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Pediatric traumatic brain injury: clinical presentation, treatment approaches, management strategies, and outcomes. Insights from the CENTER-TBI study

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Pediatric traumatic brain injury: clinical presentation, treatment approaches, management strategies, and outcomes. Insights from the CENTER-TBI study

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Research in Context

- Most pediatric TBI literature stems from small cohorts or single-center studies; large multicenter observational data are scarce, especially in ICU settings.
- Current guidelines are largely extrapolated from adult data, with limited granularity by pediatric age subgroup or treatment intensity levels.
- This study offers the most comprehensive multicenter European analysis of pediatric TBI to date, highlighting age-related differences in injury severity, management, and outcomes, and supporting the need for tailored pediatric neurocritical care strategies.

Article Tweet:

Adolescents exhibit TBI profiles comparable to adults in terms of injury type and management. Pediatric patients demonstrate a lower frequency of severe traumatic brain injury, a lower susceptibility to develop secondary brain insults, and require less intensive therapy in the intensive care setting. Pediatric TBI patients have better short- and long-term outcomes in terms of mortality and GOS-E compared to adults and the elderly.

Abstract

Objective: This observational study aims to describe the characteristics and management of pediatric head-injured patients across different pediatric age groups, compared with adults.

Design: Secondary analysis of the CENTER-TBI study

Setting: 65 centers in Europe between December 2014 and December 2017

Patients: TBI patients admitted to the hospital were divided into different age groups: pediatrics (pTBI, age ≤ 17 years), further subdivided into three groups: toddlers (from 0 to 4 years), children (from 5 to 12 years), and adolescents (from 13 to 17 years); adults (18-65 years); and elderly (> 65 years)

Interventions: None

Measurements and Main Results: 3,661 patients were included in the analysis (2,138 admitted to the ICU and 1,523 to the ward). Among these, 227 were pediatric (27 toddlers [0–4 years], 65 children [5–12 years], and 135 adolescents [13–17 years]). Most pTBI patients admitted to the ICU presented with mild injuries (Glasgow Coma Scale [GCS] 13–15; 66%), although severe injuries (GCS ≤8) were more common in adolescents (23.8%). Susceptibility to neuroworsening and seizures was low in the pediatric group (6% and 3.5%, respectively). Intracranial pressure monitoring was performed in 52 (39.4%) of 132 pediatric ICU patients. Pediatric patients received less intensive ICP-targeted therapy particularly in toddlers.

Age below 18 years was associated with a lower risk of poor neurological outcomes at six months, particularly in adolescents and children (OR=0.31, 95% CI=0.15–0.58 p<0.001 and OR=0.29, 95% CI=0.09–0.71, p<0.001, respectively). In toddlers, the association was not statistically significant (OR=0.48, 95% CI=0.07–1.94, p=0.4).

Conclusions: Pediatric TBI differs significantly from non-pediatric cases, with predominantly mild injuries, lower neuroworsening rates, and less intensive management, especially in younger children. Outcomes at six months are generally more favorable in pediatric patients, emphasizing the need for age-specific management strategies in TBI care.

INTRODUCTION

Pediatric traumatic brain injury (pTBI), affecting over 3 million children worldwide every year(1)[1], is a significant contributor to mortality and morbidity rates in the first two decades of life, leaving a lasting impact on the lives of survivors(2,3) . The distinct nature of TBI across various age groups(4,5) *complicates both its understanding and management* In toddlers, accidental falls are the primary cause of TBI, while adolescents encounter a different set of triggers, including road traffic incidents, sports-related incidents, and acts of violence(6) .

Despite the high relevance of pTBI, current literature on traumatic brain injury has been predominantly focused on adults, with some recent analyses including the elderly. A significant gap in published evidence regarding pTBI exists(7,8) , leading to uncertainties and unresolved issues in this crucial area of medicine. The lack of comprehensive studies on pTBI highlights the need for dedicated research to better understand the unique aspects associated with pediatric head injuries(9) .

The present study aims to descriptively characterize paediatric TBI management and outcomes across age groups within the ICU setting and to compare them with adult and elderly cohorts, acknowledging that differences in care intensity may partly reflect injury severity, institutional protocols, and developmental considerations. Given the challenges in clinical assessment across paediatric developmental stages, we included exploratory biomarker analysis to evaluate whether age-related differences in biomarker expression could reflect underlying pathophysiological variations and help refine age-specific management strategies.

MATERIALS AND METHODS

Study population

The Collaborative European NeuroTrauma Effectiveness in Research in Traumatic Brain Injury (CENTER-TBI) study, registered at clinicaltrials.gov (NCT02210221, 2014-12-19), is a prospective, multicenter, observational, longitudinal cohort study that enrolled traumatic brain injured patients. Data were collected between December 2014 and December 2017 across 65 participating centers in Europe.

The CENTER-TBI study had no age limit, however, the participating centers were not dedicated pediatric centers, and children were, therefore, part of the overall TBI population.

For the current sub analysis, only patients who were admitted to the ward or the Intensive Care Unit (ICU) were included. Pediatric age subgroups were defined as toddlers (0–4 years), children (5–12 years), and adolescents (13–17 years) based on clinical relevance and sample size considerations. Although our age groups do not fully align with NICHD classifications, further subdivision was avoided to preserve statistical power and interpretability. This pragmatic approach allowed for a more meaningful clinical comparison while preserving age-related distinctions across the paediatric spectrum.

The CENTER-TBI study (EC grant 602150) has been conducted following all relevant laws of the European Union (EU) and all relevant laws of the country where the recruiting sites were located. Informed Consent by the patients and/or the legal representative/next of kin was obtained for all patients recruited (see https://www.center-tbi.eu/project/ethical-approval).

Data collection

Collected data includes demographic characteristics (age, sex), details on the cause and location of the injury, the severity of the injury (Glasgow Coma Scale, (GCS); pupils' state; total Injury Severity Score (ISS) at hospital admission), the occurrence of secondary insults (seizures; neuroworsening; hypoxia; hypocapnia; hypotension), and the necessity for urgent surgery. Neuroworsening was defined as a documented decrease in GCS by ≥2 points, pupil asymmetry, or new neurologic deficit requiring escalation in care, in line with CENTER-TBI definitions.

CT abnormalities were classified using the Marshall CT classification to ensure comparability with the adult CENTER-TBI cohort and to maintain consistency with the standardized data dictionary.

Six specific serum 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) were measured in samples obtained within 48 hours from hospital admission.

Intracranial pressure (ICP) monitoring and ICP values were collected when clinically indicated. The intensity of ICP treatment was evaluated using the 38-point Therapy Intensity Level (TIL)(10,11) .

Functional outcome was assessed using the 8-point Extended Glasgow Outcome Scale (GOS-E)(12) . A pediatric version was not available or validated at the time of data collection. For toddlers, functional independence was interpreted relative to age-appropriate developmental functioning.

The Glasgow Coma Scale Extended (GOS-E), was assessed by trained study personnel during a face-to-face visit, telephone interview, or postal questionnaire(13) . Unfavorable functional outcome was defined as a GOS-E≤4, while good neurological recovery was defined as GOS-E >4. ICU mortality, mortality at six months, and length of stay in ICU were also evaluated as secondary outcomes.

Clinical data were collected using a custom web-based electronic Case Report Form (eCRF) provided by QuesGen systems Inc., San Francisco, CA. For this sub analysis, data were extracted from the CENTER-TBI Core Version 3.0 using Opal.

Statistical analysis

Data are described with absolute and relative (%) frequency, median (I-III quartile), or mean (Standard Deviation, SD), where appropriate. Between age groups comparisons (toddlers vs children vs adolescents and pediatrics vs adults vs elderly) on baseline, management, and treatment characteristics were performed by chi-squared, Fisher's exact, or Kruskal-Wallis test, according to the nature of the variable. We used the Benjamini and Hochberg (BH) approach to correct for multiple testing and we reported the adjusted p-values.

The relationship between age and each of the six biomarkers was estimated using a linear regression model with a spline and results were reported along the corresponding 95% Confidence Intervals (CI95%), stratified by GCS (≤8 and >8). Regarding the outcomes, the analysis of mortality was mainly descriptive due to the limited number of events in the pediatric population that prevented the possibility of building a regression model. On the contrary, a logistic regression model was performed to assess the association among the

different age groups and the 6 months of poor functional outcome (GOS-E≤4) considering adults as reference. The model was adjusted for the IMPACT core variables (i.e. age, pupils' reactivity, GCS motor), gender, and type of patients (ward or ICU) and results were shown as odds ratio (OR) of unfavorable outcomes with corresponding 95% CIs.

The tests were two-sided with a significant level of 0.05. All the analyses were conducted with the software R (version 4.2.1, "Beagle Scouts").

Ethical statement

Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the eCRF (see Supplemental Digital Content).

RESULTS

Baseline characteristics of pediatric TBI patients

Among the 4,509 TBI patients enrolled in the CENTER-TBI core study, 3,661 (81.2%) were admitted to the ward or ICU. Within this subgroup, 227 (6.2%) were pediatric patients, comprising 27 (12%) toddlers, 65 (28%) children, and 135 (59%) adolescents (Figure S1 in Supplemental Digital Content).

Characteristics of injury and hospital admission are shown in Table 1. At admission, severe TBI was more frequent in adolescents (n=28, 23.8%) than in children (n=9, 18.8%) and toddlers (n=3, 17.6%). At least one unreactive pupil was present in 18 (8%) pTBI. The ISS was higher in adolescents (median=25, interquartile range (IQR)=13-35.8) compared to children (median=16, IQR=10-25) or toddlers (median=16 IQR=9-22.5). A negative first CT (Marshall score 1-normal CT) scan was more frequent in toddlers (n=12, 48%) and children (n=26, 41.9%) compared to adolescents (n=41, 32.5%), while pathological CT scans were more frequent in adolescents compared to the younger patients (Marshall scores to 2, 3, and 4 resulted in n=70, 55.6%, n=9, 7.1%, and n=2, 1.6%, respectively, Table 1).

Rates of secondary insults before admission to the Emergency room were low overall: (hypotension (n=40, 17.6%), hypoxia (n=27, 11.9%), neuroworsening (n=14, 6.2%), seizures (n=8, 3.5%), with no major differences across age groups (Tabe S2).

Management of pediatric TBI patients in the ICU

Among the 132 pediatric ICU patients, 52 (39.4%) underwent ICP monitoring, monitoring, mostly with intraparenchymal catheters (n=44, 84.6%). Amidst 40 severe TBI cases (GCS ≤ 8), 28 (70%) were monitored for ICP. (Table 2). A higher proportion was observed among the adolescent group (n=37, 45.7%; Among toddlers, 3 of 16 (18.8%) received an ICP monitoring device. Pediatric group displayed a mean daily ICP value in the first week equal to 12.6 mmHg (SD=10.8 mmHg) with lower values in the toddlers' group (mean daily ICP 10.16 mmHg, SD =0.15 mmHg). ICP values distribution is shown in Figure S3.

As for the treatment of elevated ICP, a TIL extreme (TIL scale ≥ 10, TIL scale is detailed in Table S4), was utilized in 30 pediatric patients (22.7%), with greater frequency in children (n=9, 25.7%) and adolescents (n=20, 24.7%). During the stay in the ICU, the pTBI mean TIL was 3.18 (SD=4.16), and the mean maximum of 3.64 (SD=4.91) in children. Of note, the lowest mean TIL of 1.23 (SD=2.25) in toddlers (Table S3 and Table 2). No differences were found among pediatric groups in the ICP treatment; however, toddlers were treated more frequently with tier 1 interventions (i.e. elevated head position, temperature control, and optimization of sedation) (Figure 1). Focusing on the hyperosmolar therapy among the pediatric group 56 (24.7%) patients received at least one dose of mannitol and 65 (28.6%) a dose of hypertonic saline. Hyperventilation treatment was more frequent in adolescents (40%) compared to children (24%) and toddlers (.3%). Urgent intracranial and extracranial surgeries were required in 20 (8.8%) and 25 pediatric patients, respectively (11.2%). A decompressive craniectomy (DC) was performed in 9 pTBI patients (4%) overall, with no such surgery required in toddlers, 4 surgeries in children (6.2%), and 5 in adolescents (3.7%), Table 2.

During their ICU stay 87 (46.5%) pTBI needed mechanical ventilation: 59 (53.2%) were adolescents, 20 (35.7%) were children and eight (40%) were toddlers; the mean $PaCO_2$ was 34.9 mmHg (SD = 4.85), SpO_2 was 99% (SD 2%) and PaO_2 was 94.99 mmHg (SD = 8.98), and tracheostomies were required in 17 (12.9%) pediatric patients, all performed on adolescents (p=0.002) (Table S3, Table 2).

The mean heart rate (HR) was 99 bpm (SD=23.5), toddlers reached a mean value of 131 bpm (SD=25.8), children 101 bpm (SD=19.3), and, at least, adolescents 93 bpm (SD=19.7). Fluid loading was used in 35 (40.2%) pediatric patients (in 28.6% of the toddlers, 40% of the children, and 41.9% of the adolescents); furthermore, 41 (47.1%) pTBI needed vasopressor: 3 (42.9%) were toddlers, 9 (36%) were children and 29 (52.7%) were adolescents. During the first week hemoglobin levels were different among pediatric age groups and the values ranged between 10.62 g/dL (SD=1.67) in toddlers and 12.18 g/dL (SD=2.13) in adolescents (p<0.001). Eleven pediatric patients required red blood cell (RBC) transfusion with no statistically significant differences among the age groups. Toddlers had a lower creatinine value compared to children and adolescents. A similar trend was observed in sodium: the mean value was 141.09 mmol/L: children and adolescents had the same values (141 mmol/L, SD=3.3) compared to toddlers' lower value whose value was slightly lower (139.5 mmol/L, SD=3.9).

Four adolescents underwent gastrostomy tube positioning. Complications during the ICU stay were rare in pediatric patients with an occurrence of 28% overall events; the most frequent thereby were respiratory failure (n=13, 9.8%) and ventilation-associated pneumonia (n=11, 8.3%), more often in adolescents than in the other age groups (Table S3).

Short and long-term outcomes analysis

Among the pediatric group, ICU mortality at 6 months was higher in toddlers (4.8% vs 1.6% in children and 3.3% in adolescents) and unfavorable outcome (GOS-E ≤4) was slightly more frequent in adolescents (10.7%) than in toddlers (9.5%) and children (8.1%) Table 3. Highest incidence of good neurological recovery (GOS-E >4 at six months) was detected in the pediatric population (63.9%; thereby 66.7% in toddlers, 54.8% in children, and 68% in adolescents) compared to adults (47.6%) and elderly patients (41.2%) (p<0.001) (Table S3). The proportion of GOS-E at six months among the age groups is detailed in SDC.

Results from the logistic regression model on unfavorable outcomes (GOS-E ≤4) are shown in Figure 2. Pupils' reactivity and GCS motor were associated with higher odds of poor outcomes. Moreover, an age below 18yo was associated with lower odds of poor outcomes (OR=0.31, CI95%=0.15-0.58, p<0.001 in adolescents; OR=0.29, CI95%=0.09-0.71, p<0.001 in children; and OR=0.48, CI95%=0.07-1.94, p=0.4 in toddlers, Figure 2). Finally, the odds of poor neurological outcome were significantly higher in patients admitted to ICU (OR=3.90, CI95%=3.05-5.03, p<0.001).

Biomarkers and Comparison with adults and elderly

Regarding the different biomarkers, GFAP, Tau, NfL, and UCH-L1 levels increased with age, while NSE showed the opposite trend and decreased with age. Higher biomarker values were observed in patients with a GCS≤ 8

compared to those with a GCS> 8. (Figure S2). Median values for each biomarker are detailed in Table 1 and Table S1.

In depth comparison of pediatric data with adults and elderly is presented in SDC.

DISCUSSION

This study offers a detailed analysis of pTBI using data from the CENTER-TBI cohort, highlighting distinct age-related differences in presentation, management, and outcomes compared to adult and elderly patients.

Our core results can be summarized as follows: adolescents show a clinical severity and management profile similar to that of adults; adherence to pediatric TBI guidelines is only partial; toddlers and younger children receive a lower intensity of care yet experience better outcomes; and biomarker analyses reveal distinct age-related pathophysiological patterns. A key finding is that adolescents mirror adults in injury severity and treatment needs, while toddlers and children show distinct profiles—such as lower ISS scores, more frequent normal CT scans, and lower ICP values. These findings underscore that pTBI is not a uniform condition and support the need for age-specific strategies(14–19) [14-16]. The limited use of ICP monitoring and decompressive craniectomy in younger children further highlights the need for evidence-based guidelines tailored to pediatric subgroups(20–26) [20-26].

Although the third edition of the Brain Trauma Foundation pediatric TBI guidelines(7) was published after the study period, our evaluation of adherence refers to the 2012 second edition(27) , whose recommendations on ICP monitoring and hyperosmolar therapy are conceptually similar.

The 2012 and 2019 Pediatric TBI Guidelines7-8 recommend ICP monitoring for patients with a GCS score ≤ 8, aiming to maintain ICP below 20 mmHg. In this study, ICP monitoring was performed in only 39.4% of pediatric ICU patients, with a higher prevalence among adolescents compared to children and toddlers. Specifically, ICP monitoring was performed in 70% of severe cases, implying partial but not poor adherence, especially considering that two-thirds of pediatric ICU admissions were for mild injuries.

These findings suggest that ICP monitoring is underutilized, particularly in younger children, despite guideline recommendations. This discrepancy may reflect clinical hesitation due to the invasiveness of the procedure or uncertainty about its necessity in younger pediatric populations(22–24) .

The guidelines outline a tiered approach to ICP management. Pediatric patients received less aggressive ICP-directed therapy than adults, likely reflecting differences in injury severity and clinical decision-making rather than inherently lower treatment requirements. Hyperventilation, for example, was more commonly used in adolescents than in children and toddlers. Additionally, decompressive craniectomy was performed in only 4% of pediatric cases, with no toddlers undergoing the procedure. This suggests that the need for aggressive ICP management is lower in younger children or that surgical interventions may be underutilized. The limited use of decompressive craniectomy raises questions about whether surgical interventions should be more aggressively considered in pediatric TBI or whether alternative strategies should be prioritized. The guidelines recommend the use of mannitol or hypertonic saline to control elevated ICP. We found that 24.7% of pediatric

patients received mannitol, while 28.6% received hypertonic saline. These rates are comparable to those observed in adult populations(21). In this study, both mannitol and hypertonic saline were used in roughly equal proportions. Recent pediatric TBI guidelines favor hypertonic saline over mannitol due to limited pediatric evidence for the latter, and the pattern observed here likely reflects practice variability during the 2014–2017 period. The guidelines recommend maintaining a partial pressure of carbon dioxide between 35-40 mmHg. The average $PaCO_2$ in pediatric patients was 34.9 mmHg. However, adolescents exhibited a trend toward more aggressive ventilation strategies, potentially reflecting their closer physiological resemblance to adults(28). This variation raises concerns about the need for stricter adherence to ventilation targets, particularly in younger pediatric patients, where excessive hyperventilation could lead to secondary ischemic injury(19–23) .

Short- and long-term outcomes further illustrate the advantages of younger age in TBI recovery. ICU mortality was lowest in toddlers, followed by children and adolescents. At six months, pediatric patients exhibited the highest rates of good neurological recovery compared to adults and elderly patients. Adolescents demonstrated a slightly higher risk of unfavorable outcomes than younger pediatric groups, aligning with their closer resemblance to adult TBI profiles(15,18,19,29)

Our study's biomarker analysis offers additional insights into the neurobiological differences between age groups. Biomarker analysis revealed an age-related trend, with GFAP, Tau, NfL, and UCH-L1 levels increasing with age, while NSE levels decreased, reflecting distinct neurobiological responses to injury across the lifespan(25,26,28,30). The higher levels of GFAP, Tau, and NfL in the elderly suggest greater susceptibility to axonal degeneration and astroglial damage, likely due to reduced neuroplasticity, impaired repair mechanisms, and a greater burden of secondary neuroinflammatory processes. In contrast, the higher NSE levels in pediatric patients indicate greater neuronal metabolic activity and susceptibility to early excitotoxic stress, possibly due to higher neuronal turnover, greater reliance on glycolysis, and a predominance of necrotic rather than apoptotic cell death following injury(31,32). These age-related trajectories highlight fundamental differences in TBI pathophysiology across age groups, suggesting that younger brains may experience more immediate metabolic stress, while older brains exhibit more chronic neurodegenerative responses. However, evidence on age-related susceptibility to secondary brain insults is mixed. Some studies report lower systemic and intracranial insult burden in children(33,34), whereas others suggest equal or greater vulnerability due to immature autoregulation(35). The lower incidence observed in our cohort may therefore reflect less intensive monitoring rather than intrinsic resistance. Given the potential for biomarkers to improve age-specific patient stratification and guide therapeutic decisions, their integration into clinical practice should be explored in future guideline updates.

While this study provides valuable insights, several limitations should be noted. The CENTER-TBI dataset involves a heterogeneous patient population from multiple centers, introducing variability in clinical practices. The inclusion of pediatric patients managed in adult trauma centers may limit the generalizability of findings to dedicated pediatric settings. Due to the limited number of pediatric cases, especially in the youngest age groups, we adopted broader pediatric age bands that do not correspond exactly to standard developmental

stages. This may mask developmental differences, particularly between infants and older toddlers or between early and late adolescents. *Interpretation in toddlers should be cautious given the small sample size.* Future pediatric TBI studies should aim for more granular age stratification. The limited number of moderate-to-severe pediatric TBI cases and outcome events constrains the strength of inferential statistics and limits multivariable modeling, especially for mortality. Another major limitation is the use of the adult validated Marshall CT classification scale. We acknowledge that pediatric-specific CT scores may offer improved prognostic discrimination. Moreover, GOS-E scale is not validated for children under 17 years. This restricts the interpretability of pediatric functional outcomes, especially in toddlers and young children. Future research should use validated pediatric measures such as the GOS-E Peds. These findings should therefore be interpreted as exploratory and hypothesis-generating rather than confirmatory. Nonetheless, the study remains one of the largest multicenter ICU cohorts reporting pediatric TBI care patterns across Europe. Future studies should address these gaps by developing age-specific management protocols, refining pediatric ICP thresholds, validating biomarkers for clinical decision-making, and evaluating long-term neurodevelopmental outcomes.

Although this analysis draws on ICU data from 2014–2017, it remains relevant due to the continued lack of large-scale multicenter paediatric TBI datasets. While practices may have evolved slightly since then, the underlying differences in pathophysiology, monitoring, and therapeutic intensity across paediatric age groups continue to underscore the need for tailored strategies.

Conclusion

Pediatric TBI exhibits clear age-related differences, with adolescents resembling adults more closely than younger pediatric groups. Overall, pediatric patients have better outcomes than adults and elderly patients, with lower rates of secondary insults, reduced need for intensive therapies, and higher rates of neurological recovery. These findings highlight the importance of tailored treatment approaches and the need for further research to optimize pTBI management strategies, particularly in the youngest patients. Additionally, the study also suggests partial implementation of guideline-recommended monitoring and surgery in children and highlights the potential role of biomarkers in future age-specific management strategies. Addressing these knowledge gaps through further research may lead to more effective, evidence-based pediatric TBI management strategies.

DECLARATIONS

Ethical approval and consent to participate

The CENTER-TBI study was performed according to the Helsinki Declaration and the International Conference on Harmonization for Good Clinical Practice. Since comatose patients could not provide informed consent during study recruitment, each center referred to local/national law on the lack of capacity. If the patients regained capacity at the follow-up visit, they had to either provide informed consent to use the acute and

follow-up data or refuse to participate in the research. Ethical approval for the study was obtained from the Medical Ethics Committees of each participating center, and informed consent was obtained from all participants following local regulations (https://www.center-tbi.eu/project/ethical-approval). For this sub-analysis, no further ethical approval was required.

Consent for publication

Written informed consent for the publication of these data has been previously obtained.

Availability of data and materials

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

Competing interests

Authors declare no competing interests.

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Authors' contributions

Conceptualization and study definition: Giuseppe Citerio

Funding acquisition: Giuseppe Citerio

Patients' enrolment: CENTER-TBI participants and investigators.

Data verification: Francesca Graziano

Access to raw data: Giuseppe Citerio, Francesca Graziano

Formal analysis: Francesca Graziano, Paola Rebora, Stefania Galimberti

Project administration, Data access and verification: Giuseppe Citerio

Writing—original draft: Giuseppe Citerio, Francesca Graziano, Angelo Guglielmi

Writing—review and editing: All the authors

The final responsibility for the decision to submit for publication: Giuseppe Citerio

Clinical trial number

The Collaborative European NeuroTrauma Effectiveness in Research in Traumatic Brain Injury (CENTER-TBI) study, registered at clinicaltrials.gov (NCT02210221, 2014-12-19).

FIGURES

Figure 1. Therapy intensity levels (TIL) stratified by paediatric age groups.

Stacked bar plot illustrating the distribution of specific therapeutic interventions used for ICP management across pediatric subgroups (toddlers, children, adolescents). Lower-intensity measures (Tier 1) were more frequently applied in younger children, while higher TIL scores were observed predominantly in adolescents. Abbreviations: TIL = Therapy Intensity Level; CSF = Cerebrospinal fluid drainage; CPP = Cerebral perfusion pressure.

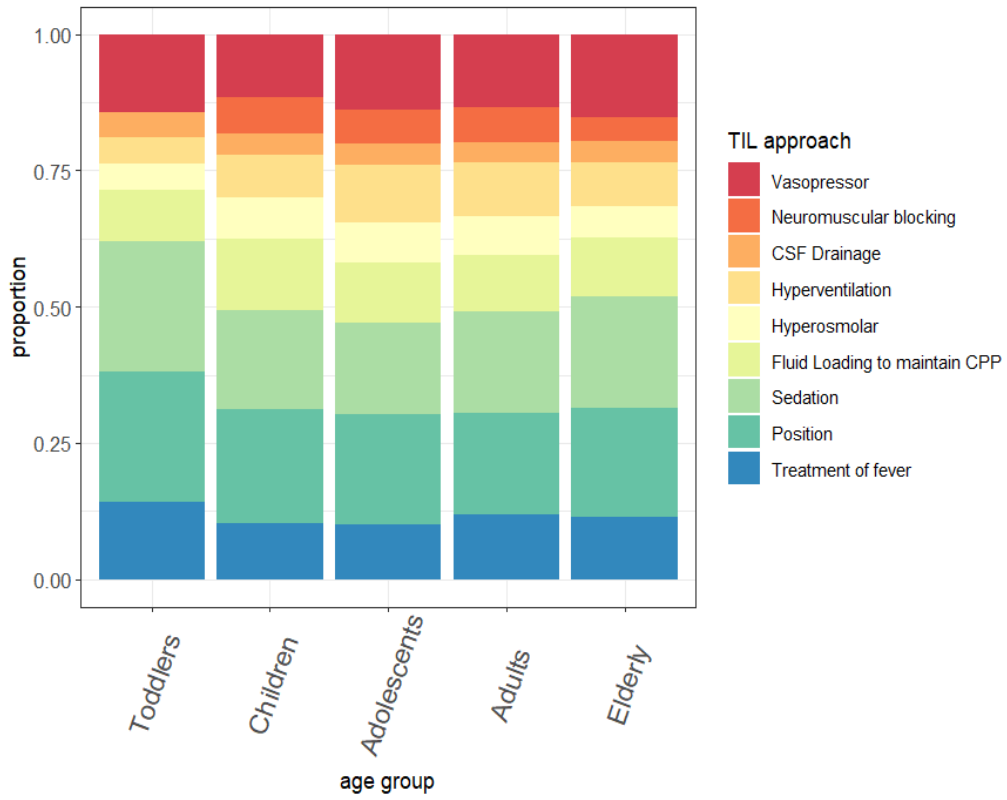
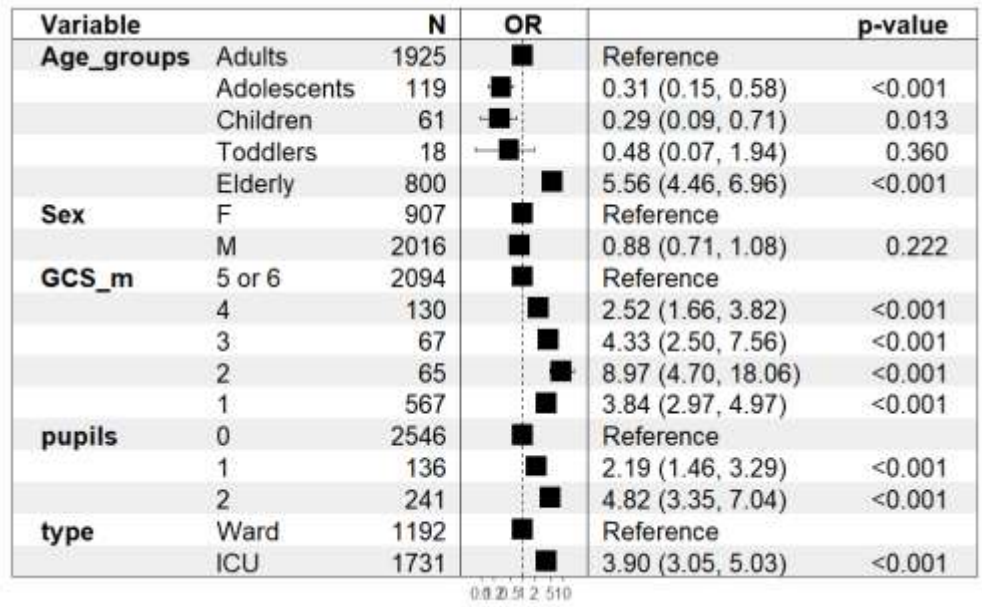


Figure 2. **Multivariable logistic regression model for unfavorable outcome (GOS-E ≤4) at 6 months.** Odds ratios with 95% confidence intervals are shown for relevant predictors of poor functional outcome. Age below 18 years was associated with a lower odds of unfavorable outcome, especially in children and adolescents.

Abbreviations: GOS-E = Glasgow Outcome Scale – Extended; GCS_m = Glasgow Coma Scale motor; ICU = Intensive Care Unit.



Variable		N	OR	p-value
Age_groups	Adults	1925	Reference	
	Adolescents	119	0.31 (0.15, 0.58)	<0.001
	Children	61	0.29 (0.09, 0.71)	0.013
	Toddlers	18	0.48 (0.07, 1.94)	0.360
	Elderly	800	5.56 (4.46, 6.96)	<0.001
Sex	F	907	Reference	
	M	2016	0.88 (0.71, 1.08)	0.222
GCS_m	5 or 6	2094	Reference	
	4	130	2.52 (1.66, 3.82)	<0.001
	3	67	4.33 (2.50, 7.56)	<0.001
	2	65	8.97 (4.70, 18.06)	<0.001
	1	567	3.84 (2.97, 4.97)	<0.001
pupils	0	2546	Reference	
	1	136	2.19 (1.46, 3.29)	<0.001
	2	241	4.82 (3.35, 7.04)	<0.001
type	Ward	1192	Reference	
	ICU	1731	3.90 (3.05, 5.03)	<0.001

Table 1. Characteristics of baseline pediatric populatio

	Pediatrics n=227	Toddlers n=27	Children n=65	Adolescents n=135
Male	146 (64.3)	16 (59.3)	43 (66.2)	87 (64.4)
GCS score				
Mild (GCS 15-13)	139 (65.9)	11 (64.7)	46 (71.9)	82 (63.1)
Moderate (GCS 12-9)	26 (12.3)	3 (17.6)	6 (9.4)	17 (13.1)
Severe (GCS ≤ 8)	40 (21.8)	3 (17.6)	9 (18.8)	28 (23.8)
Baseline Pupils				
Both reactive	205 (91.9)	25 (100)	61 (95.3)	119 (88.8)
One reactive	5 (2.2)	0 (0)	1 (1.6)	4 (3.0)
Both unreactive	13 (5.8)	0 (0.0)	2 (3.1)	11 (8.2)
Total ISS*	18 (10, 32)	16 (9, 22.5)	16 (10, 25)	25 (13, 35.8)
Marshall CT (%)				
1	79 (37.1)	12 (48.0)	26 (41.9)	41 (32.5)
2	111 (52.1)	10 (40.0)	31 (50.0)	70 (55.6)
3	13 (6.1)	1 (4.0)	3 (4.8)	9 (7.1)
4	3 (1.4)	0 (0.0)	1 (1.6)	2 (1.6)
5/6	7 3.3)	2 (8.0)	1 (1.6)	4 (3.2)
Injury cause*				
Road traffic accident	110 (48.7)	5 (18.5)	25 (38.5)	80 (59.7)
Incidental fall	78 (34.5)	20 (74.1)	28 (43.1)	30 (22.4)
Other non-intentional injury	22 (9.7)	2 (7.4)	6 (9.2)	14 (10.4)
Violence/Assault	5 (2.2)	0 (0)	0 (0)	5 (3.7)
Other	11 (4.9)	0 (0)	6 (9.2)	5 (3.7)
Injury place*				
Street/Highway	118 (52.4)	7 (25.9)	24 (36.9)	87 (65.4)
Home/Domestic	40 (17.8)	18 (66.7)	15 (23.1)	7 (5.3)
Work/School	14 (6.2)	1 (3.7)	8 (12.3)	5 (3.8)
Sport/Recreational	40 (17.8)	1 (3.7)	15 (23.1)	24 (18)
Public location	11 (4.9)	0 (0)	3 (4.6)	8 (6)
Other	2 (0.9)	0 (0)	0 (0)	2 (1.5)
Biomarkers within 48 hours				
S100B (pg/ml)	0.23 (0.25)	0.25 (0.23)	0.16 (0.15)	0.25 (0.28)
NSE (ng/mL)	26.74 (11.53)	30.72 (11.07)	27.95 (8.26)	26.00 (12.57)
GFAP (pg/mL)	12.88 (17.85)	4.29 (4.03)	13.08 (22.47)	13.34 (16.21)
UCH-L1 (pg/mL)	244.80 (338.73)	141.09 (140.80)	204.54 (316.44)	268.55 (356.32)
Tau (pg/ml)	8.13 (13.34)	4.39 (5.15)	6.74 (12.42)	8.97 (14.08)
NfL (pg/ml)	45.73 (63.36)	19.50 (16.67)	38.36 (45.78)	50.38 (70.35)

Results are expressed as n (%), mean (standard deviation, SD), or median (I-III quartile); *A significant comparison among age groups (toddlers, children, adolescents) using the adjusted p-value. CT = computed tomography; GCS = Glasgow Coma Scale; ISS = Injury Severity Scale; ISS = Injury Severity Score; S100B = S100 calcium-binding protein B; NSE = neuron-specific enolase; GFAP = Glial-fibrillary-acidic-protein; UCH-L1 = Ubiquitin C-terminal hydrolase; NfL = Neurofilament light chain.

Table 2. Management and monitoring of paediatric TBI patients admitted to the ICU.
Descriptive statistics on monitoring practices (e.g., ICP insertion), therapeutic interventions (e.g., mannitol, hypertonic saline, decompressive craniectomy), respiratory support, and laboratory parameters across pediatric age groups.

	Pediatrics n=132	**Toddlers n=16**	**Children n=35**	**Adolescents n=81**
At the ICU				
ICP monitoring insertion	52 (39.4)	3 (18.8)	12 (34.3)	37 (45.7)
Duration of ICP monitoring (days)	6 (3, 12.3)	3 (3, 8.5)	8 (4, 12)	6 (2, 12.3)
Daily ICP levels (mmHg)	12.69 (10.8)	10.16 (0.15)	12.80 (5.2)	13.53 (15.2)
TIL extreme	30 (22.7)	1 (6.2)	9 (25.7)	20 (24.7)
Total TIL during the ICU stay	3.18 (4.16)	1.23 (2.25)	3.64 (4.91)	3.37 (4.03)
Mannitol dose	56 (24.7)	7 (25.9)	16 (24.6)	33 (24.4)
Hypertonic saline dose	65 (28.6)	8 (29.6)	19 (29.2)	38 (28.1)
Decompressive craniectomy	9 (4.0)	0 (0.0)	4 (6.2)	5 (3.7)
Intracranial surgery	20 (8.8)	3 (11.1)	9 (13.8)	8 (6.0)
Extracranial surgery	25 (11.2)	1 (3.7)	6 (9.2)	18 (13.6)
Mechanical ventilation	87 (46.5)	8 (40.0)	20 (35.7)	59 (53.2)
Tracheostomy*	17 (12.9)	0 (0.0)	0 (0.0)	17 (20.9)
Fluid loading	35 (40.2)	2 (28.6)	10 (40)	23 (41.8)
Need for vasopressor	41 (47.1)	3 (42.9)	9 (36)	29 (52.7)
Hemoglobin values (g/dL)*	11.75 (2.07)	10.62 (1.67)	11.16 (1.77)	12.18 (2.13)
Transfusion of red blood cells	11 (8.3)	2 (12.5)	4 (11.4)	5 (6.2)
Creatinine	53.71 (19.37)	24.31 (5.40)	39.48 (9.15)	62.39 (16.63)

Results are expressed as n (%) or mean (standard deviation, SD) or median (I-III quartiles); ICP = intracranial pressure monitoring; ICU = intensive care unit; TIL = therapy intensity level. *A significant comparison among age groups (toddlers, children, adolescents) using adjusted p-value.

Table 3. Short- and long-term outcomes in paediatric TBI patients.

Key outcome metrics including ICU mortality, 6-month mortality, GOS-E-based functional outcome, and hospital length of stay are reported across paediatric age strata.

Outcomes	Pediatrics	Toddlers	Children	Adolescents
ICU mortality	6 (2.9)	1 (4.8)	1 (1.6)	4 (3.3)
Mortality at 6 months	6 (2.9)	1 (4.8)	1 (1.6)	4 (3.3)
Unfavorable GOS-E	20 (9.8)	2 (9.5)	5 (8.1)	13 (10.7)
Good recovery at 6 months	131 (63.9)	14 (66.7)	34 (54.8)	83 (68)
Length of Stay in hospital (days)	11.87 (18.38)	8.10 (13.77)	9.20 (14.92)	13.93 (20.42)

Results are expressed as n (%) or mean (standard deviation, SD) or median (I-III quartiles); GOS-E = Glasgow Outcome Scale Extended; ICU = intensive care unit

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