per 0·1 L increase) and worse functional outcome (1·04 [1·02 to 1·05] per 0·1 L increase); higher mean daily fluid input was also associated with higher ICU mortality (1·05 [1·03 to 1·06] per 0·1 L increase) and worse functional outcome (1·04 [1·03 to 1·04] per 1-point decrease of the GOSE per 0·1L increase). Centre-level analyses showed similar associations of higher fluid balance with ICU mortality (OR 1·17 [95% CI 1·05 to 1·29]) and worse functional outcome (1·07 [1·02 to 1·13]), but higher fluid input was not associated with ICU mortality (OR 0·95 [0·90 to 1·00]) or worse functional outcome (1·01 [0·98 to 1·03]).

Interpretation In critically ill patients with traumatic brain injury, there is significant variability in fluid management, with more positive fluid balances being associated with worse outcomes. These results, when added to previous evidence, suggest that aiming for neutral fluid balances, indicating a state of normovolaemia, contributes to improved outcome.

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*CENTER-TBI and OzENTER-TBI Collaboration Groups are listed at the end of the appendix

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Introduction

Traumatic brain injury is one of the major causes of premature death and disability worldwide.[1] Intensive care management of patients with traumatic brain injury predominantly involves monitoring of intracranial pressure and cerebral perfusion pressure.[2] However, the effect of systemic therapies, including fluid therapy (the administration of different intravenous fluids for maintenance of adequate organ tissue perfusion and oxygenation), in critically ill patients with traumatic brain injury is understudied.

Fluid therapy is essential in critically ill patients with traumatic brain injury. Fluid restriction could have adverse consequences on outcome,[3] whereas fluid overload could cause systemic complications (eg, pulmonary oedema) or brain oedema and increased intracranial pressure.[3,4] Historically, the importance and goals of fluid management in patients with traumatic brain injury have varied and shifted, from dehydration therapy (aimed at limiting cerebral oedema) in the 1970s to 1990s,[5] towards normovolaemia or even hypervolaemia.[3,6,7] These changing insights are reflected in previous versions of the Brain

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See Online for appendix

Research in context

Evidence before this study

Almost all patients with traumatic brain injury, with or without polytrauma, receive intravenous fluids. Over the past few decades, the main goal of fluid management has shifted from a dehydration strategy, including negative fluid balance, to normovolaemia (ie, neutral or net zero fluid balance) and mild hypervolaemia (ie, a slightly positive fluid balance). In 2018, the European Society of Intensive Care Medicine (ESICM) consensus on fluid therapy in neurointensive care, which also pertains to patients with traumatic brain injury, reported the findings of an extensive literature search based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the quality of evidence and formulate evidence-based treatment recommendations. However, given the absence of high-quality investigations, consensus-based practice recommendations were drafted on optimal fluid resuscitation and maintenance fluid therapy, suggesting clinicians should aim for normovolaemia (which has not been defined in detail), using arterial blood pressure and fluid balance as the main and safety endpoints to titrate fluids, and avoid restrictive fluid therapy (ie, a negative fluid balance). We updated the systematic literature search used for this ESICM consensus (which ran until Jan 19, 2017), excluding studies done in animals, case reports and reviews, and studies of non-traumatic brain injury, using the same search terms in PubMed on Feb 20, 2021: ("brain edema"[MeSH] OR "traumatic brain injury"[All Fields] OR "head trauma"[All Fields] OR "head injury"[All Fields]) AND ("Hemodynamics"[Mesh] OR "Blood volume"[MeSH] OR "Hemodilution"[MeSH] OR "fluid therapy"[Mesh] OR "Hydroxyethyl starch derivatives"[MeSH] OR "crystalloid solutions"[Supplementary Concept] OR "Hypertonic solutions"[MeSH] OR ("albumins"[MeSH Terms] OR "albumins"[All Fields] OR "albumin"[All Fields]) OR ("crystalloid solutions"[Supplementary Concept] OR "crystalloid solutions"[All Fields] OR "crystalloid"[All Fields]) OR "Hydroxyethyl starch"[All Fields] OR ("mannitol"[MeSH Terms] OR "mannitol"[All Fields]) OR ("glucose"[MeSH Terms] OR "glucose"[All Fields] OR "dextrose"[All Fields]) OR ("sodium chloride"[MeSH Terms] OR ("sodium"[All Fields] AND "chloride"[All Fields]) OR "sodium chloride"[All Fields] OR "saline"[All Fields])) AND ("humans"[MeSH Terms] AND English[lang]) NOT (child* OR infant* OR pediatrics). No additional relevant studies were retrieved.

Added value of this study

In this comparative effectiveness study of a large cohort of patients admitted to the intensive care unit (ICU) with traumatic brain injury in Europe (CENTER-TBI) and Australia (OzENTER-TBI), we found that the mean daily fluid balance was often in the normovolaemia to mild hypervolaemia range, as indicated by a neutral to positive fluid balance. Fluid management varied substantially between ICUs. Positive daily mean fluid balances were common and consistently associated with higher ICU mortality and worse functional outcome.

Implications of all the available evidence

Our findings, in combination with previous evidence, argue for a more rigorous policy of normovolaemia, carefully avoiding both hypervolaemia and hypovolaemia as indicated by mean neutral fluid balances, given the harm associated with both mean negative and positive fluid balances. However, further research is needed to establish how to implement this knowledge while still respecting individualised approaches (eg, based on haemodynamic monitoring) and taking into account cerebral perfusion pressure.

Trauma Foundation guidelines, with recommendations ranging from "euvolemia … by adequate fluid replacement" to a focus on maintaining cerebral perfusion pressure above 70 mm Hg, with fluids or vasopressors, or both.[8] In the 2007 and 2016 versions of the Brain Trauma Foundation guidelines, recommendations on fluid management were discarded because of the absence of high-quality evidence.[9,10] Notably, these last two versions also discarded the higher than 70 mm Hg target for cerebral perfusion pressure, following the trial by Robertson and colleagues[11] that found a five times higher incidence of adult respiratory distress syndrome and a substantially more positive fluid balance when aiming for a cerebral perfusion pressure higher than 70 mm Hg.

In summary, best practice guidelines for fluid management in patients with traumatic brain injury remain controversial. Potentially as a result, previous studies have shown substantial practice variation in fluid management.[3] Although variability in clinical practice is in principle undesirable, it also provides the opportunity to relate between-centre differences in management to differences in outcome.[2,12,13] In this prospective, multicentre, comparative effectiveness study, we aimed to quantify the variability in fluid management policies for patients with traumatic brain injury across intensive care units (ICUs) in Europe and Australia, and to study the association between fluid therapy and outcomes.

Methods

Study design and participants

The CENTER-TBI (Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury) study is an ongoing multicentre, longitudinal, prospective observational cohort study being done in 63 centres in 18 countries across Europe and Israel. Data were collected between Dec 19, 2014, and Dec 17, 2017. Patients were included in the study if they were admitted to the ICU within 24 h of injury with a clinical diagnosis of traumatic brain injury and had a CT scan of the brain. Patients were excluded from the study if they had a severe pre-existing

neurological disorder that would confound outcome assessment.[12] The OzENTER-TBI (Australia-Europe NeuroTrauma Effectiveness Research in Traumatic Brain Injury) study was an entirely ICU-based study that collected detailed data from patients with traumatic brain injury admitted to the ICU of two major trauma centres in Australia between Feb 1, 2015, and March 31, 2017. The OzENTER-TBI study was prospectively harmonised with and followed the same inclusion criteria as the CENTER-TBI study. For this analysis, we included patients aged 16 years or older who were admitted to the ICU in either study.

The CENTER-TBI study was approved by the medical ethics committees of all participating centres.[12] All patients or their proxies provided written informed consent within 24 h after injury. In the OzENTER-TBI study, ethical approval was granted by the human research ethics committees of Monash University, Melbourne, VIC, Australia, and of the two participating adult major trauma hospitals (The Alfred Hospital and the Royal Melbourne Hospital, Melbourne, VIC, Australia). For patients in OzENTER-TBI, patients or family members were given two opportunities to opt out of data retention and outcome assessments, but if family members could not be located, patients were included in the study with informed consent waived by the three human research ethics committees.

Procedures

CENTER-TBI and OzENTER-TBI collected detailed information about demographics, injury characteristics, clinical characteristics, laboratory values, monitoring, treatment intensity level, and outcomes. Furthermore, on a daily basis, serum sodium was documented, as well as details of whether colloids or osmotic therapy had been administered (yes or no). At each centre, data were collected and interpreted by physicians or research assistants, or both, and entered on an online data entry and analysis platform (QuesGen; Burlingame, CA, USA).

A site coordinator was designated in each centre to streamline data collection. Data collection was supported by ICON (Paris, France), a professional contract research organisation, and source data verification of major characteristics was done by ICON at all sites on a quasi-random sample of 1298 (28%) patients. For the purpose of this study, we extracted data on demographics, injury, and clinical and treatment characteristics. All patients were treated according to local hospital protocols, which were informed by the Brain Trauma Foundation guidelines in 49 (75%) of 65 centres in CENTER-TBI.[14]

Fluid balance was calculated as the difference between fluid input (all intravenous fluids including any crystalloid, hyperosmotic, or colloid fluids, blood products, enteral fluids, and renal replacement therapy fluids) and fluid loss (urine output, enteral losses, drain losses, and dialysis effluent-dialysate from continuous renal replacement therapy) per day in the ICU. Insensible fluid losses were not considered. On the case report form, cumulative fluid input was requested over a 24 h period, including fluids that were given in the operating room on days 1–7 and on days 10, 14, 21, and 28. We calculated the mean daily fluid balance and mean daily fluid input during ICU stay per patient. This estimate accounts for the fact that the number of measurements might differ per patient because of mortality or discharge from the ICU.

Outcomes

Primary outcomes were ICU mortality and the Glasgow Outcome Scale Extended (GOSE) at 6 months. The GOSE was measured by either a postal questionnaire or an interview, depending on the preference of the centre, outcome assessor, or patient, or a combination of the above.[12] The categories "vegetative state" and "lower severe disability" were combined, as these categories could not be differentiated for assessments based on postal questionnaires. Unfavourable outcome was defined as a GOSE score less than 5.

For more on the **ethical approval process of the CENTER-TBI study** see https://www.center-tbi.eu/project/ethical-approval

Statistical analyses

Baseline characteristics of included patients were presented as median values with IQRs 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.

To assess between-centre variation in fluid management, we used a linear mixed-effects model to estimate the mean balance and mean input per centre with corresponding 95% CIs. The variables from the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) prognostic models (age, Glasgow Coma Scale [GCS] motor score, pupillary reaction, hypoxia, hypotension, CT Marshall classification, traumatic subarachnoid haemorrhage, epidural haematoma, first glucose, and first haemoglobin), and any major extracranial injury (Abbreviated Injury Scale [AIS] ≥3) were assessed upon hospital admission only and added as independent variables to adjust for case-mix severity.[15] Hypotension was defined as a measured systolic blood pressure lower than 90 mm Hg at least once before hospital admission or in the emergency department.

In patient-level analyses, the associations between fluid balance and fluid input and outcome were analysed with a random-effects logistic regression (for ICU mortality) and ordinal regression (for GOSE), with adjustment for the IMPACT variables, any major extracranial injury, and a random intercept for centre. In a secondary analysis we also adjusted for cerebral perfusion pressure and serum sodium (appendix p 15), and for mean arterial pressure (appendix p 16). Additionally, we used propensity score matching (appendix p 17).

Because of the observational nature of the study, the possibility of residual confounding (beyond confounding variables based on clinical or pathophysiological

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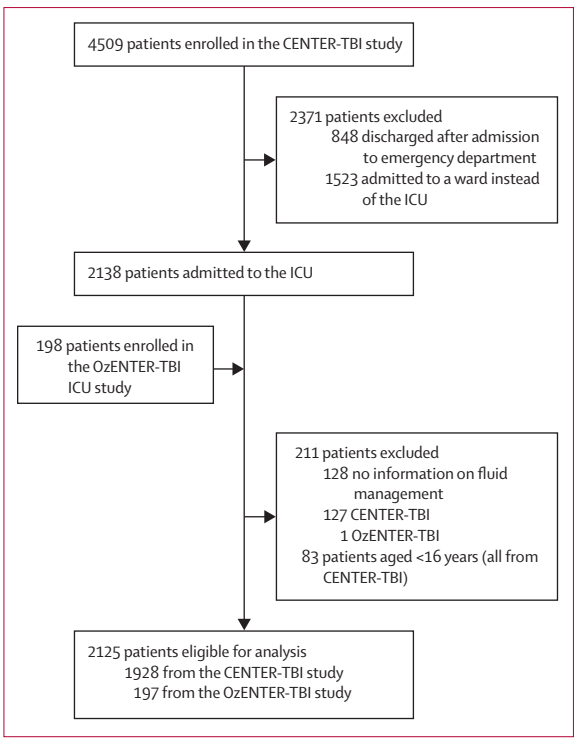


Figure 1: **Flowchart of included patients**
ICU=intensive care unit.

reasoning or previous research) in a patient-level analysis can never be fully excluded. Therefore, we also analysed the association between fluid management and outcome with instrumental variable analysis, which is less sensitive to confounding by indication. The instrumental variable was mean fluid balance and fluid input per centre, which was calculated by use of a mixed-effects linear regression with adjustment for the IMPACT variables, any major extracranial injury, and a random intercept for centre, and expressed as the deviation of the centre-specific mean balance or input from the overall mean. The association of this instrument, the centre-specific deviation, with outcome was tested by use of a mixed-effects ordinal regression model with GOSE as outcome, with adjustment for the IMPACT variables, any major extracranial injury, and a random intercept for centre, to adjust for potential confounding centre characteristics (appendix p 20).

In all models, restricted cubic splines were used to test for the non-linearity of the effect of fluid management. For fluid balance, a non-linear association with GOSE at 6 months was observed (appendix p 18) with an inflection point at a fluid balance of 0·0. Therefore, mean daily positive fluid balance (≥0 L) and mean daily negative fluid balance (<0 L) were analysed as two separate linear variables and their effect expressed as two separate odds ratios (ORs) and p values. ORs and 95% CIs for GOSE were reversed, so that an OR higher than 1 indicates worse outcome, to align the interpretation of these results with those for the effect on mortality.

All statistical analyses were done in R studio, and a two-sided p value of 0·05 was considered to be statistically significant. Data were accessed with a bespoke data management tool, Neurobot (research resource identifier: SCR_01700), version 2.1 (data freeze: June, 2020). Multiple imputation was used to handle missing values, with use of the Multiple Imputation by Chained Equations (MICE) package in R.

We did sensitivity analyses to explore the consistency of the results in the following subgroups of patients, based on the assumption that fluid management might differ between subgroups: patients with isolated traumatic brain injury (no major extracranial injury; AIS ≥3) versus those with major extracranial injury; patients with hypotension before hospital admission or in the emergency department; patients who were not treated with hypertonic saline versus those who were treated with hypertonic saline; patients who were not treated with mannitol versus those treated with mannitol; patients who survived in the ICU for at least 3 days versus patients who stayed in the ICU for a maximum of 3 days; patients with raised intracranial pressure (>20 mm Hg) versus patients who did not have raised intracranial pressure at least once during ICU stay; patients who had an intracranial pressure monitor versus patients who did not have an intracranial pressure monitor; patients with moderate and severe traumatic brain injury (GCS 13 at baseline) versus patients with mild traumatic brain injury (GCS ≥13); and patients included in CENTER-TBI versus those in the OzENTER cohort. Interactions between fluid balance or fluid input and subgroups were tested by comparing models with and without interaction terms by use of a likelihood ratio test.

To gain more insight into the potential consequences of fluid therapy, we assessed the association of fluid balance and input with intracranial pressure, cerebral perfusion pressure, and the dose of vasopressors. In a subgroup of patients in whom intracranial pressure monitoring was done, the association of daily fluid balance and input with the daily maximum intracranial pressure, mean cerebral perfusion pressure, and dose of noradrenaline (mg) on the following day was analysed with a linear mixed model, including a random intercept for patient to account for multiple observations within one patient and with adjustment for the IMPACT core variables (age, GCS motor score, and pupillary reactivity).

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or in the decision to submit for publication.

Results

4509 patients were enrolled in the CENTER-TBI study, of whom 2138 were admitted to the ICU. 198 patients admitted to an ICU were enrolled in the OzENTER-TBI study. We excluded patients for whom information about

fluid therapy was not available (n=128, including one from the OzENTER study) and those who were younger than 16 years of age (n=83). 2125 patients from 55 hospitals in 18 countries were therefore eligible for inclusion in this analysis (figure 1).

The median age of patients was 50 years (IQR 31 to 66) and 1566 (74%) were male. 1202 (57%) patients had a major extracranial injury (table 1, appendix p 4). Cranial surgery was done in 877 (42%) patients and extracranial surgery was done in 651 (31%). 582 (27%) patients

	Total; n=2125	Fluid balance ≤0·37 L (median); n=1063	Fluid balance >0·37 L (median); n=1062	p value
Median age, years	50 (31–66)	47 (30–64)	52 (31–67)	0·0090
Age ≥65 years	572/2125 (27%)	264/1063 (25%)	308/1062 (29%)	0·0034
Sex				
Female	559/2125 (26%)	258/1063 (24%)	301/1062 (28%)	0·037
Male	1566/2125 (74%)	805/1063 (76%)	761/1062 (72%)	..
Pre-injury ASA-PS classification				
Patient with no previous systemic disease	1167/2035 (57%)	604/1022 (59%)	563/1013 (56%)	0·27
Patient with mild systemic disease	658/2035 (32%)	318/1022 (31%)	340/1013 (34%)	..
Patient with severe systemic disease	210/2035 (10%)	100/1022 (9·8%)	110/1013 (11%)	..
History of cardiovascular disease	596/1995 (30%)	285/1018 (28%)	311/977 (32%)	0·068
Use of anticoagulants	117/1999 (6%)	55/1007 (5%)	62/992 (6%)	0·51
Use of antiplatelets	222/1999 (11%)	102/1007 (10%)	120/992 (12%)	0·18
GCS at baseline	9 (4–14)	9 (4–14)	8 (3–13)	0·086
Severity of traumatic brain injury				
Mild (GCS 13–15)	681/2029 (34%)	359/1024 (35%)	322/1005 (32%)	0·35
Moderate (GCS 9–12)	340/2029 (17%)	169/1024 (17%)	171/1005 (17%)	..
Severe (GCS 3–8)	1008/2029 (50%)	496/1024 (48%)	512/1005 (51%)	..
Pupillary reaction				
Both reactive	1637/2030 (81%)	837/1015 (83%)	800/1015 (79%)	0·092
Both unreactive	250/2030 (12%)	110/1015 (11%)	140/1015 (14%)	..
One reactive	143/2030 (7%)	68/1015 (6·7%)	75/1015 (7·4%)	..
Hypoxia before hospital admission or in emergency department	300/1993 (15%)	137/1012 (14%)	163/981 (17%)	0·063
Hypotension before hospital admission or in emergency department	305/2010 (15%)	132/1014 (13%)	173/996 (17%)	0·0079
Any major extracranial injury (AIS ≥3)	1202/2125 (57%)	584/1063 (55%)	618/1062 (58%)	0·14
Marshall CT classification				
I	183/1879 (10%)	93/951 (10%)	90/928 (10%)	0·48
II	901/1879 (48%)	473/951 (50%)	428/928 (46%)	..
III	153/1879 (8%)	70/951 (7%)	83/928 (9%)	..
IV	28/1879 (2%)	15/951 (2%)	13/928 (1%)	..
V or VI	614/1879 (33%)	300/951 (32%)	314/928 (34%)	..
Epidural haematoma	364/1877 (19%)	206/951 (22%)	158/926 (17%)	0·014
Traumatic subarachnoid haemorrhage	1392/1873 (74%)	702/947 (74%)	690/926 (75%)	0·89
Treatments				
Any use of vasopressors during ICU stay	1145/2002 (57%)	527/1008 (52%)	618/994 (62%)	<0·0001
ICP monitor	993/2125 (47%)	474/1063 (45%)	519/1062 (49%)	0·053
Colloids	338/2107 (16%)	132/1053 (13%)	206/1054 (20%)	<0·0001
Any hypertonic saline or mannitol	582/2125 (27%)	263/1063 (25%)	319/1062 (30%)	0·0072
Hypertonic saline	463/2125 (22%)	211/1063 (20%)	252/1062 (24%)	0·035
Mannitol	276/2125 (13%)	121/1063 (11%)	155/1062 (15%)	0·033
Cranial surgery	877/2111 (42%)	418/1050 (40%)	459/1061 (43%)	0·12
Extracranial surgery	651/2110 (31%)	313/1050 (30%)	338/1060 (32%)	0·32
Central venous pressure monitoring	961/2121 (45%)	485/1060 (46%)	476/1061 (45%)	0·71
Cardiac output monitoring	292/2122 (14%)	136/1060 (13%)	156/1062 (15%)	0·24
Renal replacement therapy	56/2122 (3%)	19/1062 (2%)	37/1060 (4%)	0·021

(Table 1 continues on next page)

	Total; n=2125	Fluid balance ≤0·37 L (median); n=1063	Fluid balance >0·37 L (median); n=1062	p value
(Continued from previous page)				
Clinical parameters during ICU stay				
Median of mean CPP during ICU stay	74 (69–79)	75 (70–80)	73 (68–78)	0·0020
Median of mean sodium during ICU stay	141 (139–144)	141 (139–143)	141 (139–144)	0·22
Complications and outcomes				
Respiratory failure	516/2109 (25%)	224/1056 (21%)	292/1053 (28%)	0·00060
Ventilator associated pneumonia	318/2109 (15%)	145/1056 (14%)	173/1053 (16%)	0·10
Duration of ICU stay, days	6·7 (2·1–15·2)	6·8 (2·2–14·7)	6·6 (2·1–15·4)	0·98
ICU mortality	283/2112 (13%)	97/1057 (9%)	186/1055 (18%)	<0·0001
Mortality at 6 months	407/1844 (22%)	158/928 (17%)	249/916 (27%)	<0·0001
Predicted probability of mortality at 6 months (IMPACT model)	32%	30%	35%	<0·0001
Unfavourable outcome at 6 months (GOSE <5)	853/1844 (46%)	380/928 (41%)	473/916 (52%)	<0·0001
Predicted probability of unfavourable outcome at 6 months (IMPACT model)	51%	48%	54%	<0·0001

Data are n (%) or median (IQR). The IMPACT model was used to calculate the expected mortality and expected proportion of patients with an unfavourable outcome (GOSE <5) at 6 months. ASA-PS=American Society of Anesthesiologists physical status. GCS=Glasgow Coma Scale. AIS=Abbreviated Injury Scale. ICU=intensive care unit. ICP=intracranial pressure. CPP=cerebral perfusion pressure. IMPACT=International Mission for Prognosis and Analysis of Clinical Trials in TBI. GOSE=Glasgow Outcome Scale Extended.

Table 1: **Baseline characteristics, management in the ICU, and outcomes of included patients**

received mannitol, hypertonic saline, or both; 338 (16%) patients received colloids, and 1145 (57%) received vasopressors during ICU stay. 56 (3%) patients received renal replacement therapy. 238 (13%) patients died in the ICU. Considering the whole duration of ICU stay, the median of the mean daily fluid balance was 0·37 L (IQR –0·08 to 0·79), and the median of the mean daily fluid input was 2·91 L (2·15 to 3·60; appendix p 19). Cerebral perfusion pressure was lower in patients with a median fluid balance higher than 0·37 L, although the absolute difference was small (73 mm Hg *vs* 75 mm Hg; p=0·0015). After 6 months, 853 (46%) patients had an unfavourable outcome (table 1; appendix pp 4–5). The median of the mean daily fluid balance ranged from –0·85 L (IQR –1·51 to –0·49) to 1·13 L (0·99 to 1·37) across centres. The median of the mean daily fluid input ranged from 1·48 L (IQR 1·12 to 2·09) to 4·23 L (3·78 to 4·94) across centres. After adjustment for case mix, substantial differences remained in fluid management between centres (figure 2). The 27 (50%) centres with a daily fluid balance higher than the median did cardiac output monitoring less often than the 28 (50%) centres with a daily fluid balance lower than the median (14% [range 0 to 70] *vs* 21% [0 to 100]). The same was true for fluid input: 13% (range 0 to 100) in the 27 (50%) centres with higher than median fluid input versus 22% (0 to 100) in the 28 (50%) centres with lower than median fluid input underwent cardiac output monitoring (appendix p 5).

In our adjusted analysis, a mean daily positive fluid balance was associated with higher ICU mortality (OR 1·10 [95% CI 1·07–1·12] per 0·1 L increase) and worse functional outcome (1·04 [1·02–1·05]; table 2; figure 3). A negative mean daily fluid balance was not associated with ICU mortality (OR 0·96 [95% CI 0·90–1·01] per 0·1 L increase) or worse functional outcome (0·99 [0·97–1·02]).

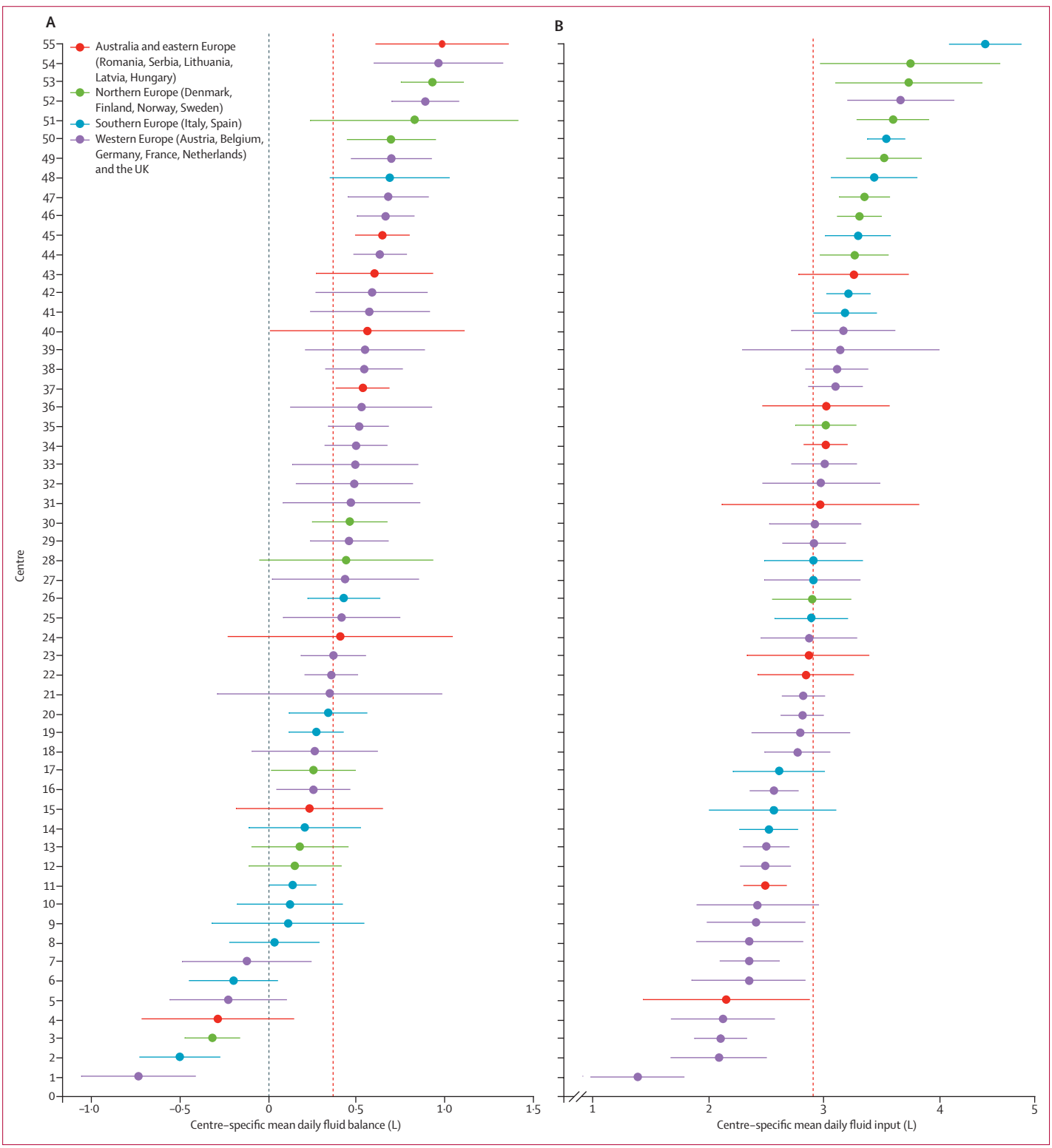
We observed a linear association between higher mean daily fluid input and higher ICU mortality (OR 1·05 [95% CI 1·03–1·06] per 0·1 L increase) and between a higher mean daily fluid input and worse functional outcome (OR 1·04 [95% CI 1·03–1·04] for a 1-point decrease of the GOSE per 0·1 L increase; table 2, figure 3, appendix p 21).

In all sensitivity analyses, similar effect estimates were observed (appendix pp 6–16), although with less statistical certainty. Higher cerebral perfusion pressure was independently associated with better outcome, whereas higher serum sodium was independently

Figure 2: **Between-centre differences in (A) mean daily fluid balance and (B) mean daily fluid input**

(A) The x-axis indicates the mean fluid balance and 95% CI posterior means per centre compared to the average mean balance for all centres. A random-effect regression model was used to correct for random variation and adjusted for case-mix severity with the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) variables (age, Glasgow Coma Scale [GCS] motor score, pupillary reaction, hypoxia, hypotension, Marshall CT classification, traumatic subarachnoid haemorrhage, epidural haematoma, first glucose, first haemoglobin) and the presence of any major extracranial injury (Abbreviated Injury Scale [AIS] ≥3). The dashed red line represents the overall mean (0·38 L; SD 0·45). (B) The x-axis indicates the mean fluid input and 95% CI posterior means per centre compared to the average input for all centres. A random-effect regression model was used to correct for random variation and adjusted for case-mix severity with the same variables as used for the analysis of fluid balance. The dashed red line represents the overall mean (2·91 L; SD 0·63). In both panels, the centres are shown in order of the means. The colour of the dot indicates the region in which the centre was located according to the UN geoscheme.

associated with worse outcome. However, these confounders did not explain the association of higher fluid balance and higher fluid input with worse outcome. In a propensity matched analysis (appendix p 17), associations were similar, although with less statistical certainty.



	ICU mortality: worse short-term outcome		Ordinal GOSE score: worse outcome at 6 months	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Unadjusted, per 0·1 L increase				
Mean daily positive fluid balance	1·10 (1·08–1·12)	<0·0001	1·06 (1·04–1·07)	<0·0001
Mean daily negative fluid balance	0·98 (0·94–1·02)	0·32	1·00 (0·98–1·03)	0·71
Mean daily fluid input	1·05 (1·04–1·06)	<0·0001	1·05 (1·04–1·05)	<0·0001
Adjusted,* per 0·1 L increase				
Mean daily positive fluid balance	1·10 (1·07–1·12)	<0·00001	1·04 (1·02–1·05)	<0·0001
Mean negative fluid balance	0·96 (0·90–1·01)	0·11	0·99 (0·97–1·02)	0·68
Mean daily fluid input	1·05 (1·03–1·06)	<0·00001	1·04 (1·03–1·04)	<0·0001

ICU=intensive care unit. GOSE=Glasgow Outcome Scale Extended. *Adjusted for age, Glasgow Coma Scale (GCS) motor score at baseline, pupillary reactivity, hypoxia, hypotension, Marshall CT classification, epidural haematoma, traumatic subarachnoid haemorrhage, first haemoglobin, first glucose, any major extracranial injury (Abbreviated Injury Scale ≥3), and a random intercept for centre.

Table 2: **Associations of mean daily fluid balance and mean daily fluid input with ICU mortality and 6-month GOSE score**

The instrumental variable analyses confirmed the association of higher fluid balance with ICU mortality (OR 1·17 [95% CI 1·05–1·29] per 0·1 L higher centre mean balance than overall mean balance) and worse functional outcome (1·07 [1·02–1·13] per 0·1 L higher centre mean balance than overall mean balance) but not the association of higher fluid input with ICU mortality (0·95 [0·90–1·00] per 0·1 L higher mean input than the overall mean) or functional outcome (1·01 [0·98–1·03] per 0·1 L higher mean input than the overall mean; figure 4).

In 993 patients with intracranial pressure monitoring, daily higher positive fluid balance was not associated with higher maximum intracranial pressure (beta –0·24 [95% CI –0·53 to 0·05] for every 1 mm Hg increase of intracranial pressure per L extra fluid balance), but it was associated with increased use of noradrenaline (beta 0·52 [95% CI 0·10 to 0·94] for every 1 mg increased use of noradrenaline), and with lower mean cerebral perfusion pressure (beta 0·70 [95% CI 0·43 to 0·97] for every 1 mm Hg decrease of cerebral perfusion pressure per L extra fluid balance; appendix p 21). Daily fluid input higher than 3 L was associated with higher maximum intracranial pressure (beta 0·49 [95% CI 0·21 to 0·78] for every 1 mm Hg increase of intracranial pressure per L extra fluid input), lower mean cerebral perfusion pressure (beta 0·75 [0·49–1·02] for every 1 mm Hg decrease of cerebral perfusion pressure per L extra fluid input), and increased use of noradrenaline (beta 0·97 [0·56–1·39] for every 1 mg increased use of noradrenaline).

Discussion

In this large, prospective, multicentre study of critically ill patients with traumatic brain injury, we found substantial differences in fluid management policies between centres across Europe and Australia. Furthermore, we found that incrementally positive daily fluid balances were associated with worse clinical outcomes. These findings suggest that positive fluid balance might be an underappreciated factor contributing to adverse outcomes. This finding is clinically relevant since a positive fluid balance could be readily modifiable by less liberal fluid administration. Taken together with the previously published evidence, these results suggest that a policy aimed at stricter avoidance of both hypervolaemia and hypovolaemia during the whole ICU stay, as indicated by a mean overall neutral fluid balance, might improve clinical outcomes in critically ill patients with traumatic brain injury.

The substantial variation observed in our study is in line with earlier studies showing between-centre differences in intensive care management of patients with traumatic brain injury.[3,12] Guidelines could help reduce treatment variation in clinical practice, and awareness of guidelines has increased.[16] The variation that we observed might be due to the fact that the Brain Trauma Foundation's guidelines do not include recommendations about fluid management.[9] More recently, a consensus statement on fluid therapy in patients in neurocritical care recommended aiming for normovolaemia, integrating more than one circulatory variable to estimate volume status.[17] However, the consensus statement also recommended avoiding restrictive fluid policies (negative fluid balances) and using fluid balances as a safety endpoint for fluid therapy. The recommendations did not include a specific statement on potential risks of positive fluid balances. In line with the study by Clifton and colleagues,[3] in a subgroup analysis in patients with an ICP monitor we found that more negative fluid balances were associated with worse outcome (appendix p 12), although in the study by Clifton and colleagues[3] positive fluid balances were not associated with worse outcome. However, in a more recent trial by Clifton and colleagues[4] of therapeutic hypothermia in patients with severe traumatic brain injury, higher daily fluid balances with hypothermia were associated with increased intracranial hypertension.

In our patient-level analyses, we controlled for measured confounders that are known to be independent predictors of outcome after traumatic brain injury. However, the possibility of residual confounding by indication always remains in observational studies analysed at a patient level. We therefore also did an instrumental variable analysis.[18,19] Although this analysis is less sensitive to confounding by indication, it is limited by a decrease in statistical power. This might explain why the association between fluid input and functional outcome was not statistically significant, as opposed to the association with fluid balance. The concordance between both analyses allows for a less cautious interpretation of the association between positive fluid balance and worse functional outcome.[13] Moreover, the associations were largely similar in subgroup analyses. However, some subgroups were based on factors observed after fluid administration and should be interpreted with caution, and some associations in subgroup analyses had less statistical certainty, which might be explained by the fact

that power to detect statistically significant effects within subgroups is by definition low. Additional adjustment for cerebral perfusion pressure and sodium, which were both perceived as strong potential confounders from a clinical perspective (eg, given that especially low cerebral perfusion pressure could trigger fluid administration), did not have any effect on the associations observed. The associations between increased fluid loading, lower cerebral perfusion pressure, and higher noradrenaline usage as a vasopressor are intriguing. However, the fact that lower cerebral perfusion pressure was independently associated with worse outcome when added as a covariable, but did not affect the association of fluid balance and outcome, argues against cerebral perfusion pressure being a strong confounder. Nonetheless, this analysis does not imply that adverse effects of fluids are entirely independent from cerebral perfusion pressure.[7,11] An additional complication in estimating the effects of time-varying treatments is the potential of time-varying confounding: low cerebral perfusion pressure triggers fluid administration, which in turn might affect cerebral perfusion pressure. Adjustment for mean cerebral perfusion pressure over ICU stay fails to address this issue and might lead to biased estimates. However, the potential for bias becomes smaller with a longer time period between treatment (and confounders) and outcome. The consistency of the effects on ICU mortality and GOSE at 6 months in the analysis, with adjustment for (potentially time-varying) confounders such as cerebral perfusion pressure and mean arterial pressure, therefore indicates that the problem of time-varying confounding was unlikely to have had any effect in our study.

Several randomised controlled trials in neurocritical care support the notion that a less liberal fluid policy can be accomplished with advanced haemodynamic monitoring and that such a policy might contribute to improved outcomes in patients with traumatic brain injury.[20,21] This theory might be congruent with the fact that study centres with lower than median fluid balances did cardiac output monitoring more often than centres with higher than median fluid balances. Moreover, our findings build on a growing evidence base indicating that positive fluid balances might be detrimental in critical care (eg, in acute respiratory distress syndrome or in septic shock after the resuscitation phase).[11,17,22,23] Furthermore, a vast body of evidence in the critical care literature indicates that large volumes of fluids are often administered unintentionally in intensive care (so-called

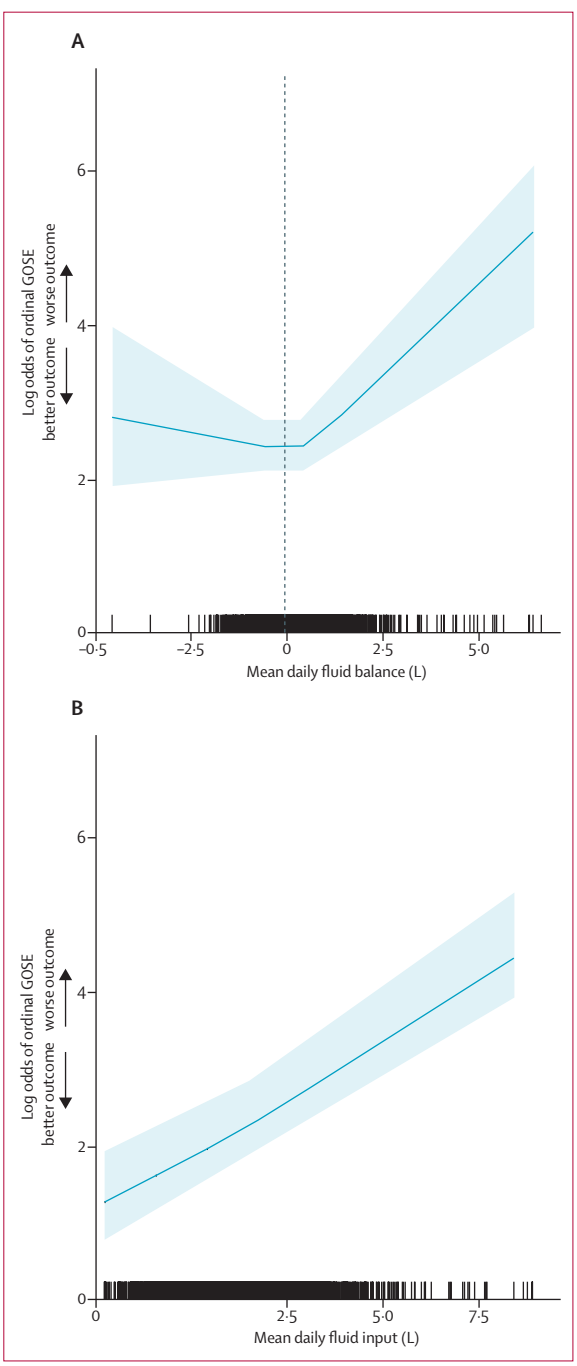
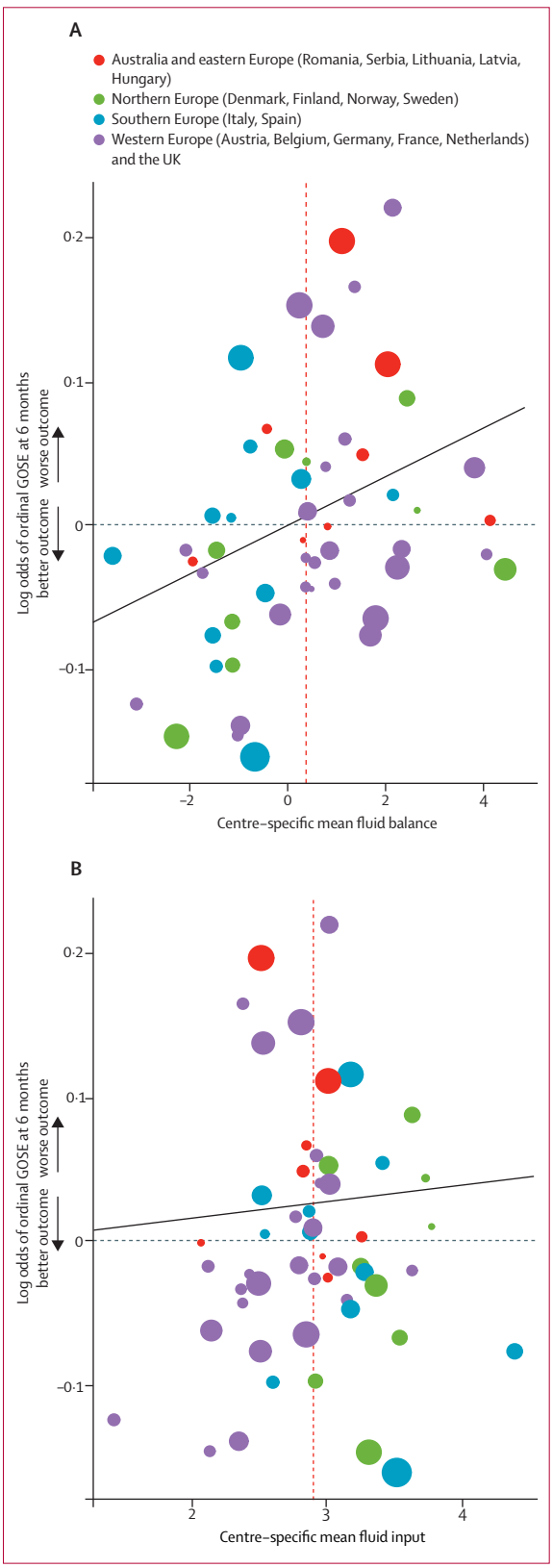


Figure 3: **Effect of mean daily fluid balance (A) and mean daily fluid input (B) on GOSE at 6 months**

(A) Effect plot for the log odds of ordinal Glasgow Outcome Scale Extended (GOSE; y-axis) for mean daily fluid balance (x-axis, per L). (B) Effect plot for the log odds of ordinal GOSE (y-axis) for mean daily fluid input (x-axis, per L). In both analyses, increasing log odds indicate worse outcomes, and decreasing log odds indicate better outcomes. This analysis was adjusted for the average patient: age 49 years, Glasgow Coma Scale (GCS) motor score at baseline of 1, both pupils reactive, no hypoxia before hospital admission or in the emergency department, no hypotension before hospital admission or in the emergency department, no epidural haematoma, Marshall CT classification of II, haemoglobin 13 g/dL, glucose 8·4 mmol/L, major extracranial injury (Abbreviated Injury Scale ≥3), and the centre that included the most patients. The average patient was defined according to the mean values for continuous variables and the most frequently occurring category for categorical variables. The shaded area represents 95% CIs. The black lines at the bottom of the x-axis correspond to individual patients' mean daily fluid balance or input during ICU stay.



fluid creep), and since we have no reason to believe that patients with traumatic brain injury are exempt from such incidents, this practice might constitute an important target for improved management of these patients.[24] The SAFE-TBI study showed that fluid resuscitation with albumin 4% (being hypotonic to serum) as opposed to saline in patients with traumatic brain injury resulted in worse outcomes, suggesting that tonicity rather than amounts of fluids alone might have a substantial effect.[25] However, adding serum sodium to our analyses, as an indicator of the net impact of hypertonic or hypotonic fluids being administered, did not change our results, while higher serum sodium was independently associated with worse outcome.

What might be the pathophysiological rationale for the association between positive fluid balance and harm in traumatic brain injury? Capillary hydrostatic back-pressure to the brain might occur due to fluid overload and raised central venous pressure, resulting in fluid accumulation into the brain interstitium. This situation might occur especially in the face of central venous pressure being close to intracranial pressure and when positive end-expiratory pressure is being applied in patients on mechanical ventilation.[26] In the injured brain, this situation will increase traumatic cerebral oedema, further facilitated by blood–brain barrier disruption.[27] Furthermore, experimental studies in rodents and clinical work have indicated that isotonic fluids per se, and especially when given in excess, could increase cerebral or systemic complications.[4,11,28] In our analysis, the finding that fluid balance and fluid intake were not strongly related to intracranial pressure might be explained by the fact that raised intracranial pressure is immediately acted upon with various medical therapies to decrease it and that the temporal resolution (up to hourly sampling) of our database might not have been sensitive enough to account for short intermittent

Figure 4: **Scatterplot for the association of (A) centre-specific mean fluid balance and (B) centre-specific mean fluid input, with log odds for ordinal GOSE at 6 months**

(A) Scatterplot for the association between the centre-specific mean fluid balance for all centres and the log odds for ordinal Glasgow Outcome Scale Extended (GOSE) at 6 months. To account for the non-linearity of fluid balance, all centres that had an average negative mean balance were assigned a mean balance of 0. The dashed red line represents the overall mean (0·38 L). (B) Scatterplot for the association between the centre-specific mean fluid input per centre for all centres and the log odds for ordinal GOSE at 6 months. The dashed red line represents the overall mean (2·9 L). In both panels, increasing log odds indicate worse outcomes, and decreasing log odds indicate better outcomes. Both analyses were adjusted for the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT)-extended model (age, Glasgow Coma Scale [GCS] motor score, pupillary reaction, hypoxia, hypotension, Marshall CT classification, traumatic subarachnoid haemorrhage, epidural haematoma, first glucose, first haemoglobin), any major extracranial injury (Abbreviated Injury Scale [AIS] ≥3), and a random intercept for centre. The size of the dot indicates the number of patients per centre. The solid line represents the regression line. The colour of the dot indicates the region in which the centre was located according to the UN geoscheme.

intracranial pressure peaks.

Our study had several limitations. First, the case record form of the CENTER-TBI and OzENTER-TBI studies did not capture important physiological variables in detail, including central venous pressure, positive end-expiratory pressure, fluid intake normalised to bodyweight, exact reasons for fluid bolus, cardiac output data when monitored, differentiation between hyperosmolar fluids and maintenance fluids (including gastric feeds, volume administered as vehicle for medication), and the tonicity and amounts of different fluid types. Documentation of these variables over time could have contributed to a mechanistic understanding of the associations observed. Second, we did not account for insensible fluid losses, resulting in possible over-estimation of fluid balances. However, adding mean temperature to the multivariable analyses did not change our results (data not shown). Third, we recognise that traumatic brain injury is a complex and heterogeneous condition in which multiple treatments are used during both the acute and post-acute phase, and that it remains challenging to determine any effect of a single treatment or policy on outcome assessed at 6 months. Fourth, the observational data in principle preclude causal inference. However, we applied advanced analytical approaches to deal with confounding by indication, yielding consistent results. The combination of the patient-level and instrumental variable approach, with similar results, supports the validity of the main findings. Furthermore, fluid balance and fluid input were captured as continuous variables. This approach results in a gain of statistical power compared with earlier studies, which categorised fluid balance and fluid input. Nevertheless, randomised controlled trials are essential to definitively assign causality to the relationships shown in this study. However, given the need to maintain a target cerebral perfusion pressure, such a trial would not simply address different strategies for fluid therapy; rather, it might need to compare vasopressor-dominant versus fluid-dominant strategies to maintain cerebral perfusion pressure. A controlled before-and-after study aiming to implement a mean neutral fluid balance (eg, with a stepped wedge design), might be another option. Additionally, such studies might be facilitated by a management protocol based on bedside haemodynamic monitors, such as ultrasound or cardiac output monitoring, to assess volume status,[29] to align a general policy of avoiding both hypervolaemia and hypovolaemia with more personalised fluid management where appropriate. Finally, as part of any intervention to improve fluid management, the administration of fluids without a clear physiological rationale should be minimised.

In summary, fluid management of patients with traumatic brain injury in the ICU varies substantially between centres, with positive fluid balances associated with worse outcomes. Together with the existing evidence, these results suggest that aiming for mean neutral fluid balances more rigorously, thereby avoiding both hypervolaemia and hypovolaemia, could improve clinical outcomes. However, further research is needed to investigate the implementation of these findings in clinical practice, taking into account cerebral perfusion pressure and adhering to personalised approaches when appropriate, such as those guided by routinely used haemodynamic monitors.

Contributors

EJAW analysed the data and drafted the tables and figures. EJAW, HFL, and MvdJ interpreted the data and drafted the manuscript. MvdJ (the clinical supervisor) and HFL (the statistical supervisor) designed the study protocol and supervised the study. EJAW, JAH, HFL, EWS, and MvdJ 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 studies and reviewed and approved the final version of the manuscript. EJAW and HFL accessed and verified the analyses. All authors guarantee that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. All authors had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Declaration of interests

DJC is an Australian NHMRC Practitioner Fellow and reports grants from the National Health and Medical Research Council of Australia and consulting fees to Monash University from PresSura Neuro. AIRM declares consulting fees from PresSura Neuro, Integra Life Sciences, and NeuroTrauma Sciences. DKM reports grants from the UK National Institute for Health Research, during the conduct of the study; grants, personal fees, and non-financial support from GlaxoSmithKline; and personal fees from Neurotrauma Sciences, Lantmaanen AB, Pressura, and Pfizer, outside of the submitted work. EWS reports personal fees from Springer, during the conduct of the study. All other authors declare no competing interests.

Data sharing

The datasets, which include individual participant data and a data dictionary defining each field in the set used or analysed during the current study, will be available upon reasonable request to the management committees of the CENTER-TBI and OzENTER-TBI study. Requests for data should be submitted online at https://www.center-tbi.eu/data or via email to center-tbi@uza.be. The data that will be made available comprise de-identified participant data. The study protocol, statistical analysis plan, R-code, and informed consent forms will be made available upon request. To access any other data from CENTER-TBI and OzENTER-TBI, a proposal should be submitted and approved by the management committees of both the CENTER-TBI and OzENTER-TBI studies. A data access agreement with the management teams of CENTER-TBI and OzENTER-TBI should be signed before access to the data will be granted.

For **CENTER-TBI data access requests** see https://www.center-tbi.eu/data

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References

1 Majdan M, Plancikova D, Brazinova A, et al. Epidemiology of traumatic brain injuries in Europe: a cross-sectional analysis. *Lancet Public Health* 2016; **1:** e76–83.

2 Cnossen MC, Huijben JA, van der Jagt M, et al. Variation in monitoring and treatment policies for intracranial hypertension in traumatic brain injury: a survey in 66 neurotrauma centers participating in the CENTER-TBI study. *Crit Care* 2017; **21:** 233.

3 Clifton GL, Miller ER, Choi SC, Levin HS. Fluid thresholds and outcome from severe brain injury. *Crit Care Med* 2002; **30:** 739–45.

4 Clifton GL, Valadka A, Zygun D, et al. Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol* 2011; **10:** 131–39.

5 Shenkin HA, Bezier HS, Bouzarth WF. Restricted fluid intake. Rational management of the neurosurgical patient. *J Neurosurg* 1976; **45:** 432–36.

6 Schmoker JD, Shackford SR, Wald SL, Pietropaoli JA. An analysis of the relationship between fluid and sodium administration and intracranial pressure after head injury. *J Trauma* 1992; **33:** 476–81.

7 Rosner MJ, Rosner SD, Johnson AH. Cerebral perfusion pressure: management protocol and clinical results. *J Neurosurg* 1995; **83:** 949–62.

8 Bullock R, Chesnut RM, Clifton G, et al. Guidelines for the management of severe head injury. Brain Trauma Foundation. *Eur J Emerg Med* 1996; **3:** 109–27.

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

10 Guidelines for the management of severe traumatic brain injury. *J Neurotrauma* 2007; **24** (suppl 1)**:** 1–106.

11 Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med* 1999; **27:** 2086–95.

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

13 Cnossen MC, van Essen TA, Ceyisakar IE, et al. Adjusting for confounding by indication in observational studies: a case study in traumatic brain injury. *Clin Epidemiol* 2018; **10:** 841–52.

14 Volovici V, Ercole A, Citerio G, et al. Variation in guideline implementation and adherence regarding severe traumatic brain injury treatment: a CENTER-TBI Survey Study in Europe. *World Neurosurg* 2019; **125:** e515–20.

15 Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLoS Med* 2008; **5:** e165.

16 Kuehn BM. IOM sets out "gold standard" practices for creating guidelines, systematic reviews. *JAMA* 2011; **305:** 1846–48.

17 Oddo M, Poole D, Helbok R, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. *Intensive Care Med* 2018; **44:** 449–63.

18 Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA* 2007; **297:** 278–85.

19 Brookhart MA, Schneeweiss S. Preference-based instrumental variable methods for the estimation of treatment effects: assessing validity and interpreting results. *Int J Biostat* 2007; **3:** 14.

20 Mutoh T, Kazumata K, Ishikawa T, Terasaka S. Performance of bedside transpulmonary thermodilution monitoring for goal-directed hemodynamic management after subarachnoid hemorrhage. *Stroke* 2009; **40:** 2368–74.

21 Luo J, Xue J, Liu J, Liu B, Liu L, Chen G. Goal-directed fluid restriction during brain surgery: a prospective randomized controlled trial. *Ann Intensive Care* 2017; **7:** 16.

22 Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; **354:** 2564–75.

23 Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; **39:** 259–65.

24 Van Regenmortel N, Verbrugghe W, Roelant E, Van den Wyngaert T, Jorens PG. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. *Intensive Care Med* 2018; **44:** 409–17.

25 Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007; **357:** 874–84.

26 Li HP, Lin YN, Cheng ZH, Qu W, Zhang L, Li QY. Intracranial-to-central venous pressure gap predicts the responsiveness of intracranial pressure to PEEP in patients with traumatic brain injury: a prospective cohort study. *BMC Neurol* 2020; **20:** 234.

27 McManus ML, Strange K. Acute volume regulation of brain cells in response to hypertonic challenge. *Anesthesiology* 1993; **78:** 1132–37.

28 Ramming S, Shackford SR, Zhuang J, Schmoker JD. The relationship of fluid balance and sodium administration to cerebral edema formation and intracranial pressure in a porcine model of brain injury. *J Trauma* 1994; **37:** 705–13.

29 Beaubien-Souligny W, Rola P, Haycock K, et al. Quantifying systemic congestion with point-of-care ultrasound: development of the venous excess ultrasound grading system. *Ultrasound J* 2020; **12:** 16.