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ORIGINAL ARTICLE IMAGING

Computed Tomography Lesions and Their Association With Global Outcome in Young People With Mild Traumatic Brain Injury

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Abstract

Mild traumatic brain injury (mTBI) can be accompanied by structural damage to the brain. Here, we investigated how the presence of intracranial traumatic computed tomography (CT) pathologies relates to the global functional outcome in young patients one year after mTBI. All patients with mTBI (Glasgow Coma Scale: 13–15) ≤24 years in the multi-center, prospective, observational Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study were included. Patient demographics and CT findings were assessed at admission, and the Glasgow Outcome Scale Extended (GOSE) was evaluated at 12 months follow-up. The association between a "positive CT" (at least one of the following: epidural hematoma, subdural hematoma, traumatic subarachnoid hemorrhage (tSAH), intraventricular hemorrhage, subdural collection mixed density, contusion, traumatic axonal injury) and functional outcome (GOSE) was assessed using multi-variable mixed ordinal and logistic regression models. A total of 462 patients with mTBI and initial brain CT from 46 study centers were included. The median age was 19 (17–22) years, and 322 (70%) were males. CT imaging showed a traumatic intracranial pathology in 171 patients (37%), most commonly tSAH (48%), contusions (40%), and epidural hematomas (37%). Patients with a positive CT scan were less likely to achieve a complete recovery 12 months post-injury. The presence of any CT abnormality was associated with both lower GOSE scores (odds ratio [OR]: 0.39 [0.24–0.63]) and incomplete recovery (GOSE <8; OR: 0.41 [0.25–0.68]), also when adjusted for demographical and clinical baseline factors. The presence of intracranial traumatic CT pathologies was predictive of outcome 12 months after mTBI in young patients, which might help to identify candidates for early follow-up and additional care.

Keywords: adolescents; children; CT findings; intracranial lesions; outcome; mild TBI

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Introduction

Traumatic brain injury (TBI) is one of the most common injuries in young people, displaying an overall prevalence of ~30% among individuals ≤25 years.[1–3] The vast majority of those patients (approximately 80–90%) is classified as mild TBI (mTBI), clinically defined by a Glasgow Coma Scale (GCS) of 13–15.[4,5] Although termed ''mild,'' increasing evidence from both pediatric and adult observational studies suggests that in a substantial proportion of patients with mTBI, the injury course is in fact not benign but associated with serious long-term sequelae such as diminished functional capacity and persistent post-concussive symptoms.[6–9]

Computed tomography (CT) scans are typically used to detect brain lesions in the acute care setting. Exposure to radiation, however, poses a strong incentive to limit the use of CT imaging to a very selected group of high-risk patients, especially among young people.[10,11] Still, a study of >43.000 pediatric and adolescent mTBI patients found that 19%–69% of patients undergo CT scanning across hospitals in the United States.[12] At the same time, according to the Center for Disease Control, intracranial injuries are only identified in 7.5% of pediatric and adolescent mTBI patients (<18 years) on brain CT.[13]

While the role of CT imaging to acutely diagnose intracranial brain lesions and guide treatment is widely acknowledged, it is decisively less clear whether the presence of intracranial pathologies on CT imaging can be used to make predictions on the long-term global outcome in young mTBI patients. Earlier studies found no additional value of CT findings compared with clinical predictors alone when predicting global outcome after mTBI in adult cohorts.[14,15]

For example, Jacobs and associates[15] found that age, extracranial injuries, and alcohol intoxication were the most important predictors of outcome, with no additional benefit of including CT findings in the prediction model for functional outcome developed in 2784 mTBI patients.[15] Similarly, CT abnormalities were not predictive of incomplete recovery after mTBI in the UPFRONT study.[16]

In contrast, recent results from large, multi-center observational studies reported a significant association between pathological CT scans and functional outcome.[6,17,18] This was demonstrated in both the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) and Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) mTBI cohorts, also when adjusted for other known outcome predictors.[6,17,18] In a study by Yuh and colleagues,[17] intracranial traumatic CT pathologies were shown to be strongly associated with outcome up to one year post-injury. Those studies were conducted in adults with mTBI.

In this study, we aimed to assess how intracranial findings on CT imaging relate to the global functional outcome 12 months after brain injury in a cohort of young people (children, adolescents, and young adults) with mTBI.

Methods

Study design and patient selection

CENTER-TBI is a prospective, multi-center, observational cohort study of patients presenting with TBI of all severities and was conducted from December 2014 to December 2017 at 65 participating study centers in Europe and Israel.[19] Patients were eligible for enrollment when presenting with a clinical diagnosis of TBI to a participating study center within 24 h and when a CT scan was performed at presentation. The indication for CT imaging was made at the discretion of each participating study center/the treating physician.

The study protocol was approved by the Institutional Review Boards of each participating study center and informed consent from each patient or their legally acceptable representatives was obtained before inclusion. The present study includes children, adolescents, and young adults aged ≤24 years at the time of enrollment who had an available initial brain CT scan and presented with a GCS score of 13–15. Data (CENTER Core version 3.0) were accessed via the clinical study data management tool Neurobot (RRID: SCR_ 017004).

CT imaging

CT scans were reviewed by a central review panel of three trained reviewers (one neuroradiologist with over 25 years of clinical experience and two neuroanatomists with training in head CT reading and 1–2 years of experience[20]) who evaluated the CT characteristics according to the National Institute of Neurological Disorders and Stroke (NINDS) TBI Common Data Elements (TBI-CDE). Reviewers were blinded to clinical information except for sex, age, and clinical care pathway (discharge, admission to the regular ward, intensive care unit (ICU) admission).[20]

For the present study, we defined ''CT Positive'' when any of the following trauma-related intracranial abnormalities were present (vs. absent) on initial brain CT: epidural hematoma (EDH), subdural hematoma (SDH), traumatic subarachnoid hemorrhage (tSAH), intraventricular hemorrhage, subdural collection mixed density, contusion and traumatic axonal injuries (focal hyperdense axonal injuries, including isolated ones that do not span multiple areas of the brain).

''CT Negative'' indicated a non-pathological CT scan or isolated skull fractures (i.e., absence of all the above-mentioned CT characteristics). CT findings coded as ''indeterminate'' by the central reviewers (4 findings)

were counted as negative findings. The final CT report was based on a consensus between the neuroradiologist and one of the two neuroanatomists.[20]

Outcome measure

The primary outcome of this study was the global functional capacity at 12-months follow-up defined by the Glasgow Outcome Scale Extended (GOSE) that ranges from 1 = death to 8 = fully returned to normal life. Complete recovery was defined as a GOSE score of 8, while scores of 7 or lower were regarded as incomplete recoveries.[21]

We used the 12-month GOSE end point variable provided in the Neurobot database, which includes both observed ratings and, when GOSE ratings were missing at 12 months, but available at other time points, centrally imputed values using a multi-state model.[22]

Statistical analysis

Group comparisons were performed using the Mann-Whitney *U* test for continuous variables and Fisher's exact test for categorical variables. Missing data were imputed using multi-level multiple imputation (100 datasets) that included the variables 12-months GOSE (outcome), sex, age, extracranial injury severity scale (ISS), GCS score <15, and intracranial CT abnormality (predictors) and study center (cluster variable).

The ''extracranial'' ISS—to reflect extracranial (poly-)traumatic injuries—was calculated as the sum of ISS[23] scores of all body regions except for those of the brain/head. Missing data were assumed to be missing at random. The association between the presence of an intracranial CT lesion on the 12-month GOSE score was evaluated using mixed ordinal regression models.

We also assessed the association between those predictors and complete recovery at 12 months using mixed logistic regression models. Models were adjusted for age, sex, extracranial ISS, GCS score <15, ± intracranial surgeries, and included a random intercept for study center. Covariables were selected based on previous literature and clinical reasoning.[24–27]

Regressions were performed on the multiply-imputed datasets, and effect estimates were subsequently pooled according to Rubin's rules.[28] Odds ratios and their 95% confidence intervals are reported. The outcome analysis was repeated as a complete-case-analysis ($n = 388$).

As additional analyses, we examined the predictive value of the Rotterdam CT score,[29] which provides an estimation of prognosis based on several CT imaging findings (basal cisterns, midline shift, epidural mass lesion, intraventricular or traumatic SAH), the four most frequent intracranial traumatic CT pathologies (traumatic SAH, contusion, EDH, and SDH), and, in addition, that of isolated skull fractures, using multi-variable ordinal regression models with the same covariables as before.

To examine the added value of CT beyond a model of clinical predictors alone, we performed a likelihood ratio test in the imputed data[30] in the comparing a full model (clinical data + CT abnormality) against a restricted model (clinical data alone). For this analysis, we extended the clinical predictor variables to additionally include injury cause (high- vs. low-energy), American Society of Anesthesiologists Classification class (healthy vs. having a mild, moderate, severe, or life-threatening systemic disease), and psychiatric history.

In addition, area under the curve (AUC) characteristics were calculated for the full and restricted model and were compared using the DeLong test. All analyses were conducted with the software R (version 4.1.1).[31]

Results

Patient characteristics

A total of 462 patients met the inclusion criteria for this study and were enrolled at 46 study centers across Europe. The median age was 19 (17–22) years and 70% were males. Road traffic incidents and incidental falls were the most common injury causes. Seventy-seven percent of individuals presented to the emergency department with a GCS score of 15, and the median extracranial ISS was 10 (5–18).

Admission to the regular ward was the most common clinical care pathway (49%). Thirty-eight patients received an intracranial surgery during the hospital course. Twelve months after mTBI, a complete recovery was achieved by almost 70% of young patients. Only four patients were dead or had severe disability at 12-months follow-up. During the first-year post-injury, 56 (12%) patients received rehabilitation (in-patient and/or outpatient) at least once by the time of the follow-up interview. All analyzed patient characteristics are summarized in Table 1.

Indications for CT imaging

The most reported reason to perform a brain CT scan in our study population was the presence of a risk factor in a patient with a GCS score of 15 (Supplementary Table S2). The second most common reason was the presence of a head wound (27%), followed by a GCS score <15. In a minority of patients, exclusion of brain injuries before discharge (13%) or suspicion of maxillofacial injuries (9%) was given as the reason to perform CT imaging. Multiple risk factors, however, could be selected for an individual patient in the CENTER-TBI questionnaire by the treating physician.

CT pathologies

Intracranial traumatic CT pathology (''CT Positive'') was detected in 171 of 462 patients (37%; Fig. 1). Among those, the most common pathologies on brain

Table 1. Patient Characteristics, Clinical Baseline Status, and Outcome in Patients With Mild Traumatic Brain Injury ≤24 Years in the CENTER-TBI Study

Variable	*Total (n = 462)*	*CT Positive (n = 171)*	*CT Negative (n = 291)*	p	*Missing/Unknown*
Age	19 (17-22)	19 (16-22)	19 (17-22)	0.433	0 (0%)
Sex				<0.001	0 (0%)
Female	140 (30%)	35 (21%)	104 (36%)		
Male	322 (70%)	136 (80%)	186 (64%)		
Care Pathway				<0.001	0 (0%)
ER discharge	132 (29%)	10 (6%)	122 (42%)		
Ward admission	225 (49%)	84 (49%)	141 (49%)		
ICU admission	105 (23%)	77 (45%)	28 (10%)		
Prior TBI	53 (12%)	15 (9%)	38 (13%)	0.126	12 (3%)
Injury Cause				0.113	2 (<1%)
Road-traffic incident	191 (41%)	79 (46%)	112 (39%)		
Incidental fall	165 (36%)	49 (29%)	116 (40%)		
Other non-intentional injury	39 (8%)	13 (8%)	26 (9%)		
Violence/assault	46 (10%)	20 (12%)	26 (9%)		
Suicide attempt	2 (<1%)	0 (0%)	2 (<1%)		
Other	17 (4%)	9 (5%)	8 (3%)		
Alcohol				0.095	21 (5%)
Definite	68 (15%)	20 (13%)	48 (17%)		
Suspected	21 (5%)	10 (6%)	11 (4%)		
Drugs				0.297	38 (8%)
Definite	10 (2%)	6 (4%)	4 (1%)		
Suspected	5 (1%)	2 (1%)	3 (1%)		
GCS score				<0.001	0 (%)
13	24 (5%)	15 (9%)	9 (3%)		
14	83 (18%)	45 (26%)	38 (13%)		
15	355 (77%)	111 (65%)	244 (84%)		
LOC				0.699	44 (10%)
Yes	201 (48%)	79 (50%)	122 (47%)		
Suspected	55 (13%)	17 (11%)	38 (15%)		
PTA				0.010	51 (11%)
Ongoing	65 (16%)	28 (20%)	37 (14%)		
Resolved	140 (34%)	47 (33%)	93 (34%)		
Suspected	12 (3%)	4 (3%)	8 (3%)		
Alteration of Consciousness				<0.001	54 (12%)
Yes, immediate	77 (19%)	29 (19%)	48 (19%)		
Not tested (LOC)	53 (13%)	22 (15%)	31 (12%)		
Suspected	11 (3%)	8 (5%)	3 (1%)		
Delayed onset	12 (3%)	9 (6%)	3 (1%)		
Extracranial ISS (median)	1 (0-9)	4 (0-9)	1 (0-8)	0.170	0 (0%)
Total ISS (median)	10 (5-18)	16 (9-25)	9 (4-13)	<0.001	1 (<1%)
GOSE at 12 months					74 (16%)
Full recovery	268 (69%)	80 (54%)	188 (77%)	<0.001	
Incomplete recovery	120 (31%)	68 (46%)	52 (21%)	<0.001	
Unfavorable outcome	4 (<1%)	0 (%)	4 (2%)	0.302	

CT = Computed tomography, ER, emergency room; ICU, intensive care unit; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; LOC, Loss of consciousness; ISS, Injury severity score; GOSE = Glasgow Outcome Scale Extended,

CT were tSAHs (48%), followed by contusions (40%), and epidural hematomas (37%). Acute subdural hematomas were identified in 29% of CT positive patients and traumatic axonal injuries in 14%. Intraventricular hemorrhages (4 patients) and subdural collection mixed densities (1 patient) were rare.

Comparison of "CT Positive" and "CT Negative" patients

Individuals with a positive CT scan displayed a higher proportion of male sex as well as differences regarding a history of alteration of consciousness and post-traumatic amnesia (Supplementary Table S1). Moreover, ''CT Positive'' patients were more likely to present with a GCS score <15 (35% vs. 16%). While there was no significant difference in extracranial ISS, the median total ISS was significantly higher in individuals with a positive CT scan (16 [9–25] vs. 9 [4–13]).

A difference between the two groups was also found regarding the clinical care pathway, where ''CT Positive'' patients were much more frequently admitted to the ICU (45% vs. 10%). While 77% of patients with a negative CT scan achieved full recovery (GOSE = 8) one year after brain injury, this was only the case in 54% of patients with a positive CT scan ($p < 0.001$).

Association of CT lesions and GOSE in multi-variable analyses

Mixed ordinal regression models were used to assess the association between traumatic intracranial CT

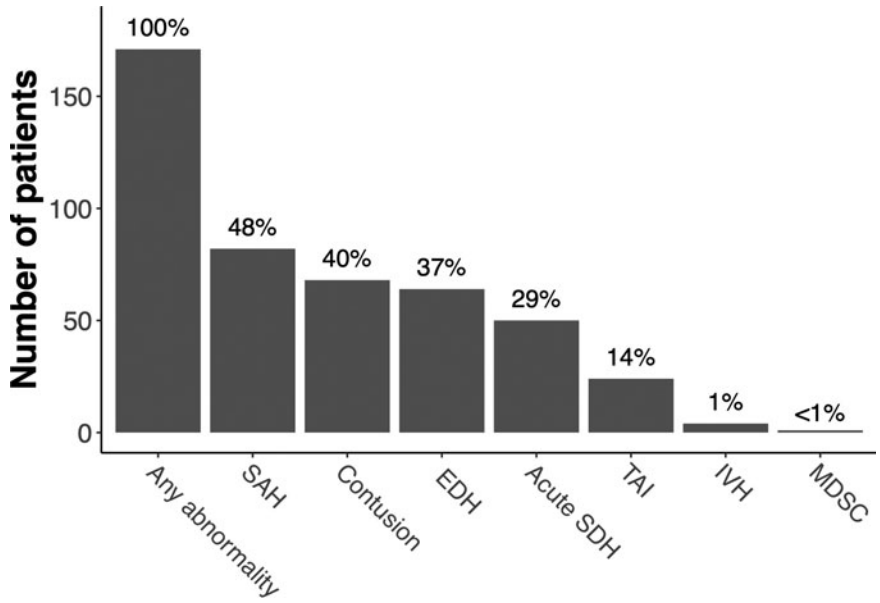

FIG. 1. Occurrence of intracranial traumatic pathologies on CT imaging.

abnormalities and GOSE scores 12 months post-injury with adjustment for the demographical variables age and sex, and the clinical variables GCS score <15 and extracranial ISS.

The presence of an intracranial pathology on brain CT scan was associated with a lower likelihood of achieving higher 12-month GOSE scores (adjusted odds ratios [OR 0.387, $0.237 - 0.633$; Supplementary Table 2). Similarly, the presence of any intracranial lesion was associated with a lower likelihood of full recovery one year after mTBI (adjusted OR 0.409 [0.248– 0.675]).

The complete-case-analyses of the same models yielded similar results (Supplementary Table S3). The Rotterdam CT score was significantly associated with the 12-months outcome even in our cohort of young mTBI patients, but the odds ratios were comparable or even smaller than for the ''intracranial pathology'' variable (Supplementary Tables S4 and S5).

The association between intracranial CT abnormalities and 12-months GOSE scores remained statistically significant when also including intracranial surgeries as a predictor in the model (adjusted OR 0.31 [0.19–0.53], Supplementary Tables S6 and S7). On the other hand, the presence of isolated skull fractures (i.e., without traumatic intracranial abnormalities) was not significantly associated with GOSE scores at 12 months post-injury (Supplementary Tables S8 and S9).

Association between tSAH, EDH, SDH, contusion and GOSE

The tSAH (adjusted OR 0.52 [$0.30 - 0.89$]), EDH (adjusted OR 0.41 (0.23–0.73]), and SDH (adjusted OR 0.52 [0.29–0.96]) were significantly associated with a lower likelihood of achieving higher GOSE scores at 12 months (Supplementary Table S10 A–C). Contusion was also associated with GOSE outcome; however, this association had wider confidence intervals (Supplementary Table 10 D).

Comparison of a model with clinical predictors + CT pathology versus a model with clinical predictors only

Finally, we tested whether including intracranial traumatic CT pathology significantly adds to the predictive capability of a model with clinical variables only. The model with clinical data plus CT abnormality showed a significantly better fit than the model with clinical data alone (F-value 19.4, $p < 0.001$), indicating that the presence of a CT abnormality has a predictive value beyond clinical data alone in this cohort. Further, the AUC for the model with clinical data plus CT abnormality was significantly greater than that of the model with clinical data only (0.71 [95% confidence interval [CI] 0.65–0.77] vs. 0.65 [95% CI 0.59–0.71], DeLong test: $p = 0.029$).

Discussion

In this study, the presence of intracranial traumatic CT pathologies was predictive of lower GOSE scores and incomplete recovery 12 months post-injury in a cohort of young people with mTBI. While the value of CT imaging for the detection of significant brain lesions is well-established, its role in predicting long-term outcome remains controversial.

On one hand, some studies showed no additional value compared with clinical factors alone; on the other hand, recent multi-center studies demonstrated a significant association with poorer outcome.[6,15,17,18] Of note, those studies were conducted in adult patients with TBI and data in younger cohorts, especially regarding long-term outcome, are scarce.

Because CT scans are performed in a considerable proportion of patients even in the young population, such young people form a large and clinically important group of patients with TBI at risk of being understudied.[12] Levin and associates described a significant relation between CT abnormalities and diminished neuropsychological recovery in children with mTBI over the first year.[32,33]

With a median age of 19 years, which is distinctively lower than in previous (adult) studies, our patient cohort of young people further underlines the association between the presence of traumatic intracranial CT abnormalities and global GOSE scores 12 months after TBI.[12] This is a clinically important finding, because identifying patients at risk for an incomplete recovery is an essential aim in the management of mTBI.

First, providing an accurate prognosis is important for patients and their relatives. Second, despite a general lack of high-quality studies, there is evidence that interventions such as patient education as well as psychological and rehabilitative measures can be effective to treat mTBI symptoms in both young and adult patients.[34–36]

The results of this study thus indicate that the presence of intracranial CT findings should be considered when predicting the outcome of young patients with mTBI, especially because adding the variable intracranial CT abnormality was found to improve the predictive ability of a ''clinical variables only'' model.

Of note, the Rotterdam CT score had no greater predictive value than the presence of any intracranial traumatic CT pathology in our cohort of young patients with mTBI. An explanation could be that this score was developed for adults with moderate to severe TBI, and its predictive value might be limited in the setting of mTBI. In fact, its first two categories (basal cisterna compression and midline shift) are rarely seen in mTBI, and in our cohort, more than 80% of patients were given a Rotterdam CT score of 2, suggesting that it was more of a general indicator of intracranial lesion than a measure of lesion severity in this setting.

In this study, we focused on intracranial abnormalities on CT and did not analyze abnormalities on magnetic resonance imaging (MRI). CT imaging is suitable for the detection of intracranial hemorrhages and contusions; however, it might miss small cortical contusions and hemorrhagic axonal injuries that are detectable by MRI.[37–39] In fact, 27% of patients with mTBI and normal CT scans on admission had abnormal findings on early brain MRI in the multi-center TRACK-TBI study.[37]

Subtle changes in the white matter detected by early (advanced) MRI scans have shown to be associated with functional recovery and post-concussion symptoms,[40] and additional MRI findings might improve outcome prediction compared with clinical and CT characteristics alone.[37]

While the role of CT is firmly established in the acute TBI care, however, the utility of MRI in the early management setting remains unclear. In light of high costs, often limited access, low frequency of findings, and possibly limited treatment consequences, MRI findings, as opposed to CT findings, will currently not be available for outcome prediction in most health care settings.

This study emphasizes the need for more research on mTBI in young people. Although widely regarded as a benign disease entity, almost one third of our study participants did not achieve complete recovery 12 months after the injury. While they were by study design (indication for CT imaging as an inclusion criterion) likely on the more serious spectrum of mTBI, this still aligns well with recent evidence from multiple studies about the unfavorable implications of sustaining a mTBI.[6,9,41,42]

We acknowledge several limitations of this study. While CENTER-TBI was open for patients of all ages, pediatric patients were underrepresented, because most centers were general hospitals, which often had separate pediatric units for children with TBI. Therefore, our sample size was limited compared with the overall CENTER-TBI core study population.

Another implication is that our cohort of young patients ≤24 years consists mostly of adolescents and young adults with relatively few children. Because of the low numbers of younger children, we did not conduct a sensitivity analysis either to explore the predictive value of head CT imaging specifically at younger ages. Therefore, our results are not generalizable to young children, and more studies are needed in this even younger age group.

It has also to be mentioned that the term ''CT positive'' encompasses a broad range of intracranial pathologies, which might have different implications for the outcome. Of note, the rate of ''traumatic axonal injuries'' reported in our study must be interpreted with caution, because such lesions can be challenging to identify on CT imaging and tend to be over- or underrated.[20]

Also, because of the observational study design, interventions and treatments might have differed between centers and were not analyzed in this study. While we did not perform further analyses with subclassifications into single lesions because of limited patient numbers, further studies are needed to address this important question. Similarly, because even our superior prediction model including cranial CT imaging displayed only a moderate AUC of 0.71, further studies are also needed to investigate and develop more accurate predictive models for young patients with mTBI. Last, imaging

characteristics at the time of follow-up (one year) were not available and could thus not be correlated with the outcome.

Conclusion

We found that intracranial traumatic CT pathologies were significantly associated with an increased likelihood of lower global outcome 12 months after mTBI in individuals ≤24 years in the CENTER-TBI study. This information might be used to develop protocols that aim to identify young patients with mTBI at risk for an incomplete recovery who might benefit from closely monitored follow-up and early treatment interventions.

Acknowledgments

Results of this study have been presented at the 73th annual meeting of the German Society of Neurosurgery, the annual meeting of the European Association of Neurological Societies 2021, and the 15th International Neurotrauma Symposium.

Ethics Statement

Ethical approval was obtained for each recruiting site. A complete list is given on https://www.center-tbi.eu/project/ethical-approval. All patients had to give their informed consent prior to enrollment in CENTER-TBI.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Table S1
Supplementary Table S2
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Supplementary Table S8
Supplementary Table S9
Supplementary Table S10

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