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Admission Glasgow Coma Scale, Pupillary Reactivity, and Age as Independent Predictors of Survival and Functional Dependency After Emergent Surgery for Traumatic Brain Injury

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ABSTRACT

Background. Early prognosis after moderate-to-severe traumatic brain injury (TBI) that needs emergent surgery is important but easily confounded. The Glasgow Coma Scale (GCS) is the usual starting point. Used alone, it can mislead.

Objective. To estimate the independent association of admission GCS with outcome after adjustment for pupillary light reactivity, age, and Marshall computed tomography (CT) class.

Methods. This retrospective cohort study included 150 consecutive patients with moderate-to-severe TBI (admission GCS 3–12) who had emergent surgery and postoperative intensive care from July to December 2024. The outcomes were in-hospital mortality (14 deaths) and unfavorable functional outcome (death or discharge to a skilled nursing or palliative facility). We used receiver operating characteristic (ROC) analysis and multivariable logistic regression (Firth-penalized for mortality).

Results. A GCS cut-off of ≤ 5.5 gave a crude odds ratio for mortality of 104.87 (95% CI 12.80–859.40), which was unstable because one death occurred above the cut-off. Admission GCS remained independently associated with mortality (adjusted odds ratio [aOR] 2.78 per point decrease, 95% CI 1.99–3.89, $p < 0.001$) and with unfavorable functional outcome (aOR 3.11, 95% CI 2.34–4.14, $p < 0.001$). Bilaterally non-reactive pupils were independently associated with mortality (aOR 5.12, 95% CI 1.81–14.50, $p = 0.002$). Age was independently associated with unfavorable functional outcome (aOR 1.07 per year, 95% CI 1.04–1.10, $p < 0.001$).

Conclusion. Admission GCS is independently associated with outcome after surgery for TBI, and it is best read together with pupillary response and age. These findings need validation in larger cohorts.

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1. Introduction

Traumatic brain injury (TBI) is a leading cause of death, lasting neurological impairment, and socioeconomic hardship worldwide, with an estimated 27 to 30 million new cases a year and more than 55 million people living with its sequelae.^{1,2} The burden falls most heavily on low- and middle-income countries (LMICs), including Indonesia, where road traffic collisions are the main cause of high-energy head trauma.^{2–4} In provincial referral hospitals, severe neurotrauma strains scarce intensive care unit (ICU) capacity and forces rapid decisions about surgery, bed allocation, and prognosis for families.^{2–5}

Outcome depends on the primary mechanical insult, which produces contusions, microvascular tearing, and diffuse axonal injury (DAI), and on a secondary cascade that unfolds over hours to days.^{1,6–9} Excitatory amino acid release, calcium overload, mitochondrial failure, oxidative stress, microglial activation, and breakdown of the blood-

brain barrier add vasogenic to cytotoxic edema and threaten salvageable peri-contusional tissue.^{8–17} Because the primary insult is irreversible, neurocritical care and neuroanesthesia focus on limiting this secondary injury.^{7,8}

The rigid cranium limits how much swelling the brain can absorb (Monro-Kellie doctrine).^{17,18} Venous blood and cerebrospinal fluid (CSF) are displaced first to compensate for an expanding hematoma, contusion, or edema, and intracranial pressure (ICP) stays below the usual treatment threshold of 20–22 mmHg.^{18–20} Once this reserve is exhausted, small volume increases cause steep ICP rises that lower cerebral perfusion pressure (mean arterial pressure – ICP), cause ischemia, and drive uncal and transtentorial herniation.^{20–23}

Survival depends on a coordinated pathway of emergency department (ED) resuscitation, emergent hematoma evacuation or decompressive craniectomy in the operating room (OR), and neurological and hemodynamic monitoring in the ICU.^{23–26} Patients who complete this ED-OR-ICU route carry the highest risk of death and severe

dependency.^{25,26} Since its introduction by Teasdale and Jennett in 1974, the GCS has anchored the first neurological assessment, and a low admission GCS is strongly linked to poor outcome.^{10–12,27,28}

However, the GCS is often used alone, without adjustment for host and anatomical factors.^{9,10,28} The same score of 7 means different things in an 18-year-old with reactive pupils and a focal epidural hematoma and in a 70-year-old with a fixed, dilated pupil and diffuse swelling.^{9,20,29} In univariate models the GCS absorbs the effect of correlated variables, mainly pupillary non-reactivity and age, which can inflate effect sizes and make estimates unstable when cells are sparse.^{30,31} Adjusted prognostic data are scarce for operated TBI cohorts in LMIC referral centers, where surgical delay, transfer logistics, and ICU capacity differ from those in high-income registries.^{18,29,32}

We therefore studied consecutive adult and pediatric patients with moderate-to-severe TBI who met surgical indications and completed the ED-OR-ICU pathway at a tertiary referral hospital. The objective was to estimate the independent association of admission GCS with in-hospital mortality and with unfavorable functional outcome after adjustment for pupillary light reactivity, age, and Marshall computed tomography (CT) class, and to show how a univariate GCS cut-off can mislead.^{10,24,33}

2. Methods

2.1. Study design and reporting

This was a single-center, retrospective, observational cohort study. It followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline and the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement.^{34,35}

2.2. Setting

The study took place at Dr. Saiful Anwar Regional General Hospital, Malang, East Java, Indonesia. It is the main provincial tertiary academic referral center for the southern and eastern parts of East Java and serves a catchment population above 5 million. The hospital is a high-volume neurotrauma center with 24-hour neurosurgical operating rooms, multi-slice CT scanners, and a tertiary ICU staffed around the clock by board-certified anesthesiologists and intensivists. All consecutive patients who presented to the ED with acute closed or open TBI between July 1 and December 31, 2024 were screened. Patients were followed until hospital discharge.

2.3. Participants and eligibility

Patients were included if they met all four of the following criteria: (1) a documented clinical diagnosis of acute TBI at ED admission; (2) an initial GCS of 3 to 12, covering moderate (GCS 9–12) and severe (GCS 3–8) injury; (3) a structural neurosurgical lesion that required, and led to, emergent decompression (decompressive craniectomy, craniotomy for hematoma evacuation, or elevation and debridement of depressed skull fractures); and (4) postoperative ICU admission for mechanical ventilation, invasive arterial pressure monitoring, and advanced neurocritical care (the ED-OR-ICU pathway).^{24,26,29}

Figure 1 shows the selection flow. We excluded patients with mild TBI (initial GCS 13–15, $n = 118$), who seldom need emergent decompression or advanced intensive care. We excluded 22 patients who arrived intubated by pre-

hospital services, because sedation or neuromuscular blockade given before arrival made a reliable baseline GCS impossible. We excluded 22 patients managed non-operatively: 14 with isolated diffuse axonal injury admitted directly to medical intensive care, and 8 moribund patients judged non-survivable who received palliative comfort care in the ED. No further patient was excluded for missing or incomplete clinical, radiographic, or outcome records, because the 162 exclusions are fully accounted for by the three groups above. Of 312 consecutive TBI patients, 150 met every criterion and formed the analyzed cohort.

2.4. Sample size

All eligible consecutive patients in the study period were analyzed.

2.5. Variables and operational definitions

Four candidate predictors were evaluated. (1) Admission GCS was the first formal neurological score recorded by the attending emergency physician or on-duty neurosurgical resident at ED triage, before any sedative, analgesic, or paralytic was given.²⁷ It was analyzed as a continuous variable (range 3–12) and as a dichotomized threshold. (2) Age was recorded in years at the time of injury. (3) Pupillary light reactivity was grouped into three ordinal categories: both reactive, one non-reactive (a unilateral fixed, dilated pupil suggesting impending uncal herniation), and bilaterally non-reactive (bilateral fixed, dilated pupils signifying advanced transtentorial herniation or severe midbrain ischemia). (4) Marshall CT class was grouped as Score II (diffuse injury with preserved basal cisterns and midline shift ≤ 5 mm), Score III/IV (diffuse injury with swelling, compressed or effaced basal cisterns, or midline shift > 5 mm, without a high- or mixed-density lesion > 25 mL), and Score V/VI (evacuated or non-evacuated mass lesion > 25 mL).³⁶

Other covariates were sex, mechanism of trauma (road traffic collision, fall from height, direct assault or other), pre-existing comorbidity (arterial hypertension, diabetes mellitus, or chronic cardiopulmonary disease; yes or no), time from ED arrival to skin incision (hours), and the surgical procedure (decompressive craniectomy with duraplasty or craniotomy with primary bone flap replacement).^{24,26}

We defined two primary endpoints. In-hospital all-cause mortality was death at any time between ED admission and final discharge. Unfavorable functional outcome was a composite of in-hospital death or discharge to dependent, non-home care (skilled nursing facility, long-term acute care hospital, or hospice or palliative facility).^{35,37} Survivors discharged directly home or to outpatient rehabilitation counted as having a favorable outcome. Formal 6-month Glasgow Outcome Scale-Extended (GOSE) interviews are hard to complete in acute trauma registries because patients are lost to follow-up. Discharge disposition was therefore used as a surrogate for severe functional dependence and neurological disability.^{24,37}

2.6. Data sources and measurement

Trained investigators extracted clinical, demographic, radiographic, and surgical data from the electronic hospital information system and verified them against paper charts, using a standardized collection form. Pupillary light reactivity was assessed in the ED before surgery with standardized focal illumination. The first non-contrast head CT, obtained on ED arrival, was graded independently

by the neurotrauma team according to the Traumatic Coma Data Bank classification (Score I to VI).³⁶

2.7. Statistical analysis

We used SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and cross-checked the results in Python (NumPy, SciPy, statsmodels). Normality was assessed with the Kolmogorov-Smirnov test and Q-Q plots. Variables that were not normally distributed, including GCS and age, are given as median and interquartile range (IQR) and also as mean and standard deviation (SD). Categorical and ordinal variables are given as counts and percentages. Outcome groups (survivors versus deceased; favorable versus unfavorable functional outcome) were compared with the Mann-Whitney U test for continuous variables and with the Pearson chi-square test for categorical variables. Fisher's exact test (Freeman-Halton extension for tables larger than 2×2) was used when expected counts were < 5.

As an exploratory analysis, we ran a receiver operating characteristic (ROC) analysis of admission GCS for mortality and took the cut-off that maximized the Youden index (sensitivity + specificity – 1). The cut-off was therefore derived from the same data. A 2×2 table at this cut-off gave crude odds ratios (OR) with 95% confidence intervals (CI). We inspected the table for sparse-data bias, defined as a configuration in which a predictor separates the outcome almost perfectly, leaving a very low cell frequency, near-zero standard errors, and very large odds ratios.^{38,39}

To obtain adjusted effects we fitted two multivariable binary logistic regression models: Model 1 for in-hospital mortality and Model 2 for unfavorable functional outcome. Predictors were selected a priori for clinical plausibility and entered together: admission GCS (continuous, per 1-point decrease), age (continuous, per 1-year increase), pupillary light reactivity (both reactive as reference, one non-reactive, bilaterally non-reactive), and Marshall CT class (Score II as reference, Score III/IV, Score V/VI).

Multicollinearity was checked with variance inflation factors (VIF), and all values were < 1.4. Model 1 had 14 deaths and 6 estimated parameters, an events-per-variable (EPV) ratio of 2.33, which leaves it open to small-sample bias. To limit sparse-data bias, we fitted Model 1 with Firth's penalized likelihood logistic regression,^{38,39} which applies a Jeffreys invariant prior to shrink coefficients and reduce maximum likelihood bias. Model 2 had 41 events and 6 parameters (EPV = 6.83). Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test and Nagelkerke pseudo-R². All tests were two-tailed, and significance was set at $\alpha = 0.05$.

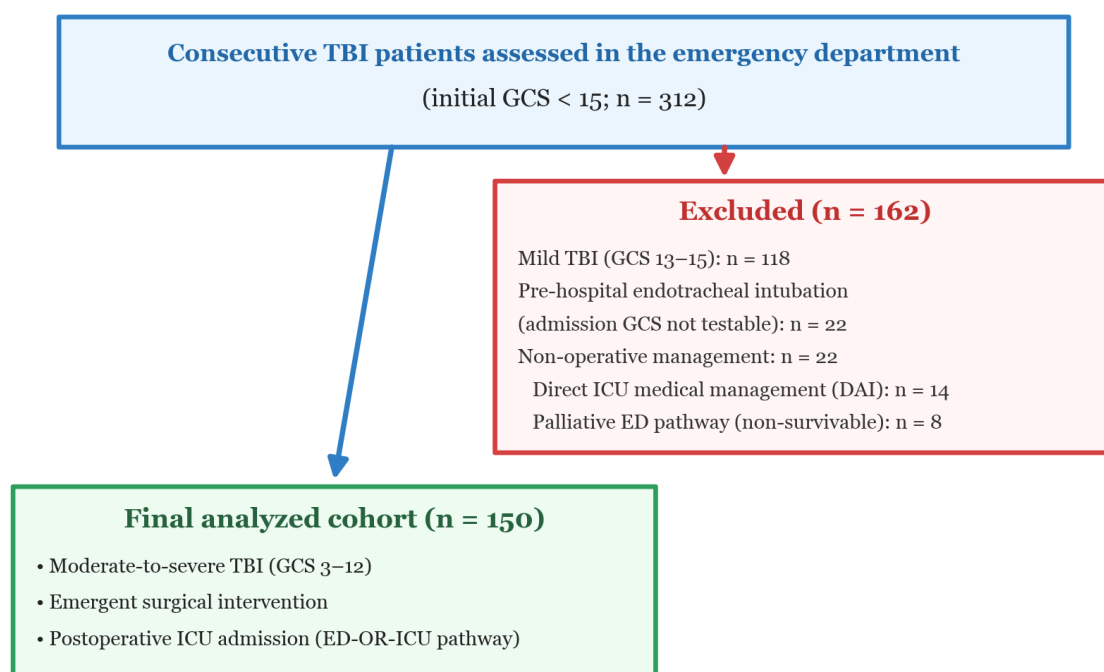
2.8. Ethics

The Health Research Ethics Committee of Dr. Saiful Anwar Regional General Hospital, Malang, East Java, Indonesia, reviewed and approved the protocol (reference 400/127/K.3/102.7/2025; approved on 15 January 2025). The study complied with the Declaration of Helsinki and its later revisions. Because the analysis used anonymized secondary records and involved no intervention, the committee waived individual written informed consent. All datasets were de-identified before analysis. National identity numbers, medical record numbers, telephone numbers, and residential addresses were removed.

3. Results

3.1. Participant flow and baseline characteristics

Of 312 consecutive TBI patients assessed in the ED, 162 were excluded and 150 were analyzed (Figure 1). Table 1 lists the baseline characteristics, and Figure 2 shows them by clinical stratum. Men made up 70.0% ($n = 105$), a male-to-female ratio of 2.33:1. Mean age was 32.87 ± 19.61 years (range 4–76) and median age was 28.0 years (IQR 18.0–45.0). By age group, 54.0% ($n = 81$) were aged 18 to 40 years, 22.0% ($n = 33$) were under 18, 14.0% ($n = 21$) were 41 to 60, and 10.0% ($n = 15$) were over 60.



ED, emergency department; GCS, Glasgow Coma Scale; TBI, traumatic brain injury; DAI, diffuse axonal injury; OR, operating room.

Figure 1. STROBE flow diagram of cohort selection through the emergency care pathway. DAI, diffuse axonal injury; ED, emergency department; GCS, Glasgow Coma Scale; ICU, intensive care unit; OR, operating room; TBI, traumatic brain injury.

Table 1. Baseline characteristics of the surgical TBI cohort (n = 150).

Characteristic	Overall (n = 150)	Survivors (n = 136)	Deceased (n = 14)	p value
Age, years, mean $\pm$ SD	32.87 $\pm$ 19.61	31.25 $\pm$ 19.04	48.57 $\pm$ 19.38	—
Age, years, median [IQR]	28.0 [18.0–45.0]	26.5 [18.0–42.0]	48.5 [34.0–68.0]	0.028*
Age category, n (%)				0.045†
< 18 years	33 (22.0)	32 (23.5)	1 (7.1)	
18–40 years	81 (54.0)	75 (55.1)	6 (42.9)	
41–60 years	21 (14.0)	18 (13.2)	3 (21.4)	
> 60 years	15 (10.0)	11 (8.1)	4 (28.6)	
Sex, n (%)				0.760†
Male	105 (70.0)	96 (70.6)	9 (64.3)	
Female	45 (30.0)	40 (29.4)	5 (35.7)	
Mechanism of injury, n (%)				0.495†
Road traffic collision	111 (74.0)	102 (75.0)	9 (64.3)	
Fall from height	27 (18.0)	23 (16.9)	4 (28.6)	
Other direct trauma	12 (8.0)	11 (8.1)	1 (7.1)	
Comorbidity present, n (%)	22 (14.7)	19 (14.0)	3 (21.4)	0.434†
Admission GCS, mean $\pm$ SD	6.90 $\pm$ 1.84	7.18 $\pm$ 1.62	4.14 $\pm$ 0.95	—
Admission GCS, median [IQR]	7 [6–8]	7 [6–8]	4 [3–5]	< 0.001*
TBI severity, n (%)				0.220†
Severe (GCS 3–8)	132 (88.0)	118 (86.8)	14 (100.0)	
Moderate (GCS 9–12)	18 (12.0)	18 (13.2)	0 (0.0)	
Pupillary light reactivity, n (%)				0.002†
Both reactive	103 (68.7)	99 (72.8)	4 (28.6)	
One non-reactive	27 (18.0)	22 (16.2)	5 (35.7)	
Bilaterally non-reactive	20 (13.3)	15 (11.0)	5 (35.7)	
Marshall CT class, n (%)				0.358†
Score II	30 (20.0)	29 (21.3)	1 (7.1)	
Score III/IV	61 (40.7)	56 (41.2)	5 (35.7)	
Score V/VI	59 (39.3)	51 (37.5)	8 (57.1)	
Time to incision, hours, median [IQR]	3.2 [2.1–4.8]	3.2 [2.2–4.7]	3.0 [1.8–5.1]	0.782*

Notes: Values are n (%) unless stated. IQR, interquartile range; SD, standard deviation; GCS, Glasgow Coma Scale; CT, computed tomography; TBI, traumatic brain injury. *Mann-Whitney U test; the p value for age is approximated from the printed U statistic (U = 612.0). †Fisher's exact test (Freeman-Halton extension for tables larger than 2×2), used because expected counts were < 5. The p values for survivors versus deceased were recomputed from the printed counts. Mean $\pm$ SD rows are descriptive and carry no separate test.

Road traffic collisions caused most injuries (74.0%, n = 111), mainly in riders of motorized two-wheel vehicles without helmets. Falls from height accounted for 18.0% (n = 27), mostly in children and elderly laborers. Direct blunt assaults and industrial crush injuries made up the remaining 8.0% (n = 12). Because the cohort was young, 85.3% (n = 128) had no documented comorbidity, whereas 14.7% (n = 22) had chronic disease, chiefly essential hypertension and type 2 diabetes mellitus.

Neurological status on ED arrival was poor. Severe TBI (admission GCS 3–8) was present in 88.0% (n = 132) and

moderate TBI (GCS 9–12) in 12.0% (n = 18). Median admission GCS was 7 (IQR 6–8; mean 6.90 $\pm$ 1.84). Pupils were both reactive in 68.7% (n = 103), unilaterally non-reactive in 18.0% (n = 27), and bilaterally fixed in 13.3% (n = 20). The Marshall classification showed diffuse injury with swelling (Score III/IV) in 40.7% (n = 61), mass lesions (Score V/VI) in 39.3% (n = 59), and diffuse injury (Score II) in 20.0% (n = 30). All patients had emergent decompression: 78.7% decompressive craniectomy with duraplasty and 21.3% craniotomy for hematoma evacuation. The median time from ED arrival to incision was 3.2 hours (IQR 2.1–4.8).

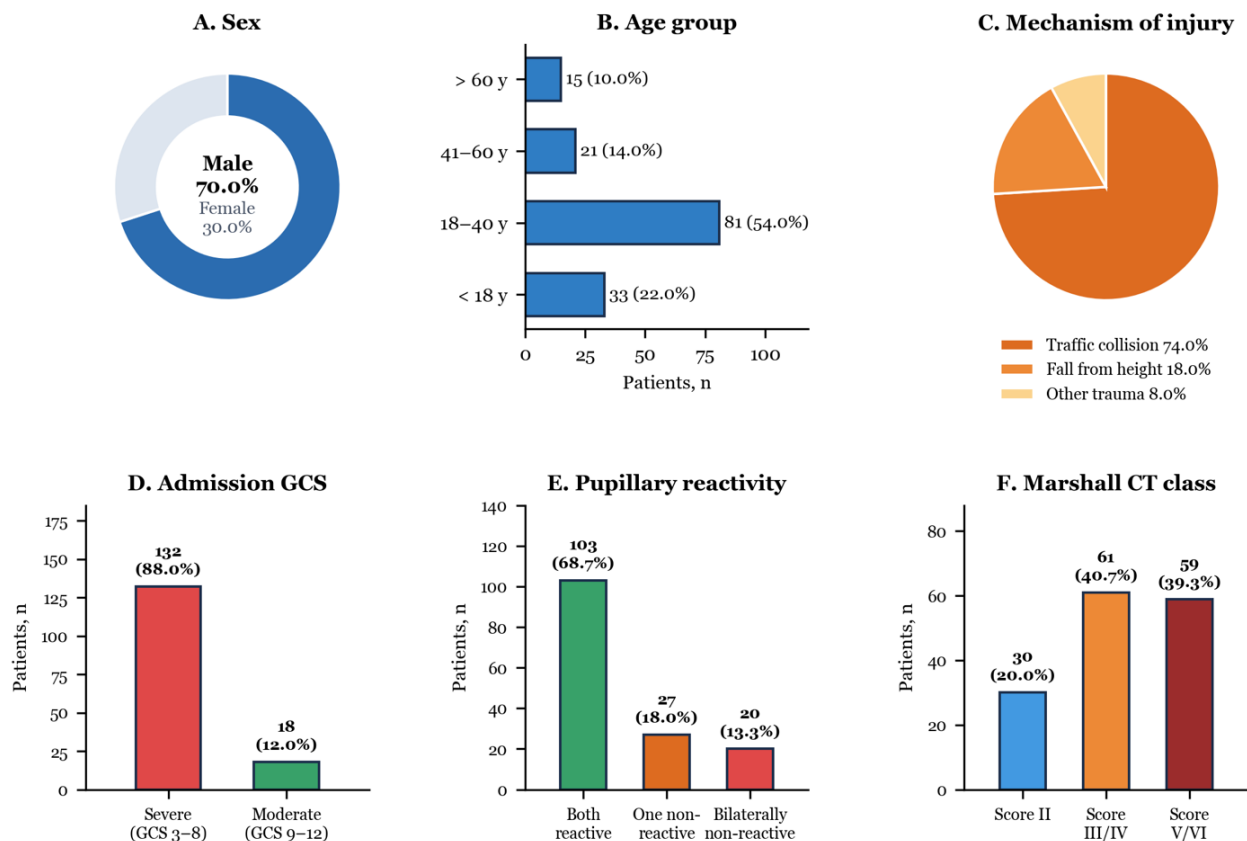


Figure 2. Baseline characteristics of the cohort (n = 150): (A) sex, (B) age group, (C) mechanism of injury, (D) admission GCS severity, (E) pupillary reactivity, and (F) Marshall CT class. Values are n (%). CT, computed tomography; GCS, Glasgow Coma Scale; TBI, traumatic brain injury.

3.2. Primary outcome

Fourteen patients died in hospital (9.3%, 95% CI 5.21%–15.18%), and 136 (90.7%) survived to discharge (Table 2, Figure 3). The composite unfavorable outcome occurred in 41 patients (27.3%, 95% CI 20.44%–35.16%). Among the

136 survivors, 109 (80.1% of survivors; 72.7% of the cohort) went directly home or to outpatient rehabilitation. The other 27 (19.9% of survivors; 18.0% of the cohort) had severe neurological deficits and were transferred to chronic institutional care.

Table 2. Primary clinical endpoints and discharge trajectories (n = 150).

Endpoint or trajectory	n	%	95% CI (%)
In-hospital mortality	14	9.33	5.21–15.18
Hospital survival	136	90.67	84.82–94.79
Composite functional outcome			
Favorable (home or outpatient rehabilitation)	109	72.67	64.84–79.56
Unfavorable (death or dependent facility)	41	27.33	20.44–35.16
Discharge of survivors (n = 136)			
Home or outpatient rehabilitation	109	80.15	72.50–86.45
Skilled nursing or long-term acute care facility	24	17.65	11.66–25.10
Palliative care or terminal transfer	3	2.20	0.46–6.30

Notes: CI, confidence interval. Unfavorable functional outcome is a composite of in-hospital death or discharge to a dependent care facility (skilled nursing, long-term acute care, or palliative care).

Primary clinical endpoints and discharge trajectories (n = 150)

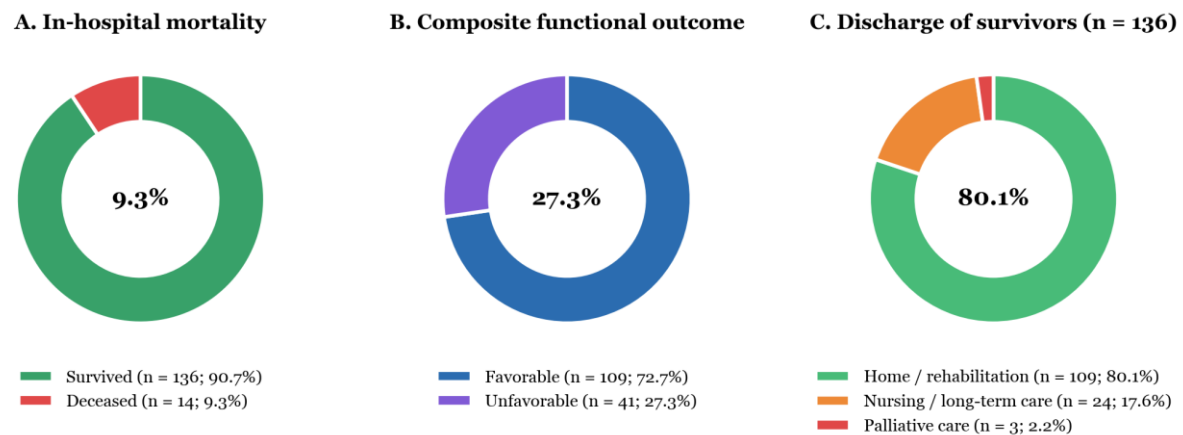


Figure 3. Clinical outcomes and discharge trajectories: (A) in-hospital mortality, (B) composite functional outcome, and (C) discharge destination of survivors (n = 136).

Table 3 compares the predictors between outcome groups. Admission GCS was much lower in deceased patients (median 4, IQR 3–5; mean 4.14 ± 0.95) than in survivors (median 7, IQR 6–8; mean 7.18 ± 1.62 ; Mann-Whitney U = 112.5, $p < 0.001$), and lower in patients with an unfavorable functional outcome (median 5, IQR 4–6; mean 5.24 ± 1.37) than in those with a favorable outcome (median 7, IQR 6–8; mean 7.52 ± 1.51 ; U = 485.0, $p < 0.001$). Deceased patients were older than survivors (median 48.5 vs 26.5 years; U = 612.0, $p = 0.028$). The age gap was larger for functional outcome (median 49.0 years, IQR 32.0–64.0 vs 25.0 years, IQR 17.0–35.0; U = 746.5, $p < 0.001$).

Pupillary reactivity was strongly associated with both endpoints. Mortality was 3.9% (4/103) with both pupils reactive, 18.5% (5/27) with one non-reactive pupil, and 25.0% (5/20) with both pupils fixed (Fisher-Freeman-Halton $p = 0.002$). Unfavorable outcome rose from 16.5% (17/103) to 44.4% (12/27) and 60.0% (12/20) across the same groups (Pearson chi-square 20.81, $p < 0.001$). Marshall class was associated with unfavorable outcome (Score II 10.0% [3/30]; Score III/IV 26.2% [16/61]; Score V/VI 37.3% [22/59]; chi-square 7.52, $p = 0.023$) but not with mortality ($p = 0.358$). Sex, mechanism of injury, comorbidity, and TBI severity category were not associated with mortality (Table 1).

Table 3. Bivariate comparison of predictors by mortality and functional outcome (n = 150).

Predictor	Survivors (n = 136)	Deceased (n = 14)	p value	Favorable (n = 109)	Unfavorable (n = 41)	p value
Admission GCS, median [IQR]	7 [6–8]	4 [3–5]	< 0.001*	7 [6–8]	5 [4–6]	< 0.001*
Age, years, median [IQR]	26.5 [18–42]	48.5 [34–68]	0.028*	25.0 [17–35]	49.0 [32–64]	< 0.001*
Pupillary light reactivity, n (%)			0.002†			< 0.001‡
Both reactive (n = 103)	99 (72.8)	4 (28.6)		86 (78.9)	17 (41.5)	
One non-reactive (n = 27)	22 (16.2)	5 (35.7)		15 (13.8)	12 (29.3)	
Bilaterally non-reactive (n = 20)	15 (11.0)	5 (35.7)		8 (7.3)	12 (29.3)	
Marshall CT class, n (%)			0.358†			0.023‡
Score II (n = 30)	29 (21.3)	1 (7.1)		27 (24.8)	3 (7.3)	
Score III/IV (n = 61)	56 (41.2)	5 (35.7)		45 (41.3)	16 (39.0)	
Score V/VI (n = 59)	51 (37.5)	8 (57.1)		37 (33.9)	22 (53.7)	

Notes: GCS, Glasgow Coma Scale; IQR, interquartile range; CT, computed tomography. *Mann-Whitney U test. †Fisher's exact test (Freeman-Halton extension). ‡Pearson chi-square test (pupils 20.81; Marshall class 7.52).

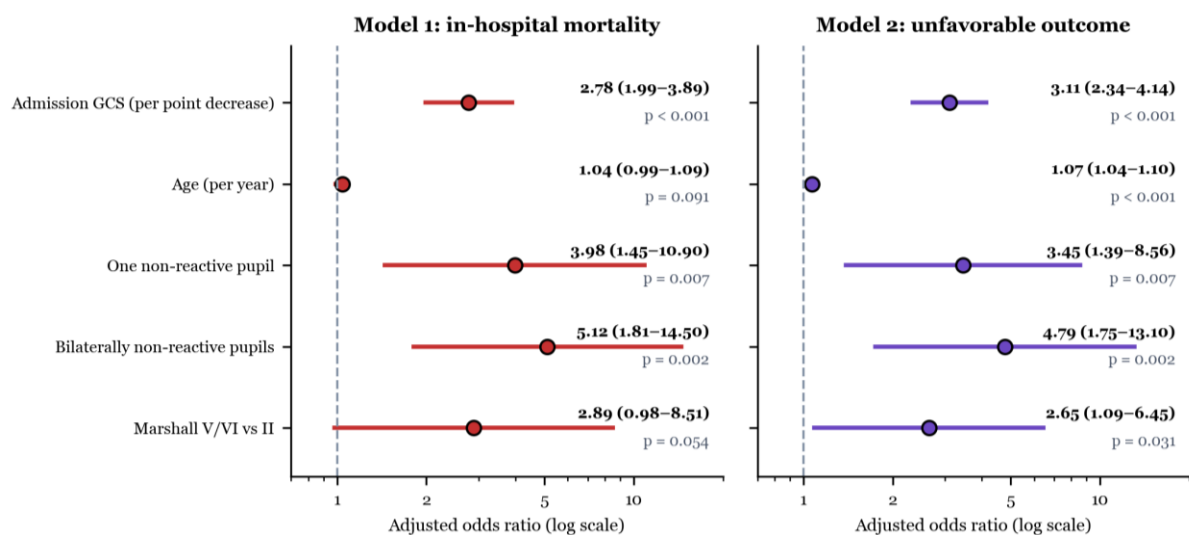
Table 4 and Figure 4 give the adjusted effects. In Model 1 (in-hospital mortality; Nagelkerke $R^2 = 0.548$; Hosmer-Lemeshow chi-square 5.15, $p = 0.742$), each 1-point decrease in admission GCS raised the odds of death by 178% (aOR 2.78, 95% CI 1.99–3.89, $p < 0.001$). Compared with reactive pupils, one non-reactive pupil raised the odds

of death almost four-fold (aOR 3.98, 95% CI 1.45–10.90, $p = 0.007$), and two non-reactive pupils more than five-fold (aOR 5.12, 95% CI 1.81–14.50, $p = 0.002$). Age (aOR 1.04 per year, 95% CI 0.99–1.09, $p = 0.091$) and Marshall Score V/VI versus II (aOR 2.89, 95% CI 0.98–8.51, $p = 0.054$) showed positive trends.

Table 4. Multivariable logistic regression models for in-hospital mortality and unfavorable functional outcome (n = 150).

Predictor	Model 1: mortality, aOR (95% CI)	p value	Model 2: unfavorable outcome, aOR (95% CI)	p value
Admission GCS (per 1-point decrease)	2.78 (1.99–3.89)	< 0.001	3.11 (2.34–4.14)	< 0.001
Age (per 1-year increase)	1.04 (0.99–1.09)	0.091	1.07 (1.04–1.10)	< 0.001
Pupillary light reactivity				
Both reactive	1.00 (reference)	—	1.00 (reference)	—
One non-reactive	3.98 (1.45–10.90)	0.007	3.45 (1.39–8.56)	0.007
Bilaterally non-reactive	5.12 (1.81–14.50)	0.002	4.79 (1.75–13.10)	0.002
Marshall CT class				
Score II	1.00 (reference)	—	1.00 (reference)	—
Score III/IV	1.82 (0.64–5.18)	0.261	1.74 (0.72–4.20)	0.218
Score V/VI	2.89 (0.98–8.51)	0.054	2.65 (1.09–6.45)	0.031
Events per variable	2.33 (14 events, 6 parameters)		6.83 (41 events, 6 parameters)	
Nagelkerke pseudo-R ²	0.548		0.612	
Hosmer-Lemeshow chi-square	5.15		5.66	
	0.742		0.685	

Notes: aOR, adjusted odds ratio; CI, confidence interval; GCS, Glasgow Coma Scale; CT, computed tomography. Predictors were entered simultaneously. Model 1 used Firth's penalized likelihood because of the low events-per-variable ratio. Variance inflation factors were < 1.4 for all predictors.



Points: adjusted odds ratio; bars: 95% confidence interval. Model 1: EPV 2.33 (Firth-penalized); Model 2: EPV 6.83.

Figure 4. Forest plot of adjusted odds ratios (log scale) with 95% confidence intervals for in-hospital mortality (Model 1) and unfavorable functional outcome (Model 2). EPV, events per variable; GCS, Glasgow Coma Scale.

In Model 2 (unfavorable functional outcome; Nagelkerke $R^2 = 0.612$; Hosmer-Lemeshow chi-square 5.66, $p = 0.685$), admission GCS (aOR 3.11 per point decrease, 95% CI 2.34–4.14, $p < 0.001$) and age (aOR 1.07 per year, 95% CI 1.04–1.10, $p < 0.001$) were independent predictors. One and two non-reactive pupils (aOR 3.45 and 4.79) and Marshall Score V/VI (aOR 2.65) were also associated with unfavorable outcome.

3.3. Secondary and exploratory analyses

In an exploratory ROC analysis of admission GCS for in-hospital mortality (Figure 5), the unadjusted area under the curve (AUC) was 0.945 (95% CI 0.856–1.000, $p < 0.001$). The Youden index was greatest ($J = 0.818$) at an admission GCS of ≤ 5.5 , which separates deep coma with extensor or absent motor responses (GCS 3–5) from higher scores (GCS 6–12). This cut-off gave a sensitivity of 92.86%

(95% CI 66.13%–99.82%) and a specificity of 88.97% (95% CI 82.41%–93.72%).

Table 5 shows the 2×2 table at this cut-off: 13 true positives (GCS ≤ 5.5 , deceased), 15 false positives (GCS ≤ 5.5 , survived), 121 true negatives (GCS > 5.5 , survived), and a single false negative (GCS > 5.5 , deceased). That patient was elderly, had an initial GCS of 7, and died of delayed cerebral herniation on postoperative day 5. The cross-product ratio $(13 \times 121) / (15 \times 1)$ gives a crude OR of 104.87 (Woolf logit 95% CI 12.80–859.40; $p < 0.001$). The size of this estimate and the width of its interval (more than 825) reflect instability from a sparse cell, not a genuine biological effect. A univariate GCS threshold can therefore overstate predictive power, because GCS absorbs the effect of concurrent uncal herniation, mass-lesion volume, and host age.

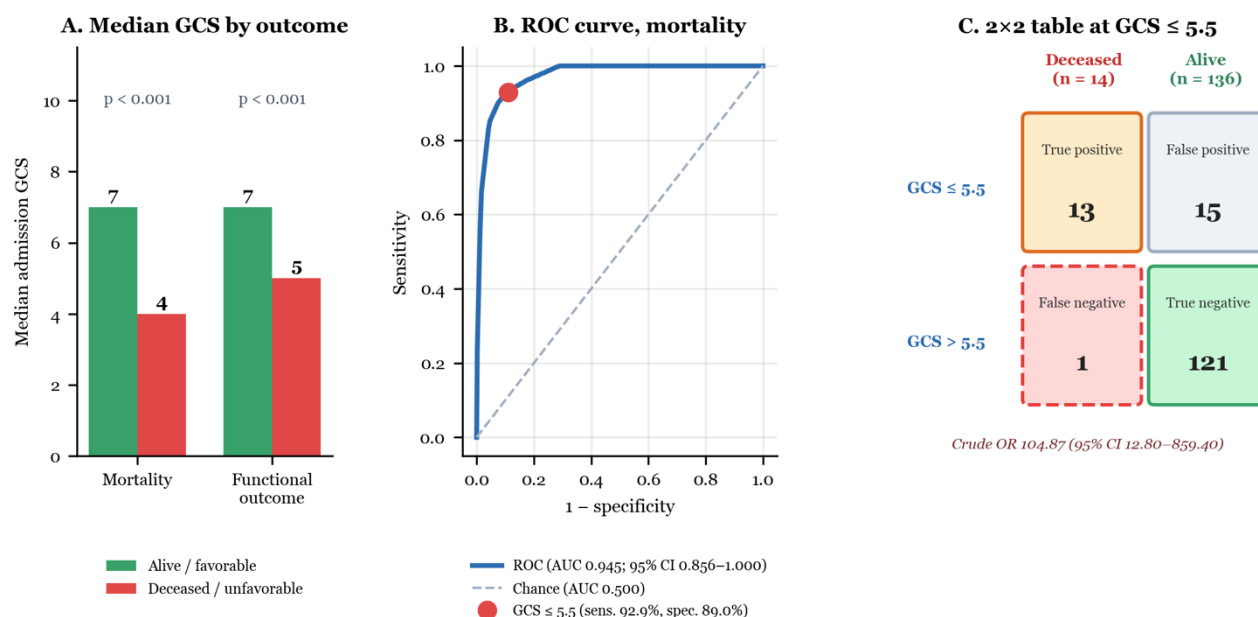


Figure 5. Exploratory GCS discrimination: (A) median admission GCS by outcome (Mann-Whitney U test), (B) ROC curve for in-hospital mortality with the Youden cut-off at GCS ≤ 5.5, and (C) 2×2 table at this cut-off showing the single false-negative case. AUC, area under the curve; OR, odds ratio; ROC, receiver operating characteristic.

Table 5. 2×2 table of admission GCS ≤ 5.5 versus in-hospital mortality, illustrating sparse-cell instability.

Classification	Deceased (n = 14)	Survivors (n = 136)	Total	Diagnostic performance
GCS ≤ 5.5 (predicted death)	13 (true positive)	15 (false positive)	28	Sensitivity 92.86% (95% CI 66.13–99.82)
GCS > 5.5 (predicted survival)	1 (false negative)*	121 (true negative)	122	Specificity 88.97% (95% CI 82.41–93.72)
Total	14	136	150	Positive predictive value 46.43%
Crude odds ratio	104.87	95% CI 12.80–859.40	p < 0.001	Negative predictive value 99.18%

Notes: GCS, Glasgow Coma Scale; CI, confidence interval. *The single patient in the false-negative cell makes the crude odds ratio unstable (Woolf logit 95% CI 12.80–859.40). The AUC was 0.945 (95% CI 0.856–1.000). At GCS ≤ 5.5 (deep coma with extensor or absent motor responses, n = 28), 13 of 14 deaths occurred; at GCS 6–12 (n = 122), 121 patients survived. The cut-off was derived from the same data and the analysis is exploratory.

4. Discussion

4.1. Principal findings

In 150 operated patients with moderate-to-severe TBI, in-hospital mortality was 9.3% and unfavorable functional outcome was 27.3%. Admission GCS remained independently associated with both mortality (aOR 2.78 per point decrease) and unfavorable functional outcome (aOR 3.11) after adjustment for pupils, age, and Marshall class.^{10,20} Bilaterally non-reactive pupils carried the highest adjusted odds of death (aOR 5.12). Age was independently associated with unfavorable functional outcome (aOR 1.07 per year, about 1.97 per decade) but showed only a non-significant trend for mortality (aOR 1.04, p = 0.091). A GCS cut-off of ≤ 5.5 discriminated mortality well (AUC 0.945), but its crude odds ratio of 104.87 was unstable because a single death occurred above the cut-off.^{32,33}

4.2. Comparison with the published literature

In the prospective multicenter CENTER-TBI and TRACK-TBI studies, multivariable models for general TBI populations that use the IMPACT and CRASH core variables (GCS motor score, pupillary reactivity, age, and CT characteristics) clearly outperformed single univariate predictors, with ROC AUC values of 0.80 to 0.88.^{1,10,38} Our findings agree that the combination is more informative than GCS alone. We did not report the AUC of our multivariable models, so we cannot compare discrimination directly.

General severe TBI registries report mortality of 25% to 40%.^{1,18,28} Our mortality of 9.3% reflects a highly selected “surgical survivor” group: patients who were resuscitated in the ED, judged physiologically fit for emergent surgery, survived anesthesia, and reached the ICU.^{24,26} Patients with non-survivable injuries who went straight to palliative comfort care (n = 8) and those intubated before arrival (n = 22) were excluded by protocol.⁴⁰ Recent surgical series, such as those of Hutchinson et al. (2021) and Corriero et al. (2024), also describe selected operated cohorts.^{33,40} By adding the composite unfavorable outcome (27.3%), we captured the burden of neurological devastation among acute survivors and avoided looking at mortality alone.

The surgical context also matters. In RESCUEicp, secondary decompressive craniectomy for refractory intracranial hypertension lowered mortality compared with medical management (26.9% vs 48.9%), although more survivors were left in a vegetative state or with severe disability.⁴¹ In DECRA, early bifrontal craniectomy quickly reduced ICP and ICU length of stay in diffuse injury, but six-month functional outcomes were worse than with standard medical care.⁴² In our cohort, emergent primary decompressive craniectomy with expansive duraplasty (78.7% of cases) was performed to restore intracranial volume.^{26,29,33}

4.3. Interpretation and possible mechanisms

The GCS reflects hierarchically organized structures, from the caudal brainstem to association cortex.²⁷ Eye opening reflects the ascending reticular activating system (ARAS), a

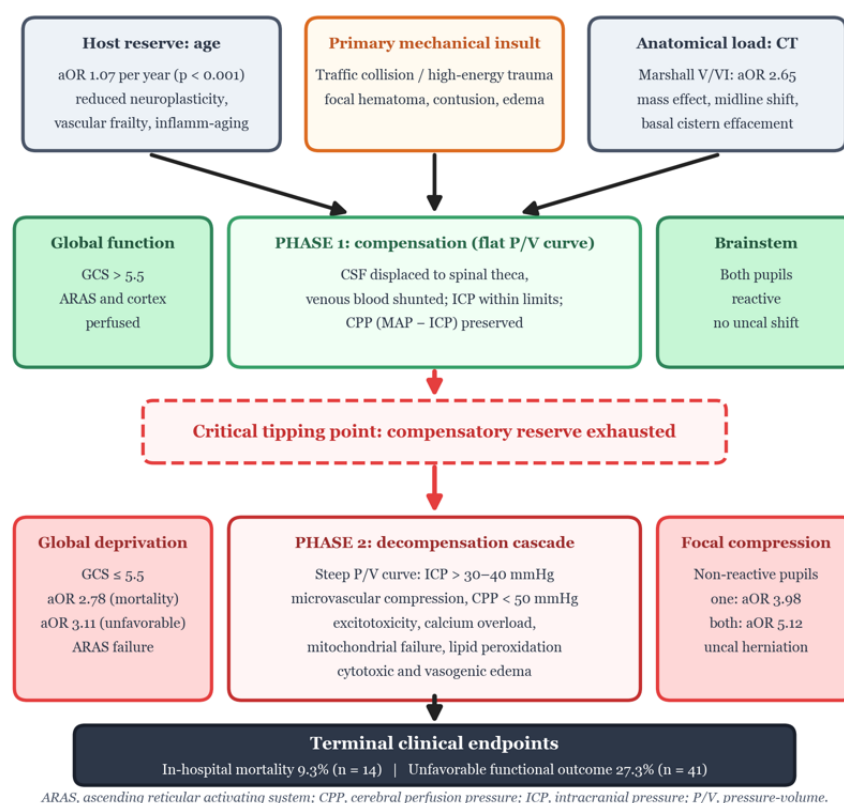
network of cholinergic, noradrenergic, and serotonergic nuclei in the rostral brainstem tegmentum and thalamus that sustains cortical arousal.^{11,28} Motor response tests the primary motor cortex, the corticospinal tracts, and subcortical extrapyramidal pathways. Decorticate posturing (abnormal flexion) suggests extensive bihemispheric damage with sparing of the rubrospinal tract, and decerebrate posturing (abnormal extension) suggests damage reaching the midbrain and upper pontine tegmentum.^{11,27,28} Each point on the scale therefore reflects a step in central neurological reserve, which may help explain why each 1-point decrease more than doubled the adjusted odds of death and more than tripled those of adverse functional dependency.^{10,12} These anatomical correlates were not measured in this study.

The Monro-Kellie doctrine offers a way to link the statistics to physiology (Figure 6). Intracranial volume is fixed and shared among brain parenchyma (80%), CSF (10%), and blood (10%).^{18,43} While compensation lasts, ICP stays

below the treatment threshold of 20–22 mmHg, the ARAS projections still work (admission GCS > 5.5), the perimesencephalic cisterns stay open, and third cranial nerve conduction is preserved (reactive pupils).^{43,44} When reserve is exhausted, elastance rises sharply and small volume increases produce large ICP surges, brainstem distortion, uncal herniation, and neurological collapse.^{41–44} Beyond that point, rising ICP lowers cerebral perfusion pressure (below about 50 mmHg), and ischemia, cytotoxic swelling, and blood-brain barrier breakdown add fluid to the rigid cranium in a self-reinforcing cycle.^{16,20–22} An admission GCS of ≤ 5.5 and non-reactive pupils may reflect this decompensated state, and 13 of the 14 deaths occurred at or below the cut-off. ICP and compliance were not measured, so this explanation is an inference. The cut-off of 5.5 may therefore act as a statistical proxy for this tipping point. A univariate model that loads the effects of pupillary herniation, CT mass effect, and host reserve onto one term can produce an inflated and unstable odds ratio.^{30–33}

Monro-Kellie decompensation and the prognostic triad

Alignment of admission GCS, pupillary reactivity, and age with intracranial dynamics



ARAS, ascending reticular activating system; CPP, cerebral perfusion pressure; ICP, intracranial pressure; P/V, pressure-volume.

Figure 6. Conceptual framework linking the Monro-Kellie compliance curve, the tipping point at GCS ≤ 5.5, and uncal herniation to admission GCS, pupillary reactivity, age, and CT class. This framework is an interpretation and was not tested by the data. ARAS, ascending reticular activating system; CPP, cerebral perfusion pressure; ICP, intracranial pressure; P/V, pressure-volume.

Pupillary non-reactivity is a recognized sign of uncal herniation. An expanding supratentorial mass or massive hemispheric edema pushes the uncus medially and downward through the tentorial notch.^{23,25} The parasympathetic pupilloconstrictor fibers run on the outer surface of the oculomotor nerve and are vulnerable to compression against the tentorial edge, which leaves sympathetic dilator tone unopposed and gives a dilated, poorly reactive pupil on the same side.^{8,23,25} If intracranial hypertension persists, both oculomotor nerves and the pretectal nuclei may be compressed and both pupils

become fixed.^{23,25} A patient with GCS 7 and reactive pupils therefore has a different prognosis from one with GCS 7 and a fixed pupil.^{10,25}

Age was strongly associated with functional dependency and only weakly with death. One possible explanation is that modern surgery and intensive care may prevent immediate herniation-related death in older patients yet often cannot spare them long-term dependency.^{5,20,30} Several mechanisms may contribute, but none was measured here. Aging brings reduced neuroplasticity and

limited neurogenic capacity.^{5,20} Preexisting atrophy gives extra intracranial space, so a subdural hematoma can become large (often > 50–100 mL) before ICP rises enough to lower the GCS.²⁰ Chronic low-grade neuroinflammation (“inflamm-aging”) with primed microglia may amplify the M1 response and cytokine release (TNF- α , IL-1 β) after trauma.^{5,14,15} Age is also a proxy for frailty and limited cardiopulmonary reserve.^{20,30}

Marshall CT class gives an objective anatomical map of the primary injury.³⁷ High scores (V/VI) were associated with unfavorable functional outcome (aOR 2.65, $p = 0.031$) and showed a trend toward higher mortality (aOR 2.89, $p = 0.054$) relative to diffuse injury. High scores reflect parenchymal destruction, midline shift above 5 mm, and effacement of the basal cisterns, a radiographic sign that compliance is exhausted.^{23,37}

4.4. Implications for practice

For neuroanesthesiologists and intensivists who manage emergent surgical TBI, admission GCS alone should not be the basis for prognosis.^{10,24} A statement such as “the patient has a GCS of 6” is incomplete. A fuller formulation also states the pupillary response and age. A GCS of 6 with brisk bilateral pupils in a 22-year-old with an isolated extradural hematoma suggests a better recovery after rapid decompression than a GCS of 6 with a fixed pupil in a 68-year-old with a mass lesion.^{10,20,25} These statements are illustrations drawn from the model, not validated decision rules.

4.5. Strengths

The main strengths are a homogeneous cohort of consecutive surgical patients on one ED-OR-ICU pathway, removal of confounding by pre-hospital sedation, evaluation of both mortality and functional dependency, and a transparent demonstration of how a data-derived GCS cut-off distorts the odds ratio.^{24,32,33,40}

4.6. Limitations

The study is retrospective, single-center, and observational, so unmeasured confounding is likely and may bias associations in either direction.⁴⁰ The cohort of 150 is sizeable for an operative neurotrauma series, but only 14 patients died. The mortality model therefore had an EPV of 2.33, and its adjusted estimates and wide intervals are best viewed as exploratory; standard maximum likelihood estimation risks overfitting and inflated standard errors with fewer than 10 events per variable, and Firth's penalization gives finite estimates with reduced bias but cannot supply the missing information.^{38,39} The GCS cut-off was derived from the same data and probably overstates discrimination, and no internal validation was done. Children and adults were pooled, although the GCS may behave differently in young children. The cohort was restricted to patients who reached surgery and the ICU, which excludes patients who died early and may lower observed mortality. Functional status came from discharge disposition, not from in-person 6-month GOSE interviews, and this proxy probably misclassifies some patients.^{33,34} Finally, the single-center setting limits generalizability to systems with different pre-hospital care or rehabilitation capacity.^{3,4}

4.7. Recommendations for future research

Future prospective multicenter studies in Southeast Asia should add continuous invasive ICP monitoring, automated quantitative pupillometry, multimodal brain tissue

oxygenation monitoring, and standardized 6- and 12-month functional assessments to validate and extend this model.^{21,23,25} As a rule of thumb, a validation cohort for a model with six parameters needs at least 60 deaths (10 events per parameter), which at a mortality of about 9% means roughly 650 operated patients.

5. Conclusion

Among patients with moderate-to-severe TBI who had emergent neurosurgery and intensive care, admission GCS, pupillary light reactivity, and age were independently associated with in-hospital mortality and unfavorable functional outcome. Admission GCS was independently associated with both outcomes, but its value emerged only in a multivariable analysis, because a univariate cut-off produced an unstable odds ratio from a sparse cell. Non-reactive pupils were the strongest physical sign associated with death, and older age was independently associated with functional dependency. Prognostic counseling may benefit from reading coma severity, pupillary response, and age together. These findings come from a single-center retrospective cohort with 14 deaths and need validation.

6. Declarations

Ethical approval and consent to participate. The study protocol was reviewed and approved by the Health Research Ethics Committee of Dr. Saiful Anwar Regional General Hospital, Malang, East Java, Indonesia (reference number 400/127/K.3/102.7/2025, approved on 15 January 2025). The study was conducted in accordance with the Declaration of Helsinki and its later amendments. The requirement for individual written informed consent was waived by the ethics committee because of the retrospective, non-interventional design and the anonymization of patient records.

Consent for publication. Not applicable. No individual personal details, photographs, or identifying patient images are included in this publication.

Availability of data and materials. The de-identified datasets analyzed during the current study are available from the corresponding author on reasonable academic request, subject to institutional ethical review and data-sharing agreements.

Artificial intelligence (AI) use statement. The authors declare that no generative artificial intelligence tool was used in the preparation of this manuscript.

Author contribution statement. R.S.: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. A.A.A.: Validation, Supervision, Project administration, Writing – review & editing. B.H.L.: Validation, Methodology, Supervision, Writing – review & editing. All authors approved the final version of the manuscript.

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Conflict of interest (competing interests) statement. The authors declare that they have no competing interests.

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