Supplemental Online Content

Nattino G, Gamberini L, Brissy O, et al; CREACTIVE Consortium. Comparative effectiveness of intracranial pressure monitoring on 6-month outcomes of critically ill patients with traumatic brain injury. *JAMA Netw Open*. 2023;6(9):e2334214. doi:10.1001/jamanetworkopen.2023.34214

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. HOMOGENEITY AND QUALITY OF THE DATA

A senior intensivist (see Appendix) is responsible for protocol and data integrity at each ICU. A detailed definition of all items to collect is immediately visible in the layout of the electronic case report form (eCRF) and a comprehensive, user-friendly, fully indexed, online, operative manual can be easily accessed during data entry.

A complex, multidimensional, validation system ensures maximum data quality. A first level of controls is implemented behind the data collection and follows three different rules: grouping, enabling or disabling, and mutually excluding items. Second-level controls come into operation during data collection and include: completeness checks, warnings on borderline values, and errors. They are of five types: validity (e.g., incorrect date); plausibility (e.g., very high body mass index); logical congruency (e.g., hospital discharge cannot precede ICU discharge); clinical congruency (e.g., a patient with acute respiratory distress syndrome - ARDS - cannot have PaO2/FiO2>200); score congruency (e.g., a patient with brain coma cannot have Glasgow Coma Scale - GCS - >8). The system allows inconsistent or implausible data to be saved but marks the record as problematic.

The data of each individual unit are synchronized with the central server every 12 hours and centrally processed, searching for inconsistencies that cannot be automatically picked up by the system during data input (e.g., the average mortality of patients with a GCS of 3 should not be lower than in patients with a GCS of 4-5). A data quality report with any remaining unsolved queries is produced twice a year and sent to the centers.

To ensure complete patient recruitment, queries are sent to centers with significant heterogeneity in the number of monthly admissions, assessed using the Chi-square test. Finally, to avoid selection bias, patients admitted in months with over 10% incomplete or inconsistent records (presence of errors or unsolved warnings) were excluded.

Site visits are performed by certified monitors on a random sample of participating ICUs to assess the correspondence between medical records and data entered in the eCRF.

After passing the validation system, data from ICUs with at least four months' valid data were merged to form the aggregate database, ready for statistical analyses.

eAppendix 2. SENSITIVITY ANALYSIS FOR NON-MISSING OUTCOME SELECTION

Of the 1,837 patients eligible for the main analysis, we excluded the 389 (21.2%) patients lost at the 6-month follow-up evaluation (see Figure 1 of the paper). In this sensitivity analysis, we aimed to evaluate whether the selection of patients with non-missing outcome impacted the study results.

First of all, we report in Table S.1 the distribution of the pre-treatment covariates for patients with missing and non-missing outcomes. We observed significant differences in key confounders, such as age, whether the patient underwent surgical intervention, primary head injury, cardiovascular failure at ICU admission, and Marshall CT classification. Such differences suggest that the excluded patients were not a random sample of the patients eligible for the analysis.

To enhance the generalizability of our study results, we addressed the missing data problem with a weighting method (Little and Rubin, Statistical Analysis with Missing Data, 2002). First, the probability of a non-missing outcome was estimated, based on the sample including both patients with non-missing and missing outcomes. Second, when performing statistical analyses on the patients with non-missing outcomes, individuals were weighted by the inverse of the estimated probability, reconstructing the result of the analyses on the sample that included all the patients. Since our main analyses, based on a full matching design, already required weighted procedures, we were able to naturally integrate this missing data approach into the main analyses, by considering weights that were the product of the matching weights (making control and treated patients similar) and missing outcome weights (generalizing the estimates to the whole study sample).

We estimated the probabilities of non-missing outcomes using logistic regression. The estimated odds ratios and the corresponding 95% confidence intervals are provided in Table S.2. Model calibration was evaluated with the Hosmer-Lemeshow goodness-of-fit test (statistic: 12.02, degrees of freedom: 8, p-value: 0.15) and the calibration belt (Figure S.1). No evidence of lack of fit emerged from either of the two approaches.

The model was used to compute the estimated probabilities for all 1,448 patients with non-missing outcomes, included in the main analysis. The distribution of these probabilities is reported in the left panel of Figure S.2, which shows that most are in the 80-90% range, with no patients characterized by very small probabilities, which would result in very large weights. The right panel of Figure S.2 depicts the distribution of the weights, defined as the inverse of these probabilities. The weights were standardized so that the total would correspond to the actual sample size.

Before using the product of the matching weights and missing outcome weights to estimate the effect of ICP monitoring on all the eligible patients, regardless of the missingness of the outcome, we verified that the product of the weights balanced all the confounders, using weighted standardized mean differences (Table S.3). All of the values were smaller than 10%, suggesting that the computed weights were sufficient to make the treated and control groups comparable with respect to key confounders. The balance was also evaluated by comparing the distribution of demographic and clinical characteristics on ICU admission after weighting (Table S.4).

Table S.5 compares the primary and secondary outcomes of the study between patients receiving and not receiving ICP monitoring, after weighting for matching and missing outcome weights. These results adjust the estimates for nonrandom treatment allocation and for the selection of patients with non-missing outcomes. Notably, the similarity of these estimates with those presented in the main analysis (Table 3 of the paper), based on complete patients, supports the robustness of our results to the exclusion of patients with non-missing outcomes.

Table S.1. Distribution of demographic and clinical characteristics of the eligible patients at ICU admission, separately for patients with missing and non-missing 6-month outcome.

Variables		Missing outcome	Non-missing outcome	p-value
N		389	1448	
Age				< 0.001
	Mean (SD)	50.5 (20.3)	56.3 (21.0)	
	Median (Q1-Q3)	50.0 (33.0, 66.0)	59.0 (40.0, 75.0)	
Sex (Female) – N (%)		102 (26.2%)	400 (27.6%)	0.58
Comorbidities – N (%)				
Any comorbidity[3]		176 (45.2%)	777 (53.7%)	0.003
Antiplatelet therapy		28 (7.2%)	133 (9.2%)	0.22
COPD		13 (3.3%)	59 (4.1%)	0.51
Dementia		7 (1.8%)	31 (2.1%)	0.67
Drug-induced coagulopathy		13 (3.3%)	75 (5.2%)	0.13
Heart failure		8 (2.1%)	38 (2.6%)	0.53
Liver disease		16 (4.1%)	44 (3.0%)	0.29
Renal disease		4 (1.0%)	35 (2.4%)	0.09
Penetrating trauma – N (%)		7 (1.8%)	49 (3.4%)	0.11
Pre-treatment GCS – N (%)				0.99
	Mean (SD)	5.3 (1.8)	5.3 (1.9)	
	Median (Q1-Q3)	6.0 (3.0, 7.0)	6.0 (3.0, 7.0)	
Main lesion – N (%)				
	Cerebral contusion/laceration	111 (28.5%)	370 (25.6%)	0.23
	Extradural/epidural hematoma	33 (8.5%)	79 (5.5%)	0.03
	Traumatic subdural hematoma	115 (29.6%)	499 (34.5%)	0.07
	Intraparenchymal bleeding	21 (5.4%)	139 (9.6%)	0.009
	Diffuse injury without edema	45 (11.6%)	141 (9.7%)	0.29
	Diffuse injury with edema	13 (3.3%)	60 (4.1%)	0.47
	Subarachnoid hemorrhage	42 (10.8%)	148 (10.2%)	0.74
	Skull fracture	9 (2.3%)	12 (0.8%)	0.01
Injuries other than TBI[4] – N (%)				
	Abdomen	44 (11.3%)	156 (10.8%)	0.76
	Chest	144 (37.0%)	482 (33.3%)	0.17
	Pelvis, bones, joints and muscles	96 (24.7%)	356 (24.6%)	0.97
	Major vessels	9 (2.3%)	44 (3.0%)	0.45
	Spine	85 (21.9%)	326 (22.5%)	0.78
	Other	3 (0.8%)	6 (0.4%)	0.37
Pupils at ED arrival – N (%)				0.009
	Bilaterally reactive/miotic	286 (73.5%)	964 (66.6%)	
	Unilaterally dilated/non-reactive	103 (26.5%)	484 (33.4%)	
Hypotension – N (%)				0.13
Yes		61 (15.7%)	258 (17.8%)	
No		298 (76.6%)	1114 (76.9%)	
Information not available		30 (7.7%)	76 (5.2%)	

Variables	Missing outcome	Non-missing outcome	p-value
Hypoxia – N (%)			0.17
Yes	123 (31.6%)	445 (30.7%)	
No	228 (58.6%)	900 (62.2%)	
Information not available	38 (9.8%)	103 (7.1%)	
Transfer from another ICU due to hospital expertise – N (%)	13 (3.3%)	27 (1.9%)	0.08
Surgery before ICU admission – N (%)	169 (43.4%)	741 (51.2%)	0.007
Neurosurgery within 2 days from injury[5] – N (%)	124 (31.9%)	547 (37.8%)	0.03
Cardiovascular failure at ICU admission – N (%)			< 0.001
None	252 (64.8%)	776 (53.6%)	
Without shock	58 (14.9%)	323 (22.3%)	
With shock	79 (20.3%)	349 (24.1%)	
Metabolic failure at ICU admission – N (%)	69 (17.7%)	341 (23.5%)	0.01
Renal failure at ICU admission – N (%)	36 (9.3%)	181 (12.5%)	0.08
Worst CT scan of the first 48h in ICU – N (%)			
Marshall scale			< 0.001
Diffuse Injury I	34 (8.7%)	113 (7.8%)	
Diffuse Injury II	187 (48.1%)	501 (34.6%)	
Diffuse Injury III	33 (8.5%)	154 (10.6%)	
Diffuse Injury IV	13 (3.3%)	60 (4.1%)	
Mass lesion (V or VI)	122 (31.4%)	620 (42.8%)	
Midline shift >5mm	100 (25.7%)	514 (35.5%)	< 0.001
Lesion volume >25ml	87 (22.4%)	516 (35.6%)	< 0.001
Petechiae	166 (42.7%)	668 (46.1%)	0.22
Cistern condition			< 0.001
Normal	227 (58.4%)	626 (43.2%)	
Compressed or distorted	124 (31.9%)	604 (41.7%)	
Absent	38 (9.8%)	218 (15.1%)	

Table S.2. Estimated odds ratios (ORs) and corresponding 95% confidence intervals of the logistic regression model estimating the probability of non-missing outcome.

Variables		OR (95% CI)
Age		1.15 (1.07,1.23)
Sex (female vs. male)		0.97 (0.74,1.27)
Comorbidities		
	Antiplatelet therapy (Yes vs. No)	0.96 (0.60,1.53)
	COPD (Yes vs. No)	0.99 (0.51,1.90)
	Dementia (Yes vs. No)	0.76 (0.32,1.84)
	Drug-induced coagulopathy (Yes vs. No)	0.97 (0.51,1.83)
	Cardiac disease (Yes vs. No)	0.73 (0.32,1.69)
	Liver disease (Yes vs. No)	0.67 (0.36,1.25)
	Renal disease (Yes vs. No)	1.91 (0.63,5.81)
Penetrating trauma (Yes vs. No)		2.00 (0.84,4.78)
Pre-treatment GCS		
	3	0.83 (0.56,1.22)
	4-5	0.74 (0.49,1.09)
	6-7	0.85 (0.59,1.21)
	8	1 (ref.)
Main lesion		
	Cerebral contusion/laceration	3.95 (1.45,10.78)
	Extradural/epidural hematoma	2.20 (0.74,6.54)
	Traumatic subdural hematoma	3.49 (1.26,9.70)
	Intraparenchymal bleeding	5.87 (1.98,17.43)
	Diffuse injury without edema	4.89 (1.73,13.84)
	Diffuse injury with edema	4.91 (1.53,15.74)
	Subarachnoid hemorrhage	3.03 (1.14,8.07)
	Skull fracture	1 (ref.)
Injuries other than TBI		
	Abdomen (Yes vs. No)	1.01 (0.67,1.52)
	Chest (Yes vs. No)	0.84 (0.63,1.12)
	Pelvis, bones, joints and muscles (Yes vs. No)	1.05 (0.78,1.43)
	Major vessels (Yes vs. No)	1.43 (0.67,3.05)
	Spine (Yes vs. No)	1.11 (0.81,1.52)
Pupils at ED arrival unilaterally dilated/non-reactive (Yes vs. No)		1.13 (0.85,1.50)
Hypotension (Yes vs. No)		1.04 (0.73,1.49)
Hypoxia (Yes vs. No)		0.94 (0.72,1.22)
Transfer from another ICU due to hospital expertise (Yes vs. No)		0.52 (0.26,1.06)
Surgery before ICU admission (Yes vs. No)		1.38 (0.93,2.04)
Neurosurgery within 2 days from injury (Yes vs. No)		0.79 (0.50,1.27)
Cardiovascular failure on ICU admission		
	None	1 (ref.)
	Without shock	1.67 (1.20,2.32)
	With shock	1.09 (0.77,1.53)
Metabolic failure at ICU admission (Yes vs. No)		1.36 (0.98,1.87)

Variables		OR (95% CI)
Renal failure at ICU admission (Yes vs. No)		0.97 (0.63,1.47)
Marshall CT classification		
	Diffuse Injury I	1 (ref.)
	Diffuse Injury II	1.23 (0.61,2.47)
	Diffuse Injury III	1.44 (0.65,3.16)
	Diffuse Injury IV	1.78 (0.65,4.91)
	Mass lesion (V or VI)	1.24 (0.54,2.86)
Midline shift >5mm (Yes vs. No)		0.83 (0.49,1.42)
Lesion volume >25ml (Yes vs. No)		1.74 (1.07,2.82)
Petechiae (Yes vs. No)		1.33 (1.01,1.75)
Cistern condition		
	Normal	1 (ref.)
	Compressed or distorted	1.36 (0.82,2.25)
	Absent	2.67 (1.41,5.07)

Figure S.1. Calibration belt of the logistic regression model estimating the probability of non-missing outcome.

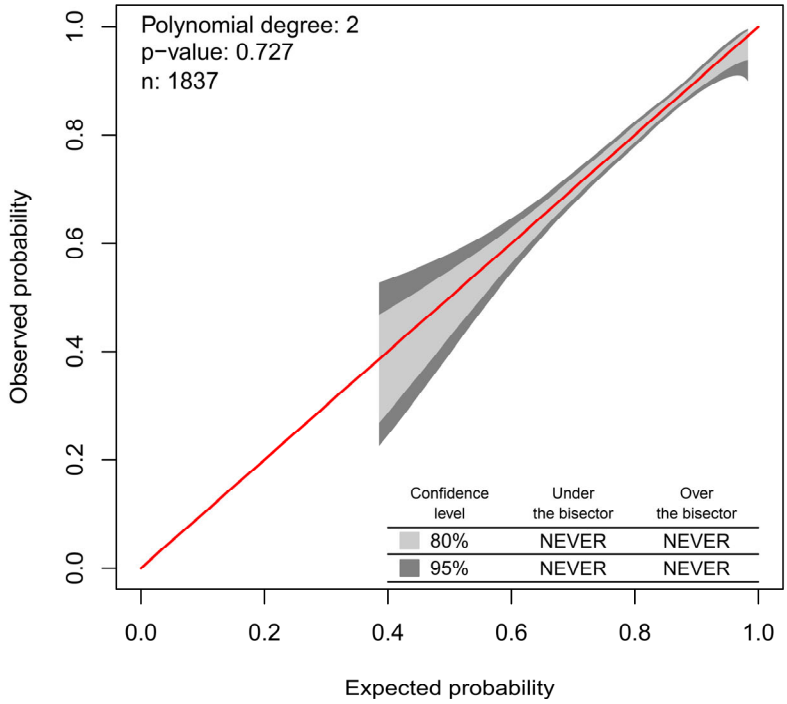


Figure S.2. Distribution of the estimated probabilities of non-missing outcome and corresponding weights, computed as the inverse of the probabilities.

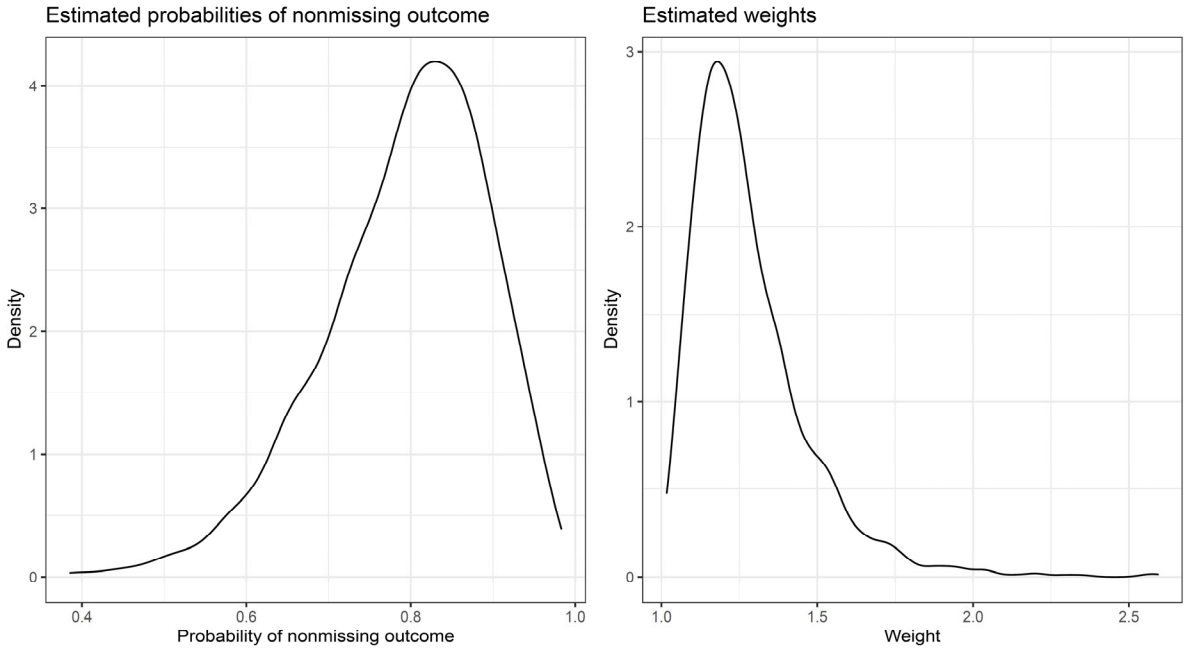


Table S.3. Absolute weighted standardized mean differences (SMDs) comparing the treatment groups on all pre-treatment variables. The SMDs are weighted using the product of the matching and missing outcome weights.

Variables	Absolute weighted SMDs
Age	0.008
Sex (Female)	0.085
Comorbidities	
Antiplatelet therapy	0.006
COPD	0.003
Dementia	0.013
Drug-induced coagulopathy	0.020
Heart failure	0.078
Liver disease	0.072
Renal disease	0.002
Penetrating trauma	0.038
Pre-treatment GCS	0.083
Main lesion	
Cerebral contusion/laceration	0.021
Extradural/epidural hematoma	0.011
Traumatic subdural hematoma	0.012
Intraparenchymal bleeding	0.063
Diffuse injury without edema	0.079
Diffuse injury with edema	0.050
Subarachnoid hemorrhage	0.011
Skull fracture	0.031
Injuries other than TBI	
Abdomen	0.013
Chest	0.054
Pelvis, bones, joints, and muscles	0.051
Major vessels	0.001
Spine	0.059
Pupils at ED arrival unilaterally dilated/non-reactive	0.005
Hypotension	0.014
Hypoxia	0.001
Transfer from another ICU due to hospital expertise	0.033
Surgery before ICU admission	0.013
Neurosurgery within 2 days from injury	0.074
Cardiovascular failure at ICU admission	
None	0.025
Without shock	0.061
With shock	0.035
Metabolic failure at ICU admission	0.033
Renal failure at ICU admission	0.026
Marshall CT classification	

Variables		Absolute weighted SMDs
	Diffuse Injury I	0.020
	Diffuse Injury II	0.060
	Diffuse Injury III	0.059
	Diffuse Injury IV	0.044
	Mass lesion (V or VI)	0.009
Midline shift >5mm		0.005
Lesion volume >25ml		0.019
Petechiae		0.061
Cistern condition		
	Normal	0.095
	Compressed or distorted	0.093
	Absent	0.004

Table S.4. Demographic and clinical characteristics at ICU admission of the patients after weighting for both matching and missing outcome weights.

Variables		No ICP monitoring	ICP monitoring	p-value
N		945	503	
Weighted N		503	503	
Age				0.90
	Mean (SD)	45.1 (18.2)	45.0 (18.5)	
	Median (Q1-Q3)	43.0 (29.0-58.0)	44.0 (29.0-60.0)	
Sex (Female) – %		18.4%	21.8%	0.13
Comorbidities – %				
Any comorbidity		38.0%	34.0%	0.17
Antiplatelet therapy		4.7%	4.9%	0.92
COPD		2.2%	2.2%	0.96
Dementia		0.3%	0.4%	0.97
Drug-induced coagulopathy		2.4%	2.7%	0.67
Heart failure		0.6%	1.3%	0.46
Liver disease		3.4%	2.2%	0.22
Renal disease		0.5%	0.5%	0.99
Penetrating trauma – %		3.7%	4.4%	0.57
Pre-treatment GCS – %				0.18
	Mean (SD)	5.1 (1.8)	5.2 (1.8)	
	Median (Q1-Q3)	5 (3-7)	5 (3-7)	
Main lesion – %				
	Cerebral contusion/laceration	33.1%	32.2%	0.73
	Extradural/epidural hematoma	8.6%	8.3%	0.89
	Traumatic subdural hematoma	26.8%	27.3%	0.84
	Intraparenchymal bleeding	7.9%	9.7%	0.33
	Diffuse injury without edema	10.5%	8.3%	0.13
	Diffuse injury with edema	6.1%	7.3%	0.52
	Subarachnoid hemorrhage	6.3%	6.5%	0.84
	Skull fracture	0.6%	0.4%	0.94
Injuries other than TBI – %				
	Abdomen	12.7%	12.3%	0.84
	Chest	39.9%	42.5%	0.40
	Pelvis, bones, joints and muscles	24.6%	26.8%	0.35
	Major vessels	3.6%	3.6%	0.98
	Spine	25.3%	27.9%	0.34
	Other	0.3%	0.6%	0.90
Pupils at ED arrival – %				0.94
	Bilaterally reactive/miotic	67.4%	67.6%	
	Unilaterally dilated/non-reactive	32.6%	32.4%	
Hypotension – %				0.93
	Yes	16.9%	17.4%	

Variables	No ICP monitoring	ICP monitoring	p-value
No	78.6%	77.8%	
Information not available	4.5%	4.8%	
Hypoxia – %			0.76
Yes	33.7%	33.7%	
No	58.8%	59.9%	
Information not available	7.5%	6.4%	
Transfer from other ICU for hospital expertise – %	3.4%	2.9%	0.67
Surgery before ICU admission – %	59.5%	60.1%	0.83
Neurosurgery within 2 days from injury – %	41.6%	45.2%	0.28
Cardiovascular failure on ICU admission – %			0.62
None	41.3%	40.0%	
Without Shock	29.3%	32.1%	
With Shock	29.5%	27.9%	
Metabolic failure on ICU admission – %	25.4%	24.0%	0.60
Renal failure on ICU admission – %	6.6%	7.3%	0.64
Worst CT scan of the first 48h in ICU – %			
Marshall scale			0.73
Diffuse Injury I	4.2%	3.8%	
Diffuse Injury II	37.9%	35.0%	
Diffuse Injury III	13.8%	15.9%	
Diffuse Injury IV	2.6%	3.4%	
Mass lesion (V or VI)	41.4%	41.8%	
Midline shift >5mm	31.0%	31.2%	0.93
Lesion volume >25ml	32.9%	33.8%	0.78
Petechiae	48.7%	51.8%	0.36
Cistern condition			0.31
Normal	47.8%	43.0%	
Compressed or distorted	42.1%	46.7%	
Absent	10.2%	10.3%	

Table S.5. Outcome of the patients after weighting for both matching and missing outcome weights.

Variables		No ICP monitoring	ICP monitoring	p-value
N		945	503	
Weighted N		503	503	
ICU mortality – %				0.79
	Alive	76.1%	76.7%	
	Dead	23.9%	23.3%	
Hospital mortality – %				0.50
	Alive	70.1%	71.8%	
	Dead	29.9%	28.2%	
6-month GOS-E – %				0.003
	Dead (1)	32.7%	31.4%	
	Vegetative State (2)	5.8%	6.0%	
	Lower severe disability (3)	17.7%	25.1%	
	Upper severe disability (4)	7.3%	8.5%	
	Lower moderate disability (5)	4.8%	8.0%	
	Upper moderate disability (6)	11.2%	8.3%	
	Lower good recovery (7)	7.7%	5.9%	
	Upper good recovery (8)	12.8%	6.8%	

eAppendix 3. EXTENDED METHODS

To address our research question, we applied a propensity-score-matched design. Using logistic regression, we calculated the propensity score, i.e., the probability of receiving ICP monitoring based on pre-treatment variables. As recommended (Stuart, *Matching Methods for Causal Inference: A Review and a Look Forward*, 2010), the variables included in the model were identified by a panel of clinicians (AG, LG, VC) based on a priori knowledge of the factors influencing both the decision to initiate ICP monitoring and the patient outcome. The panel deemed three of these factors essential to both the decision to start ICP monitoring and patient outcome: age group (<40, 40-64, 65-74, 75-79, ≥80), mass lesion (Marshall CT classification V or VI), and pre-hospital hypotension. Therefore, we matched patients on these same factors, i.e., we matched on the propensity score only patients with the same value for these three variables. To control for any bias that could have been introduced by an unbalanced distribution of the study countries, characterized by very different patient outcomes and TBI management policies, we also matched patients according to the country. We excluded patients from the countries where high-quality matching was not possible.

A 1:1 matched design was not feasible, as it was not possible to find one eligible control with a similar propensity score to each treated patient because of the distributions of the propensity score in the two groups. We opted for a full matching design, characterized by a series of matched sets with either one treated patient and multiple controls or one control and multiple treated patients (Rosenbaum, *A Characterization of Optimal Designs for Observational Studies*, 1991). The flexibility of this design facilitates the formation of well-balanced matched samples in conditions of poor overlap, where 1:1 matching algorithms are not appropriate. The matched sample was generated with the optimal full matching algorithm, implemented in the R package *optmatch* (Hansen and Klopfer, *Optimal Full Matching and Related Designs via Network Flows*, 2006). Following best practices, we excluded the control patients with an estimated propensity score lower than the minimum value of the treated group, being considered non-comparable to the treated patients in terms of pre-treatment covariates (Stuart and Rubin, *Best Practices in Quasi–Experimental Designs: Matching Methods for Causal Inference*, 2008).

Given the variable number of treated and control patients across matched sets, the post-matching analyses had to be weighted (Stuart and Green, *Using Full Matching to Estimate Causal Effects in Nonexperimental Studies: Examining the Relationship Between Adolescent Marijuana Use and Adult Outcomes*, 2008). As suggested, all treated subjects were assigned a weight of 1. In sets with one treated and k controls, controls were assigned a weight of 1/k, while in sets with k treated and one control, controls were assigned a weight of k. To avoid the formation of matched sets with a very large number of treated or control subjects, where controls would receive an overly large or small weight, we limited the maximum number of treated patients and controls to be included in each set to 5. All statistical analyses comparing the treatment groups of the matched sample were performed with weighted tests in weighted bivariate regression models, using the generated weights. Standard errors and p-values were computed using robust clustered standard errors, accounting for the possible correlation within the matched sets.

eAppendix 4. RESULTS OF THE ATTEMPT OF MATCHED ANALYSIS ON ALL COUNTRIES

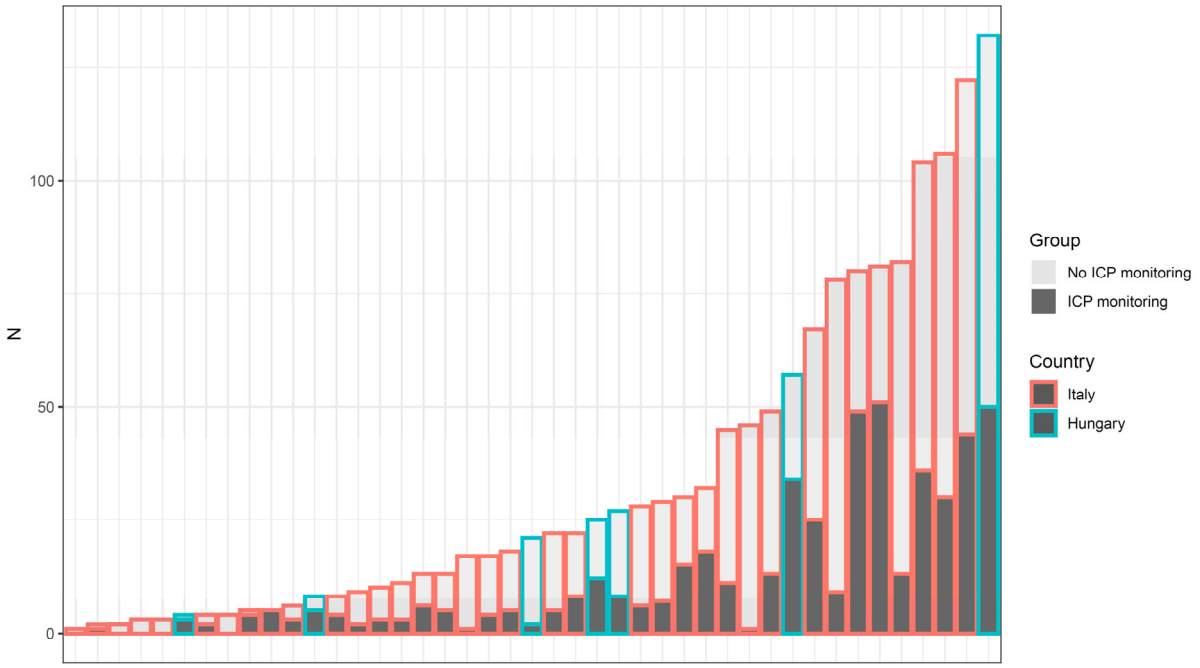
Table S.6. The table provides the results of the analysis in which we sought to generate a matched sample within the full cohort, including all the countries involved in the study. The table reports the absolute standardized mean differences (SMDs) before matching (left column) and the SMDs weighted by the matching weights. The presence of SMDs>10% for key confounders after weighting indicates that pre-treatment covariates are not adequately balanced. Such poor balance led to the selection of patients admitted to ICUs in Italy and Hungary, where control groups were larger.

Variables	SMDs before matching	Weighted SMDs after matching
Age	0.576	0.009
Sex (Female)	0.132	0.072
Comorbidities		
Antiplatelet therapy	0.202	0.002
COPD	0.126	0.001
Dementia	0.108	0.010
Drug-induced coagulopathy	0.117	0.004
Heart failure	0.063	0.041
Liver disease	0.079	0.020
Renal disease	0.117	0.025
Penetrating trauma	0.070	0.014
Pre-treatment GCS	0.068	0.042
Main lesion		
Cerebral contusion/laceration	0.175	0.107
Extradural/epidural hematoma	0.064	0.024
Traumatic subdural hematoma	0.168	0.004
Intraparenchymal bleeding	0.075	0.084
Diffuse injury without edema	0.094	0.002
Diffuse injury with edema	0.152	0.192
Subarachnoid hemorrhage	0.155	0.028
Skull fracture	0.037	0.081
Injuries other than TBI		
Abdomen	0.015	0.012
Chest	0.179	0.051
Pelvis, bones, joints and muscles	0.019	0.060
Major vessels	0.015	0.063
Spine	0.111	0.045
Pupils at ED arrival unilaterally dilated/non-reactive	0.075	0.017
Hypotension	0.005	0.000
Hypoxia	0.065	0.050
Transfer from another ICU due to hospital expertise	0.053	0.075
Surgery before ICU admission	0.303	0.089
Neurosurgery within 2 days from injury	0.294	0.140
Cardiovascular failure at ICU admission		
None	0.457	0.095

Variables		SMDs before matching	Weighted SMDs after matching
	Without shock	0.351	0.095
	With shock	0.151	0.003
Metabolic failure at ICU admission		0.009	0.015
Renal failure at ICU admission		0.190	0.009
Marshall CT classification			
	Diffuse Injury I	0.213	0.012
	Diffuse Injury II	0.014	0.147
	Diffuse Injury III	0.179	0.168
	Diffuse Injury IV	0.036	0.092
	Mass lesion (V or VI)	0.019	0.000
Midline shift >5mm		0.097	0.010
Lesion volume >25ml		0.006	0.019
Petechiae		0.081	0.004
Cistern condition			
	Normal	0.004	0.180
	Compressed or distorted	0.116	0.193
	Absent	0.181	0.018

eAppendix 5. ICP MONITORING ACROSS ICUs

Figure S.2. Number of eligible patients admitted to each Italian and Hungarian ICU, dividing monitored and nonmonitored patients.



eAppendix 6. RESULTS OF THE MATCHED ANALYSIS ON ITALY AND HUNGARY

Table S.7. Estimated odds ratios (ORs) and corresponding 95% confidence intervals of the logistic regression model estimating the propensity score.

Variables		OR (95% CI)
Age (10 year increase)		0.67 (0.62, 0.72)
Sex (Female vs. Male)		0.78 (0.58, 1.06)
Comorbidities		
	Antiplatelet therapy (Yes vs. No)	1.02 (0.61, 1.71)
	COPD (Yes vs. No)	0.94 (0.46, 1.93)
	Dementia (Yes vs. No)	0.22 (0.05, 1.02)
	Drug-induced coagulopathy (Yes vs. No)	0.95 (0.49, 1.85)
	Heart failure (Yes vs. No)	0.98 (0.37, 2.58)
	Liver disease (Yes vs. No)	0.63 (0.29, 1.38)
	Renal disease (Yes vs. No)	0.42 (0.12, 1.48)
Penetrating trauma (Yes vs. No)		1.02 (0.49, 2.12)
Pre-treatment GCS		
	3	0.92 (0.60, 1.40)
	4-5	1.10 (0.71, 1.70)
	6-7	0.94 (0.63, 1.40)
	8	1 (ref.)
Main lesion		
	Cerebral contusion/laceration	3.85 (0.68, 21.94)
	Extradural/epidural hematoma	2.07 (0.34, 12.60)
	Traumatic subdural hematoma	1.93 (0.34, 11.07)
	Intraparenchymal bleeding	3.30 (0.56, 19.36)
	Diffuse injury without edema	2.02 (0.34, 11.89)
	Diffuse injury with edema	4.62 (0.74, 29.02)
	Subarachnoid hemorrhage	3.37 (0.59, 19.26)
	Skull fracture	1 (ref.)
Injuries other than TBI		
	Abdomen (Yes vs. No)	0.67 (0.43, 1.04)
	Chest (Yes vs. No)	1.35 (0.98, 1.85)
	Pelvis, bones, joints and muscles (Yes vs. No)	0.91 (0.64, 1.28)
	Major vessels (Yes vs. No)	1.16 (0.57, 2.35)
	Spine (Yes vs. No)	1.32 (0.95, 1.85)
Pupils at ED arrival unilaterally dilated/non-reactive (Yes vs. No)		0.96 (0.71, 1.31)
Hypotension (Yes vs. No)		0.77 (0.53, 1.13)
Hypoxia (Yes vs. No)		0.99 (0.74, 1.32)
Transfer from another ICU due to hospital expertise (Yes vs. No)		1.76 (0.69, 4.46)
Surgery before ICU admission (Yes vs. No)		1.21 (0.80, 1.84)
Neurosurgery within 2 days from injury (Yes vs. No)		2.39 (1.47, 3.88)
Cardiovascular failure at ICU admission		
	None	1 (ref.)
	Without shock	3.33 (2.42, 4.60)

Variables		OR (95% CI)
	With shock	2.26 (1.57, 3.27)
Metabolic failure at ICU admission (Yes vs. No)		0.95 (0.69, 1.32)
Renal failure at ICU admission (Yes vs. No)		0.71 (0.45, 1.12)
Marshall CT classification		
	Diffuse Injury I	1 (ref.)
	Diffuse Injury II	2.04 (0.85, 4.91)
	Diffuse Injury III	2.61 (1.06, 6.41)
	Diffuse Injury IV	3.67 (1.17, 11.52)
	Mass lesion (V or VI)	2.21 (0.84, 5.81)
Midline shift >5mm (Yes vs. No)		0.41 (0.24, 0.69)
Lesion volume >25ml (Yes vs. No)		1.67 (0.96, 2.90)
Petechiae (Yes vs. No)		0.75 (0.56, 1.01)
Cistern condition		
	Normal	1 (ref.)
	Compressed or distorted	1.85 (1.05, 3.27)
	Absent	0.98 (0.51, 1.91)

Table S.8. Absolute weighted standardized mean differences (SMDs) comparing the treatment groups on all the pre-treatment variables. The SMDs are weighted using the weights defined by the full matching design.

Variables	SMDs before matching	Absolute weighted SMDs
Age	0.489	0.029
Sex (Female)	0.071	0.090
Comorbidities		
Antiplatelet therapy	0.120	0.004
COPD	0.127	0.002
Dementia	0.043	0.002
Drug-induced coagulopathy	0.102	0.007
Heart failure	0.003	0.079
Liver disease	0.119	0.071
Renal disease	0.095	0.003
Penetrating trauma	0.117	0.042
Pre-treatment GCS	0.062	0.099
Main lesion		
Cerebral contusion/laceration	0.149	0.024
Extradural/epidural hematoma	0.079	0.012
Traumatic subdural hematoma	0.088	0.013
Intraparenchymal bleeding	0.066	0.053
Diffuse injury without edema	0.183	0.094
Diffuse injury with edema	0.219	0.083
Subarachnoid hemorrhage	0.181	0.024
Skull fracture	0.073	0.013
Injuries other than TBI		
Abdomen	0.016	0.016
Chest	0.192	0.076
Pelvis, bones, joints and muscles	0.003	0.033
Major vessels	0.034	0.010
Spine	0.115	0.055
Pupils at ED arrival unilaterally dilated/non-reactive	0.032	0.027
Hypotension	0.006	0.000
Hypoxia	0.069	0.012
Transfer from another ICU due to hospital expertise	0.060	0.005
Surgery before ICU admission	0.277	0.004
Neurosurgery within 2 days from injury	0.286	0.071
Cardiovascular failure at ICU admission		
None	0.444	0.003
Without shock	0.358	0.050
With shock	0.141	0.048
Metabolic failure at ICU admission	0.034	0.032
Renal failure at ICU admission	0.122	0.029
Marshall CT classification		

Variables		SMDs before matching	Absolute weighted SMDs
	Diffuse Injury I	0.258	0.019
	Diffuse Injury II	0.173	0.068
	Diffuse Injury III	0.266	0.074
	Diffuse Injury IV	0.015	0.053
	Mass lesion (V or VI)	0.131	0.000
Midline shift >5mm		0.016	0.019
Lesion volume >25ml		0.110	0.004
Petechiae		0.101	0.040
Cistern condition			
	Normal	0.196	0.084
	Compressed or distorted	0.295	0.081
	Absent	0.135	0.004

Table S.9. Distribution of hospital and ICU characteristics of eligible patients.

Variables	No ICP monitoring		ICP monitoring	p-value[2]
	All	Weighted distribution[1]		
N	945	503	503	
Vascular surgery – N (%)	928 (98.2%)	97.8%	498 (99.0%)	0.69
Interventional neuroradiology – N (%)	804 (90.4%)	91.9%	428 (89.5%)	0.33
Interventional vascular radiology – N (%)	906 (95.9%)	94.0%	485 (96.4%)	0.08
Number of trauma patients/year				0.45
Mean (SD)	137.7 (66.8)	134.2 (64.7)	137.7 (67.5)	
Median (Q1, Q3)	122.4 (91.2, 184.7)	122.4 (90.8, 184.7)	123.8 (92.4, 184.7)	
Number of TBI patients/year				0.14
Mean (SD)	76.5 (29.2)	74.7 (27.4)	77.5 (28.6)	
Median (Q1, Q3)	73.5 (55.6, 93.3)	73.5 (55.6, 93.3)	82.2 (54.9, 93.3)	

[1] Patients in the No ICP monitoring group are weighted, to make them comparable to patients in the ICP monitoring group with respect to pre-treatment covariates. Weights are defined by the matched design.
[2] P-value of the weighted tests comparing the no-ICP-monitoring and ICP monitoring groups.

eAppendix 7. COMORBIDITIES

Table S.10. List of the comorbidities collected in the CREACTIVE study.

Area	Comorbidity
Respiratory	Asthma
	Moderate COPD
	Severe COPD
	Restrictive lung disease
Cardiovascular	Arrhythmia
	Myocardiopathy
	Heart failure (NYHA class II-III or ACC stage C)
	Heart failure (NYHA class IV or ACC stage D)
	Myocardial infarction
	Hypertension
	Peripheral vascular disease
Neurologic	Dementia
	Hemiplegia or paraplegia or quadriplegia
	Cerebrovascular disease
	Neurodegenerative/Neuromuscular disease
Gastrointestinal and hepatic	Peptic ulcer disease
	Mild liver disease
	Moderate or severe liver disease
Renal	Moderate or severe renal disease
	End-stage renal disease
Endocrine	Diabetes Type I
	Diabetes Type II with insulin treatment
	Diabetes Type II without insulin treatment
Malignancy	Any tumour without metastasis
	Metastatic cancer
	Malignant hematological disease
Other	Autoimmune disease
	Immunosuppression
	Drug-induced coagulopathy
	Coagulation disorder
	Antiplatelet therapy
	AIDS
	Severe malnutrition

eAppendix 8. INJURIES

Table S.11. List of the injuries collected in the CREACTIVE study.

Body region	Lesion
Spine	Cervical spinal cord injury with tetraplegia
	Cervical spinal cord injury with incomplete neurologic deficit
	Dorsal spinal cord injury with paraplegia
	Dorsal spinal cord injury with incomplete neurologic deficit
	Lumbar spinal cord injury with complete neurologic deficit
	Lumbar spinal cord injury with incomplete neurologic deficit
	Vertebral fracture without neurologic deficit
Chest	Major laceration of trachea/larynx
	Esophagus: rupture/perforation
	Traumatic emothorax and/or pneumothorax
	Traumatic massive hemothorax
	Tension pneumothorax
	Flail chest
	Severe lung contusion/laceration
	Cardiac trauma
	Diaphragmatic rupture
	Other injuries of the chest
Abdomen	Stomach: Rupture or perforation
	Bowel: Complete transection or perforation
	Pancreas: Laceration
	Liver: Moderate-severe laceration
	Liver: Massive laceration
	Spleen: Moderate-severe laceration
	Spleen: Massive rupture
	Kidney: Rupture/laceration
	Minor injuries of the abdomen
Pelvis, bones, joints and muscles	Long bone fracture
	Very severe or open fracture of the pelvis with unstable pelvis
	Multiple fracture of the pelvis
	Massive crush/amputation of one or more limbs
	Extremity compartment syndrome
Major vessels	Aorta: rupture/dissection
	Cava: rupture/transection
	Major thoracic vessels: transection
	Major abdominal vessels: transection
	Major vessels of the neck: dissection/transection
	Major vessels of the proximal limbs: transection
Other	Burns (> 30% of total body surface area)
	Inhalation injury