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ORIGINAL

Early systemic insults following traumatic brain injury: association with biomarker profiles, therapy for intracranial hypertension, and neurological outcomes—an analysis of CENTER-TBI data

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Abstract

Purpose: We analysed the impact of early systemic insults (hypoxemia and hypotension, SIs) on brain injury biomarker profiles, acute care requirements during intensive care unit (ICU) stay, and 6-month outcomes in patients with traumatic brain injury (TBI).

Methods: From patients recruited to the Collaborative European neurotrauma effectiveness research in TBI (CENTER-TBI) study, we documented the prevalence and risk factors for SIs and analysed their effect on the levels of brain injury biomarkers [S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE), neurofilament light (NfL), glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), and protein Tau], critical care needs, and 6-month outcomes [Glasgow Outcome Scale Extended (GOSE)].

Results: Among 1695 TBI patients, 24.5% had SIs: 16.1% had hypoxemia, 15.2% had hypotension, and 6.8% had both. Biomarkers differed by SI category, with higher S100B, Tau, UCH-L1, NSE and NfL values in patients with hypotension or both SIs. The ratio of neural to glial injury (quantified as UCH-L1/GFAP and Tau/GFAP ratios) was higher in patients with hypotension than in those with no SIs or hypoxia alone. At 6 months, 380 patients died (22%), and 759 (45%) had GOSE ≤ 4. Patients who experienced at least one SI had higher mortality than those who did not (31.8% vs. 19%, $p < 0.001$).

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Conclusion: Though less frequent than previously described, SIs in TBI patients are associated with higher release of neuronal than glial injury biomarkers and with increased requirements for ICU therapies aimed at reducing intracranial hypertension. Hypotension or combined SIs are significantly associated with adverse 6-month outcomes. Current criteria for hypotension may lead to higher biomarker levels and more negative outcomes than those for hypoxemia suggesting a need to revisit pressure targets in the prehospital settings.

Keywords: Traumatic brain injury, Serum biomarkers, Outcome, Hypoxemia, Hypotension, Systemic insults

Introduction

Traumatic brain injury (TBI) is among the leading causes of mortality and long-term disability worldwide [1, 2]. Clinical outcome is substantially related to the severity of primary injury and its impact on driving secondary injury mechanisms [3–5]. However, the outcome can be considerably worsened by systemic insults (SIs), such as hypoxemia and hypotension, which can amplify the cascade of events after the initial damage and negatively impact mortality and long-term disability.

The incidence and detrimental effects of SIs on outcome after TBI were seminally documented over 45 years ago by Miller [6] and confirmed by Chesnut et al. in 1993 [7]. In 2007, the IMPACT-TBI study [8] corroborated the association between SIs and unfavourable 6 months outcomes [3]. SIs may enhance cellular, biochemical, and molecular events occurring after TBI, including local and systemic inflammation [9, 10], activate microglia [9] and coagulative cascades [11, 12] and alter blood–brain barrier (BBB) function [13].

However, while these associations are established, it remains unclear whether the worse outcomes are directly related to increased neurological injury caused by SIs in the acute phase or simply represent an association with worse intra- and extracranial injury. Indeed, we have little objective quantification of the impact of SIs on acute neurological injury or acute therapy needs—both of which are critical issues in determining the mechanisms by which SIs drive worse outcomes and how their impact might be mitigated. Little data on the impact of SIs on protein biomarker levels are available [13], a limitation of fundamental importance, as biomarkers are now known to reflect injury severity and brain computed tomography (CT) abnormalities [14–16] and contribute to prognostication [17].

To address this issue, we undertook an analysis of data from intensive care unit (ICU) patients enrolled in the Collaborative European neurotrauma effectiveness research in TBI (CENTER-TBI) study, aiming to investigate the occurrence of initial SIs, assess the factors associated with SIs occurrence, analyse the biomarker profiles related to these insults, and evaluate the correlation between early SIs, biomarkers, and 6-month outcomes.

Take-home message

Early systemic insults after traumatic brain injury have become less common compared to the past. Their occurrence is closely tied to the severity of trauma and extracranial injuries

Systemic insults are associated with brain biomarker release, characterised by distinct profiles. Given current thresholds, low blood pressure, rather than oxygen deficiency, exerts a more pronounced impact on neurons than glial cells, as suggested by different biomarker profiles, and on unfavourable neurological outcomes. When both systemic insults occur concurrently, this produces higher biomarkers release and is associated with a worse clinical outcome and mortality

Finally, we explored the difference in the need for acute care and interventions during the ICU stay between patients with or without SIs, mainly focusing on therapies to reduce intracranial pressure (ICP).

Methods

Design and inclusion criteria

The CENTER-TBI study (clinicaltrials.gov NCT02210221) is a longitudinal, prospective observational study including TBI patients across 65 centres in Europe and Israel. Details regarding the study design, methodology, screening, and enrolment process have been previously described [18, 19]. The study was approved by the Medical Ethics Committees of each participating centre, and informed consent was obtained according to local regulations (https://www.center-tbi.eu/project/ethical-approval). This study, which was pre-registered on the CENTER-TBI proposal platform, was approved by the CENTER-TBI proposal review committee.

The inclusion criteria in this study were patients:

- Who experienced TBI and who were included in the CENTER-TBI study,
- Aged ≥ 18 years old,
- Admitted to ICU,
- With available data on arterial blood pressure and oxygenation in the prehospital settings and/or at hospital arrival,

- With a 6-month neurological outcome (Glasgow Outcome Score—Extended, GOSE) evaluated.

The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (electronic supplementary material, ESM).

Data collection

Details on data collection and management of the CENTER-TBI study have been previously published [18, 19]. The CENTER-TBI core database v3.0 data was used and downloaded via Opal data warehouse [20].

Data collected included patients' demographic characteristics, pre-injury comorbidities, TBI mechanism, and a series of parameters at admission, such as neuroradiological features (as for Marshall CT score [21]), neurological status [as for Glasgow Coma Scale (GCS), pupil's reactivity], presence of extracranial injury [quantified using the total Injury Severity Score (ISS), and with major extracranial injury defined as an Abbreviated Injury Scale [22] (AIS) score ≥ 3], arterial blood gas (ABG) values [i.e., pH, arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), base excess], and laboratory data (e.g., creatinine, glucose).

We also collected variables regarding the need for neurosurgical treatment and ICP monitoring, the treatments used for ICP management [i.e., therapy intensity level (TIL) [23], etc.], the need for extracranial and intracranial surgeries (e.g., damage control procedures), need for blood transfusion, need for intubation and mechanical ventilation, need for tracheostomy.

Early serum biomarkers

We extracted the results of biomarker measurements in samples obtained within 48 h from hospital admission for six specific serum biomarkers associated with TBI [24]: S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE), neurofilament light (NfL), glial fibrillary acidic protein (GFAP), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), and protein Tau. Notably, GFAP and S100B are recognised as biomarkers of glial injury, UCH-L1 and NSE indicate neuronal cell body injury, and Tau and NfL are markers for dendritic and axonal damage. We then calculated the ratios between neuronal or dendritic and glial markers. Specifically, UCH-L1/GFAP was used to gauge the relative extent of neuronal body versus glial injury. Tau/GFAP was used to assess the degree of dendritic and axonal injury versus glial injury. The selection of these three biomarkers for the two ratios (GFAP, UCH-L1, and Tau) was based on their high specificity to the central nervous system, as well as their reasonably similar kinetics, with time-to-peak values of 8 h for GFAP and UCH-L1, and 24 h for Tau [25]. This choice allowed for a meaningful comparison of the impact of these serum indicators on different cellular components in the aftermath of TBI. It is important to note that, despite its short half-life, we opted not to include S100B in this analysis due to potential release from extracranial lesions. Furthermore, we excluded NSE and NfL from the analysis because of their significantly divergent kinetics, with time-to-peak values of 72 h and 1–2 weeks, respectively [25, 26].

Definition of early SIs

Data on hypotension and hypoxemia were collected in the prehospital settings and/or at hospital arrival. A hypotensive episode was defined, as per the Traumatic Coma Data Bank (TCDB [7]), as a systolic blood pressure (SBP) < 90 mmHg or a clinical definition of shock. A hypoxemic episode was described as a $PaO_2 < 60$ mmHg and/or peripheral oxygen saturation (SpO_2) $< 90\%$ or as evidenced by cyanosis, apnoea, or respiratory distress.

According to the occurrence of SIs in the prehospital setting or/and at arrival, patients were allocated into four different groups: "Hypoxemia" if they had a hypoxemic event, "Hypotension" if they had a hypotensive event, "Both" if both events were recorded, and "No" if no SI was observed.

Clinical outcomes

Mortality and functional outcome, defined by the GOSE [27], were assessed at 6 months. GOSE scores range from 1 (dead) to 8 (good recovery), and an unfavourable functional outcome was defined as GOSE ≤ 4. All responses were obtained by trained study personnel during a face-to-face visit, telephone interview, or postal questionnaire [28].

Statistical analysis

Data were expressed as median (interquartile ranges, IQR) or frequency (%) where appropriate. Comparisons between the four SIs groups were performed by the Chi-squared or Kruskal–Wallis test, according to the nature of the variables. Description of metabolic and biomarker profiles for each group were visualised using radar plots in which the median of each variable (metabolic or biomarkers) was mapped. The axes of each radar ranged from the minimum to the maximum value of the median calculated for each group. To identify factors associated with the occurrence of SIs, multivariable logistic regression was applied, including sex, age, cause of injury, and presence of extracranial injury (defined as AIS ≥ 3 for any of abdomen–pelvis, face–head–neck, thorax–chest, extremities, external, and spine region) as regressors. The differences in biomarker values and the two ratios

(UCH-L1/GFAP and Tau/GFAP) among SIs were also evaluated and correlations quantified by the Pearson index. The Wilcoxon's test was used to perform pairwise comparisons between SIs groups on the two ratios with corrections for multiple testing using the Benjamini–Hochberg approach.

A logistic regression model for unfavourable outcomes and a Cox regression model for mortality were fitted to estimate the impact of SIs on outcomes, by considering each biomarker and their potential interactions. In both cases, the models were also adjusted for the variables in the core IMPACT scheme (i.e., age, pupillary reactivity, and GCS motor at baseline). Finally, we described the need for acute care and interventions during the ICU stay among SIs in the first 48 h and during the hospital stay. Results are shown as the odds ratio (OR) or hazard ratio (HR) with the corresponding 95% confidence interval (CI). All analyses were performed using R software (version 4.3.1, "Beagle Scouts").

Results

Patient characteristics, systemic insults occurrence

From 4509 patients in the CENTER-TBI study, 1695 patients fulfilled the inclusion criteria and were included in the analysis (ESM, Figure S1). They were mostly men ($n=1243$, 73.3%) and the median age was 52 years (IQR = 33–67).

The most common causes of TBI were road traffic collisions ($n=741$, 45.2%) or incidental falls ($n=689$, 42%). Median GCS at arrival was 9 (IQR = 4–14), and 792 patients (49%) presented with GCS ≤ 8. On the first CT, 642 patients (43%) had a Marshall CT score of 3–6, indicating significant injury.

Among the study population, 1280 (75.5%) patients had no SIs in the prehospital setting and/or at arrival. Hypoxemic insults were documented in 158 (9.3%) and hypotension in 142 (8.4%), while 115 (6.8%) patients had documented both hypoxemic and hypotensive insults. In total, 273 (16.1%) patients had hypoxemia and 257 (15.2%) hypotension. When further splitting patients into different categories of GCS (Table 1), patients with GCS 3–5 had the highest incidence of SIs (48% hypoxemia, 44.4% hypotension, 66.7% both SIs, $p<0.001$).

The four groups were similar in age and sex but had distinct clinical profiles (Table 1 and ESM, Table S1). The group with both SIs was characterised by significantly worse neurological status (defined using the GCS), lower pH, a higher incidence of major extracranial injury and extracranial injury severity, lower base excess, and higher lactate, glucose, and creatinine levels ($p<0.001$, Table 1 and ESM, Table S1 and Figure S2). At multivariable analysis (ESM, Figure S3), the involvement in a road traffic collision or a suicide attempt increases the risk of occurrence of early SIs compared to incidental fall (OR = 1.52, 95% CI 1.16–2.01 and OR = 3.89, 95% CI 1.82–8.52, respectively). Moreover, the presence of abdominal/pelvic (OR = 2.35, 95% CI 1.73–3.2) and chest trauma (OR = 1.9, 95% CI 1.45–2.5) were independently associated with the occurrence of early SIs when compared to patients without extracranial injury.

Biomarker profiles and systemic insults

The values of the biomarkers and the ratios in the whole population and in the four SIs groups are presented in ESM, Table S2.

Figure 1 shows the biomarkers values according to the presence of SIs. Patients with hypotension and both SIs had higher biomarker values compared to patients with no SIs or only hypoxemia (Fig. 1). Surprisingly, GFAP values were not significantly different between the SIs groups. In contrast, the other biomarker values showed an increase in patients with at least one insult with the maximum values in patients with both SIs (ESM, Table S2).

The correlogram in Fig. 2 shows the correlation between the biomarkers (log-transformed) according to the presence of SIs. A significant correlation between individual biomarkers was observed, with correlation coefficients higher than 0.6 in most cases. However, these correlations were modified by SIs, most prominently in the case of hypotension and combined insults.

The relative balance of glial and neuronal injury, defined using early UCH-L1/GFAP and Tau/GFAP ratios, was significantly different between the SIs groups (Fig. 3), with lowest ratios in patients who did not suffer any SIs, higher values in those who suffered hypoxemia alone and hypotension alone, and highest values in individuals who sustained both insults (Fig. 3 and ESM, Table S2).

Need for ICU care and ICP lowering strategies

ICP monitoring was more frequently used in patients who presented with SIs compared to those who did not, i.e., in 59% of patients in the hypoxemia group and 54% of those with both SIs and only in 40% of patients without SIs ($p<0.001$) (ESM, Table S3). The median TIL score across the entire cohort was 2 (IQR = 0–6) but varied across SIs groups. In particular, the median TIL was higher in patients with SIs, especially with both SIs [median TIL for both SIs was 4 (IQR = 1–6), versus 2 (IQR = 0–5) for no SIs, $p<0.001$]. Blood transfusions, need for mechanical ventilation, and tracheostomy were more common in patients who experienced both SIs or hypotension alone ($p<0.001$). Extracranial surgery in the first 48 h was more frequent in patients with SIs ($p<0.001$) (ESM, Table S3).

Table 1 Patient's characteristics overall and according to the occurrence of systemic insults

	Overall	No SIs*	Hypoxemia	Hypotension	Both	*p* value
N (%)	1695	1280 (75.5)	158 (9.3)	142 (8.4)	115 (6.8)	
Age, years	52 (33, 67)	52 (33, 67)	50 (32, 64)	51 (34, 67)	55 (34, 65)	0.879
Age ≥ 65	457 (27)	355 (27.7)	36 (22.8)	38 (26.8)	28 (24.3)	0.534
Sex (male)	1243 (73.3)	933 (72.9)	113 (71.5)	103 (72.5)	94 (81.7)	0.204
Cause of injury						< 0.001
Incidental fall	689 (42)	565 (45.6)	55 (35.9)	36 (26.5)	33 (29.5)	
Other	114 (6.9)	87 (7)	9 (5.9)	9 (6.6)	9 (8)	
Road traffic accident	741 (45.2)	520 (41.9)	82 (53.6)	80 (58.8)	59 (52.7)	
Suicide attempt	36 (2.2)	15 (1.2)	2 (1.3)	10 (7.4)	9 (8)	
Violence/assault	61 (3.7)	53 (4.3)	5 (3.3)	1 (0.7)	2 (1.8)	
Any extra cranial injury	1288 (76)	933 (72.9)	130 (82.3)	124 (87.3)	101 (87.8)	< 0.001
Spine	322 (19)	199 (15.5)	33 (20.9)	49 (34.5)	41 (35.7)	< 0.001
External	49 (2.9)	35 (2.7)	4 (2.5)	6 (4.2)	4 (3.5)	0.747
Extremities	306 (18.1)	191 (14.9)	32 (20.3)	45 (31.7)	38 (33)	< 0.001
Abdomen/pelvis	299 (17.6)	158 (12.3)	35 (22.2)	62 (43.7)	44 (38.3)	< 0.001
Thorax/chest	620 (36.6)	391 (30.5)	77 (48.7)	73 (51.4)	79 (68.7)	< 0.001
Face/head/neck	990 (58.4)	739 (57.8)	96 (60.8)	83 (58.5)	72 (62.6)	0.705
Total ISS	29 (25, 41)	26 (21, 38)	34 (25, 45)	41 (29, 51)	50 (34.75, 66)	< 0.001
Intubated at hospital arrival	746 (44.4)	487 (38.5)	92 (58.6)	81 (57)	86 (75.4)	< 0.001
MV at hospital arrival	701 (42.1)	454 (36.2)	83 (52.9)	83 (58.9)	81 (71.1)	< 0.001
GCS at arrival	9 (4, 14)	10 (5, 14)	6 (3, 11)	7(3, 13)	3(3, 6)	< 0.001
GCS ≤ 8	792 (49)	518 (42.2)	103 (68.7)	81 (60)	90 (85.7)	< 0.001
GCS (%)						< 0.001
3–5	521 (32.2)	319 (26)	72 (48)	60 (44.4)	70 (66.7)	
6–8	271 (16.8)	199 (16.2)	31 (20.7)	21 (15.6)	20 (19)	
9–12	258 (16)	221 (18)	16 (10.7)	17 (12.6)	4 (3.8)	
13–15	567 (35.1)	488 (39.8)	31 (20.7)	37 (27.4)	11 (10.5)	
Marshall CT score						0.028
1	156 (10.4)	114 (10)	16 (11.1)	14 (11.1)	12 (12.8)	
2	701 (46.8)	531 (46.8)	63 (43.8)	59 (46.8)	48 (51.1)	
3	124 (8.3)	82 (7.2)	11 (7.6)	15 (11.9)	16 (17)	
4	24 (1.6)	20 (1.8)	1 (0.7)	2 (1.6)	1 (1.1)	
5/6	494 (33)	388 (34.2)	53 (36.8)	36 (28.6)	17 (18.1)	
Epidural hematoma	274 (18.3)	220 (19.3)	23 (16)	20 (15.7)	11 (11.8)	0.210
Subarachnoid haemorrhage	1117 (74.5)	838 (73.9)	108 (75.5)	101 (79.5)	70 (73.7)	0.568

Data are expressed as median (interquartile range, IQR) or number, *n* (%) unless otherwise specified; *p* value refers to the comparison between the four SIs groups.
* Any extra cranial Injury, defined has abbreviated injury score, AIS ≥ 3 for one of the body regions

CT computed tomography, *GCS* Glasgow Coma Scale, *ISS* Injury severity score, *MV* mechanical ventilation, *SIs* systemic insults

6-month outcome

At 6 months, 380 patients had died (22%), and a total of 759 (45%) had GOSE ≤ 4. At unadjusted analysis, patients who experienced at least one SI had higher mortality than those who did not (31.8% vs. 19%, $p < 0.001$, ESM, Table S4 and Figure S4), with the highest percentage in patients with both SIs (45.2%). Further, poor neurological outcomes (defined as GOSE ≤ 4) were more frequently seen in patients who experienced hypotension (63.4%) or both SIs (64.3%) when compared to other groups (40.1% for no SI and 51.9% for hypoxemia alone, $p < 0.001$).

In the logistic regression model, patients with hypotension showed a significantly higher risk of unfavourable neurological outcomes (Table 2A). Increasing levels of individual biomarkers (log-transformed) were significantly associated with unfavourable outcomes. There was no interaction between SIs and any individual biomarker (ESM, Table S5).

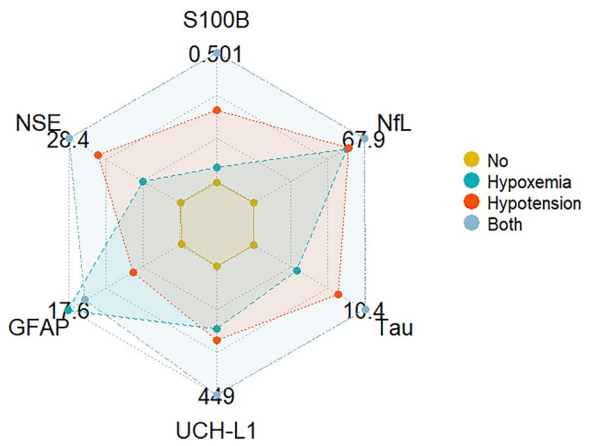

Fig. 1 Radar plot of serum biomarker levels according to the presence of systemic insults. The centre of the radar shows the minimum median value for each serum biomarker. The outer shows the maximum value. *S100B* S100 calcium-binding protein B, *NSE* Neuron Specific Enolase, *NfL* neurofilament light chain protein, *UCH-L1* ubiquitin carboxy-terminal hydrolase L1, *GFAP* glial fibrillary acidic protein

In the Cox regression model adjusted for NfL, GFAP, or UCH-L1 biomarkers (log-transformed), patients with both SIs showed a significant increase in 6-month mortality. In contrast, no statistical differences were found in SIs groups in the models adjusted for NSE, S100B, or Tau biomarkers (Table 2B). In all models, increasing levels of individual biomarkers (log-transformed) were significantly associated with mortality at 6 months (Table 2B). There was no interaction between SIs and any biomarker on the outcome (ESM, Table S5).

Discussion

In this analysis of a large cohort of TBI patients admitted to the ICU, we have explored the incidence, associations, and impact of early hypotension and hypoxemia after brain injury, specifically focusing on their relationships with protein biomarkers of brain injury.

The main findings of our study can be summarised as follows:

- The incidence of SIs in the early phases of TBI is lower than in past studies.
- Patients who experience SIs have more frequent extracranial injuries and a more deranged metabolic profile at presentation.
- Patients with hypotensive or combined hypoxemic and hypotensive events presented with the most deranged biomarkers profile. All neuronal injury biomarkers had the highest values in patients with hypotension or both SIs compared to other subgroups.
- A significant correlation between individual biomarkers was observed in the overall population and stratified by SIs.
- However, while patients who suffered SIs did not show significantly higher GFAP levels than those without SIs, they showed increased neuronal injury biomarkers. Consequently, the UCH-L1/GFAP and Tau/GFAP ratios showed a clear hierarchy: No SI < hypoxemia alone < hypotension alone < combined hypoxemia and hypotension.
- Patients with SIs more frequently required tracheal intubation, mechanical ventilation, and extracranial surgery and had a significantly higher TIL score over the first week of their ICU stay.
- Hypotension and increasing levels of individual biomarkers were associated with increased mortality and unfavourable neurological outcomes, but there was no interaction between SIs and biomarker levels.

Previous reports indicate that patients presenting with TBI showed an incidence of 36% of hypotensive events and up to 44% of hypoxemia [7, 29, 30]. Over the last decade, the characteristics and epidemiology of TBI patients have been changing [1, 2] as road safety is improving and the population is becoming older, resulting in an increase in incidental falls and fewer road traffic accidents as cause of injury. Due to these changes and better out-of-hospital systems [31], the prevalence of SIs has also decreased over time [28]. Our results reflect these changes in epidemiology, with a lower incidence of hypoxemia and hypotension than previously described. However, the incidence presented here is higher than the incidence described in a previous CENTER-TBI manuscript [31], but this apparent discrepancy is explained by the different inclusion criteria and definition of systemic insults.

Even though the harmful effect of SIs on TBI patient outcomes has been previously recognised, little is known about the clinical features and the biomarkers profile that characterise these patients. Our large sample size and multicentre nature make our results unique in this context, reflecting contemporary European TBI management. Our defined SIs groups showed clear differences in the severity of TBI and the presence of extracranial injuries. We also found that patients with SIs had more significant metabolic compromises regarding tissue oxygen debt (higher lactate and base deficit), suggesting that both the injury and the ability of host physiology to cope with the injury insult were more deranged in patients with SIs. Critically, even when controlling for TBI severity, patients with SIs showed higher levels of brain injury biomarkers, suggesting that the systemic physiological

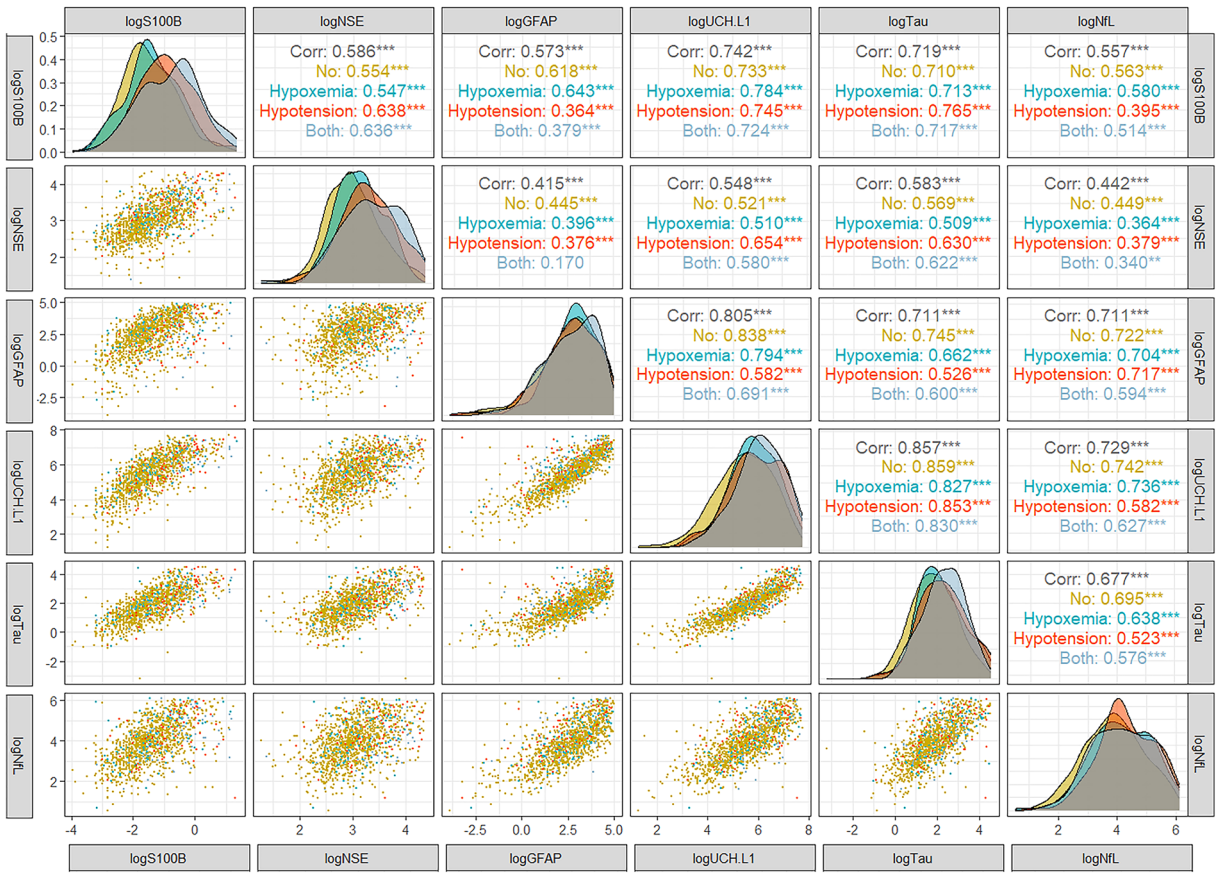

Fig. 2 Correlation between the logarithm of serum biomarker levels in all patients and according to the presence of SIs. The labelling of the *x* and *y* axes is presented on each side of the figure. Following parameters are displayed in logarithm scale: logS100B, logNSE, logGFAP, logUCH-L1, logTau and logNfL. In the diagonal, the distributions of each serum biomarker by SIs are shown with different colours (yellow = No SIs, light blue = Hypoxemia, orange = Hypotension and grey = Both SIs). The lower triangular matrix comprises the bivariate scatter plots of serum biomarkers (on the logarithm scale). Patients in the four classes of SIs are represented with different colours. In the diagonal plots, the distribution of each biomarker is shown by the presence of SIs. The upper triangular matrix of the correlogram shows the Pearson correlation coefficient and its significance level estimated on all patients (Corr) and in each SIs group (No, Hypoxemia, Hypotension, Both). As an explicative example, in the middle panel correspondent to log GPAP and log UCH-L1 (row 4 and column 3), it is shown the scatter plots of the two biomarkers coloured according to the different SIs categories denoting high linear correlation among the two. In the panel at row 3 and column 4 the correlation coefficients between the two biomarkers are provided: 0.805 in the overall population, 0.83 in patients without SI, 0.79 in patients with only hypoxemia, 0.58 in those with only hypotension, and 0.69 in those with both SIs; all being significantly different from 0 ($p < 0.001$). In the diagonal panels (raw and column 3 and raw and column 4), we present the distribution of log GPAP and UCH-l1 among the different categories of SIs, respectively. *P* values are as follows: ***< 0.001, **0.001. *Corr* correlation, *GFAP* glial fibrillary acidic protein, *NfL* neurofilament light, *NSE* neuron-specific enolase, *SIs* systemic insults, *S100B* S100 calcium-binding protein B, *UCH-L1* ubiquitin carboxy-terminal hydrolase L1

compromise had translated to significantly increased neurological injury.

These associations of SIs with systemic physiological compromise and incremental neurological injury are novel findings. Notably, the latter finding allows us to dissociate the effect of injury from that of the SI insults. This increased neural injury translated to a more aggressive disease course requiring higher therapy intensity levels.

We also found that SIs were strongly associated with a need for extracranial surgery. This is unsurprising, given the association of SIs with major extracranial injury. However, while essential, these extracranial operations pose the risk of additional physiological stress and may deliver further insults to a particularly vulnerable brain. The issue of when extracranial surgery should be undertaken in patients with TBI is much debated, and individual considerations of risk and benefit are required to optimise the timing of such surgery. Our data suggest that a history of early SIs, particularly when associated with marked biomarker elevation, indicates a particularly vulnerable brain, and adds to the risk side of this calculation.

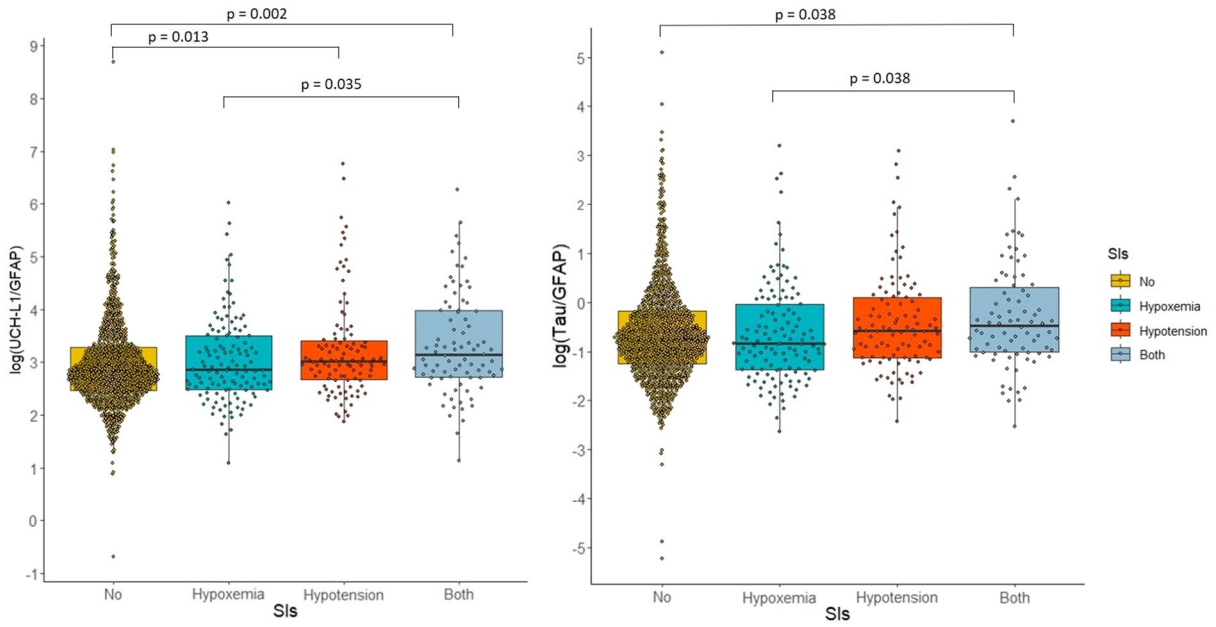

Fig. 3 Distribution of the ratio UCH-L1/GFAP and Tau/GFAP (log-transformed) among systemic insults. Significant adjusted *p* values of the pairwise comparisons are reported. *GFAP* glial fibrillary acidic protein, *SIs* systemic insults, *UCH-L1* ubiquitin carboxy-terminal hydrolase L1

Additional novel insights provided by our results rest, in large part, on data regarding specific cerebral biomarkers and behaviour after SIs. A growing body of literature highlights the importance of biomarkers as prognostic tools and indicators of disease progression after TBI [14, 15]. Each biomarker, resulting from a specific pathophysiological mechanism, may reflect injury to specific cell populations [29]. GFAP and S100B have been suggested as markers of glial injury, UCH-L1 and NSE as markers of neural cell body injury, and NfL and total Tau as markers of axonal and dendritic injury [32]. However, these putative relationships are confounded by other factors and may not be reflected in clinical TBI. For example, an extracranial injury may result in immediate S100B elevation that does not reflect TBI [33, 34], and the prolonged release kinetics of NSE and NfL means that a definitive peak may be delayed by days or weeks [25]. Further, biomarkers have shown stronger correlations with the burden of injury seen on CT scans [35, 36] than with the pathoanatomical type of injury, and a panel of biomarkers have improved the ability to predict outcomes when added in established predictive models such as IMPACT and CRASH more than any biomarker alone [14]. The behaviour of biomarkers in response to SIs, provides an opportunity to examine the magnitude of insult posed by different classes of SIs, and, in turn, assess the cellular specificity of biomarkers from a different perspective. GFAP, UCH-L1, and Tau have sufficiently similar kinetics (time to peak: 8 h, 8 h, and 24 h, respectively [25]) to allow comparison of the effects of SIs on different cellular compartments following TBI.

Our aim was to compare the impact of physiological insults on glial versus neural (rather than dendritic/axonal) compartments. The range of blood biomarkers available in TBI reflects injury to different tissue compartments in the brain—including glia (S100B, GFAP), neuronal cell bodies (NSE, UCH-L1), and axons and dendrites (Tau, NfL) [37], and might be expected to show specificity for pathoanatomical types of injury. However, the levels of all biomarkers scale with the overall burden of injury rather than being specific to pathoanatomical kinds of injury [38, 39]. For example, GFAP, though a glial marker, is a sensitive marker of CT-occult diffuse axonal injury [40]. Given the lack of pathoanatomical specificity of individual biomarkers in relation to initial mechanical impact, we explored whether the more nuanced physiological insults provided by hypoxemia and hypotension might result in differential effects on cell populations, which would be reflected in the ratios of glial and neuronal derived biomarkers.

Interestingly, in the absence of SIs, GFAP, UCH-L1, and Tau showed high correlations, providing a benchmark for parallel amounts of glial and neuronal injury [41]. However, this correlation was altered by SIs, with a relatively more significant increase of biomarkers of neural injury (UCH-L1 and Tau) than glial injury (GFAP). None of the SIs were associated with higher levels of GFAP, but all showed increases in UCH-L1 and Tau, and, consequently,

Table 2 Results from logistic (poor neurological outcome, extended Glasgow Outcome Scale—mortality at 6 months—and Cox regression models)

(A) Poor neurological outcome at 6 months						
	LogS100B	LogNSE	LogNfL	LogGFAP	LogTau	LogUCH-L1
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
SIs						
No	1	1	1	1	1	1
Hypoxemia	1.2 (0.77–1.88) $p=0.421$	1.09 (0.70–1.71) $p=0.688$	1.12 (0.71–1.76) $p=0.623$	1.19 (0.76–1.87) $p=0.449$	1.07 (0.68–1.70) $p=0.76$	1.03 (0.65–1.63) $p=0.91$
Hypotension	1.83 (1.14–2.93) $p=0.012$	1.85 (1.16–2.97) $p=0.01$	2.14 (1.31–3.5) $p=0.002$	2.72 (1.67–4.43) $p<0.001$	2.16 (1.32–3.54) $p=0.002$	2.17 (1.32–3.56) $p=0.002$
Both	0.91 (0.52—1.58) $p=0.728$	1.04 (0.61–1.79) $p=0.88$	1.24 (0.71–2.15) $p=0.451$	1.34 (0.77–2.33) $p=0.301$	0.99 (0.56–1.77) $p=0.989$	1.03 (0.59–1.81) $p=0.918$
Log(biomarker)	2.29 (1.94 -2.72) $p<0.001$	2.78 (2.11–3.66) $p<0.001$	2.05 (1.77–2.37) $p<0.001$	1.6 (1.44–1.78) $p<0.001$	2.05 (1.78–2.36) $p<0.001$	2.2 (1.90–2.56) $p<0.001$
(B) Mortality at 6 months						
	LogS100B	LogNSE	LogNfL	LogGFAP	LogTau	LogUCH-L1
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
SIs						
No	1	1	1	1	1	1
Hypoxemia	1.17 (0.77–1.76) $p=0.46$	1.13 (0.76–1.69) $p=0.54$	1.28 (0.87–1.89) $p=0.21$	1.09 (0.74–1.62) $p=0.65$	1 (0.67–1.51) $p=0.98$	1.05 (0.7–1.56) $p=0.81$
Hypotension	0.66 (0.39–1.09) $p=0.1$	0.7 (0.42–1.17) $p=0.18$	0.86 (0.53–1.41) $p=0.56$	0.81 (0.49–1.33) $p=0.4$	0.8 (0.48–1.31) $p=0.37$	0.68 (0.41–1.13) $p=0.14$
Both	0.99 (0.64–1.54) $p=0.97$	1.31 (0.87–1.96) $p=0.19$	1.61 (1.07–2.43) $p=0.02$	1.71 (1.15–2.55) $p=0.01$	1.37 (0.9–2.08) $p=0.15$	1.48 (0.99–2.22) $p=0.05$
Log(biomarker)	2.26 (1.92–2.66) $p<0.001$	3 (2.3–3.92) $p<0.001$	1.68 (1.45–1.94) $p<0.001$	1.47 (1.3–1.65) $p<0.001$	1.76 (1.54–2.01) $p=0.001$	1.86 (1.6–2.17) $p<0.001$

OR odds ratio, *Log* logarithm, *GCS* Glasgow Coma Scale, *SIs* systemic insults, *CI* confidence interval, *S100B* S100 calcium-binding protein B, *NSE* neuron-specific enolase, *NfL* neurofilament light, *GFAP* glial fibrillary acidic protein, *HR* hazard ratio, *UCH-L1* ubiquitin carboxy-terminal hydrolase L1

higher ratios of UCH-L1/GFAP and Tau/GFAP. These elevations in neuronal injury biomarkers were more prominent in patients who suffered hypotension rather than hypoxemia and were highest in those who suffered a combined SI. These findings are in keeping with data on vulnerability and responses of different cell types to modelled SIs [39, 42].

This imbalance between neural and glial injury was worse with hypotension than hypoxemia and further accentuated by the combination of both. These data suggest that all insults are associated with more significant neuronal than glial insults. This excess neuronal injury may be more prominent with hypotension than hypoxemia and the combination of both insults further accentuates this imbalance, suggesting that current thresholds defined for hypoxic SIs ($PaO_2 < 60$ mmHg or $SpO_2 < 90\%$) and current thresholds defined for hypotensive SIs (SBP < 90 mmHg) may not be equally harmful. The dominant harms of a hypotensive SI threshold of SBP < 90 mmHg is in keeping with recent data suggesting that optimal blood pressure may be as high as 110–130 mmHg to minimise secondary hypotensive insults [40]. This finding also has implications for how aggressively we should manage prehospital systemic insults, given the increasing trend to allow permissive hypotension in extracranial injury with bleeding. This should pave the way for further studies that can help define the optimal threshold of arterial blood pressure to adopt in this population in the early phases [39, 43].

Our results highlight the need to identify and characterise patients at risk for second insults early through a more specific assessment and quantify their impact by measuring differential neuronal and glial injury biomarker levels. Such data could help us understand the pathophysiological events occurring after SIs and refine our understanding of how they impact outcomes. However, our results also support the integration of biomarkers in established prognostic models with SIs to improve precision in prognosis and decision-making in the context of multimodal strategies and evaluation. The lack of interaction of biomarkers with SIs on outcomes suggests that the precise behaviour of biomarkers after SIs needs

still to be fully understood and requires specific studies exploring the changes over time of biomarkers and the dynamics of cerebral damage.

Limitations

Firstly, it is imperative to acknowledge that our study, by its observational nature, does not establish causal relationships concerning the observed outcomes. While we employed robust statistical models and adjusted for potential confounding variables, the limitations inherent to the observational studies' analysis persist.

Secondly, the absence of data on the dynamic biomarker changes limits our ability to comprehensively depict our TBI patients' disease progression and establish a more precise correlation with their outcomes. We cannot elucidate the trajectories of these biomarkers and discern the impact of therapeutic interventions on their kinetics. A single measurement obtained at the initial hospital presentation is probably inferior in defining prognosis to biomarker measurements taken later. These limitations emphasise the necessity for prudence when interpreting our results and underscore areas with potential for enhancement in future research endeavours. Notably, using point-of-care tests at the bedside, enabling real-time monitoring of biomarker trajectories, presents an exciting avenue for future research improvement. The inclusion criteria and the granularity of the data may not fully reflect the heterogeneity of the clinical picture. For instance, the Marshall-CT score does not take into account brainstem injuries, which are significantly associated with mortality and poor neurological outcomes. Further, no data are available regarding the duration of SIs and their trajectory over time, which are essential variables to quantify the dose of injury received by patients. Finally, the low incidence of SIs might be due to other factors, such as incomplete documentation, or the inclusion of patients with less severe TBI (GCS $\geq$ 9).

Conclusion

Systemic insults are less frequent in the early phases of TBI in our study when compared to past studies. They are generally related to the severity of trauma and the presence of extracranial injuries. They are associated with a more deranged metabolic profile and higher values of biomarkers at admission. Individual SIs are associated with different biomarker profiles, which provide insights into the specific vulnerability of neuronal and cellular populations to these insults. Given our current thresholds for defining hypoxic and hypotensive SIs, our data suggest a more significant insult to neuronal populations from hypotension than hypoxemia, and a still larger insult from the combination of the two. Further studies are warranted to validate and confirm our results.

Supplementary Information

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Conceptualisation and study definition: GC, DM, FG, CR. Funding acquisition: GC, AM, DKM. Patients' enrolment: CENTER-TBI participants and investigators. Data verification: FG. Access to raw data: FG, GC. Formal analysis: FG, PR, SG. Project administration, Data access and verification: GC. Writing—original draft: GC, DM, FG, CR. Writing—review and editing: All authors. The final responsibility for the decision to submit for publication: GC.

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Data availability

Data supporting the study's findings are available on reasonable request after approval of a proposal from the corresponding author (GC). Data collected for the analysis, including deidentified individual participant data and a data dictionary defining each field in the set, will be made available to others on request. Related documents such as the study protocol, statistical analysis plan, and informed consent form will also be available on request.

Declarations

Conflicts of interest

GC reports grants and personal fees as a speakers' bureau member and advisory board member from Integra Neurosciences, NeurOptics, Biogen, Invex Ltd and Idorsia, all outside the submitted work. DKM reports consultancy fees, speaker fees, or research collaborations with NeuroTrauma Sciences, Lantmannen AB, GlaxoSmithKline Ltd, Pressura Neuro Ltd, Integra Neurosciences, and Invex Ltd. CR reports speaker fees from Edwards Life Sciences and Masimo. The other authors did not declare competing interests.

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