

Clinical, Metabolic, and MRI Findings Associated with Early Outcomes in Pediatric Traumatic Axonal Injury: A Single-Center Retrospective Cohort Study

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2 Clinical, Metabolic, and MRI Findings Associated with Early Outcomes in 3 Pediatric Traumatic Axonal Injury: A Single-Center Retrospective Cohort Study

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12 Abstract

13 **Background** Diffuse axonal injury (DAI) is one of the most severe forms of pediatric traumatic brain injury. Single-center
14 pediatric series combining detailed clinical, metabolic, and MRI-based radiological data remain scarce. We aimed to
15 describe the clinical, biochemical, and radiological characteristics of pediatric DAI patients and to identify factors
16 associated with in-hospital mortality and early functional outcome.

17 **Methods** We retrospectively analyzed 68 pediatric patients (under 18 years) with clinically and radiologically confirmed
18 DAI treated at the single pediatric intensive care unit of a regional referral hospital between 2019 and 2024. Admission
19 clinical, biochemical, and MRI-based Adams grade data were compared between outcome groups using standard non-
20 parametric tests, with false discovery rate correction and Monte Carlo exact tests for sparse categorical comparisons.
21 Penalized logistic regression was used for mortality odds ratios given the small number of events; bootstrap confidence
22 intervals were computed for receiver operating characteristic analyses. Because the unfavorable outcome group (Glasgow
23 Outcome Scale score 1-3) included in-hospital deaths, a sensitivity analysis restricted to the 60 survivors (scores 2-3 versus
24 4-5) was performed.

25 **Results** In-hospital mortality was 8/68 (11.8%); 34/68 (50.0%) achieved favorable functional outcome at discharge. Lower
26 admission consciousness level, lower mean arterial pressure, and higher glucose and lactate were associated with mortality.
27 In multivariable analysis, admission consciousness level and DAI grade remained independently associated with favorable
28 outcome; admission consciousness level discriminated mortality with an area under the curve of 0.810. Among survivors

only, consciousness level, DAI grade, mean arterial pressure, glucose, lactate, and several hospital-course variables remained associated with outcome, whereas history of resuscitation, transfusion, pupillary deficit, and coagulation status lost statistical significance.

Conclusions Admission consciousness level and MRI-based DAI grade are independently associated with early in-hospital outcome in pediatric DAI and may support bedside risk stratification, pending confirmation in larger, prospective, multicenter cohorts with standardized long-term follow-up.

Trial registration Not applicable. This is a retrospective observational cohort study and does not report the results of a healthcare intervention on human participants.

Keywords Diffuse axonal injury, Pediatric traumatic brain injury, Glasgow Coma Scale, Magnetic resonance imaging, Outcome

Background

Diffuse axonal injury (DAI) is one of the most severe pathoanatomical forms of traumatic brain injury (TBI), resulting from stretching and shearing damage to axons caused by sudden acceleration-deceleration and rotational forces during high-energy trauma [1-3]. The grading system based on the histopathological description by Adams and colleagues, in which lesions are classified according to involvement of the hemispheric white matter (Grade 1), corpus callosum (Grade 2), and dorsolateral brainstem (Grade 3) [1,3], remains, in its MRI-adapted form, the most widely used radiological staging method today. Pediatric TBI is a major public health problem affecting approximately 5.4 million children worldwide each year, with marked regional variation [4,5]; data from the Middle East and North Africa region likewise indicate that the clinical burden and resource limitations of pediatric TBI are particularly notable in this geography [6]. DAI is recognized as a major determinant of TBI-related mortality and morbidity, particularly in children [2].

Although admission Glasgow Coma Scale (GCS) score [7], radiological DAI grade, and systemic biochemical markers (such as glucose and lactate) have been shown to be associated with mortality and early functional outcome [8-11], data specific to the pediatric population remain limited and largely derive from small sample sizes [12] or multicenter administrative databases [5,8]. Although the prognostic importance of radiological lesion depth (corpus callosum, brainstem) has been demonstrated in adult series [13,14], the consistency of this finding in the pediatric age group and the additional prognostic value that MRI-based DAI grade contributes to core clinical variables remain debated in the literature. A recent pediatric series reported that DAI grade did not provide a significant contribution to a core clinical model (of the IMPACT type) [15], while a national database study showed that the effect of Grade III DAI on mortality was more limited than expected [8]. Furthermore, pediatric DAI cases that initially appear severe have been reported to show marked improvement over months [12,16]; therefore, in-hospital/early outcome should be considered separately from

59 long-term neurodevelopmental prognosis. Single-center pediatric series that jointly evaluate brainstem and corpus callosum
60 involvement (bearing in mind that these are defining components of DAI grade), duration of ventilation and intensive care,
61 nosocomial infection, coagulopathy/transfusion requirements [17], and admission metabolic parameters, with a high level
62 of clinical detail, remain scarce in the literature.

63 This single-center series is, to our knowledge, among the more detailed pediatric DAI cohorts to jointly evaluate clinical,
64 metabolic, and MRI-based radiological data, and is drawn from a region with Turkey's highest fertility rate and a
65 correspondingly high pediatric trauma burden, which we believe adds a distinct regional perspective of relevance to a
66 broader pediatric critical care and trauma readership. In this study, we aimed to describe the clinical, biochemical, and
67 radiological characteristics of pediatric patients followed with a diagnosis of DAI between 2019 and 2024 at the region's
68 only pediatric intensive care unit; to identify factors associated with in-hospital mortality and early functional outcome
69 (GOS) at discharge; and to evaluate the association of admission GCS and MRI-based DAI grade with these early
70 endpoints.

71 Methods

72 This is a retrospective cohort study conducted at Şanlıurfa Training and Research Hospital. The hospital where the study
73 was conducted serves as the region's maternity and children's hospital, with a high patient volume, and is the only
74 healthcare institution in the region with a pediatric intensive care unit (PICU). This characteristic makes the center a
75 referral point for a substantial proportion of severe pediatric trauma cases in the region.

76 Pediatric patients younger than 18 years who were followed in the PICU between 2019 and 2024 and whose diagnosis of
77 DAI was confirmed both clinically and radiologically (MRI, Adams grading) were included in the study. Patients with
78 impaired consciousness not explained by sedation or systemic causes, and with small hemorrhagic and/or non-hemorrhagic
79 lesions on MRI compatible with traumatic axonal injury at the gray-white matter junction, hemispheric white matter,
80 corpus callosum, or brainstem, were included. Patients who did not meet the DAI diagnostic criteria were not included in
81 the cohort definition. Patients with suspected hypoxic-ischemic injury were excluded from the study. Of the patients
82 identified in this manner, 3 were excluded from the study because of missing radiological, progress, or laboratory data, and
83 the analysis was conducted on data from 68 patients. MRI was performed in all patients using a 1.5-Tesla scanner; DWI,
84 ADC, SWI, FLAIR, and T2 sequences were evaluated. In addition to the hospital radiology reports, MRI findings were
85 independently assessed by two neurosurgeons blinded to clinical outcome. Inter-rater agreement for Adams DAI grade, an
86 ordinal variable, was measured using the linear weighted Cohen's kappa coefficient. Agreement for the presence of
87 hemispheric white matter, corpus callosum, and brainstem involvement was assessed using unweighted Cohen's kappa.
88 Disagreements between raters were resolved by consensus. DAI grade was assigned according to the deepest anatomical

89 location of the traumatic axonal lesions: Grade I, hemispheric white matter; Grade II, corpus callosum; and Grade III,
90 brainstem. When lesions were present at more than one level, the highest grade was recorded. Patient data were obtained
91 by individually screening daily progress notes through the hospital information management system (HIMS); all laboratory
92 and radiological data were likewise obtained through the HIMS. The study was designed and reported in accordance with
93 the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for observational studies
94 [18].

95 Level of consciousness at presentation was determined using the Glasgow Coma Scale (GCS) recorded at the time of first
96 admission to hospital [7]. Functional outcome was assessed using the Glasgow Outcome Scale (GOS) evaluated at the time
97 of discharge [19]; therefore, all endpoints reported in this study (mortality and functional outcome) are in-hospital/early
98 outcomes and do not reflect long-term neurodevelopmental course after discharge. Because the GOS 1 category includes
99 death, the unfavorable outcome group, defined as GOS 1-3, also includes in-hospital deaths; mortality and unfavorable
100 functional outcome are therefore not presented as two entirely independent endpoints. To assess the extent to which this
101 overlap affected the functional outcome findings, a sensitivity analysis comparing GOS 2-3 (poor) with GOS 4-5 (good)
102 among the 60 survivors only was additionally performed (see Results).

103 Analysis variables were divided into two conceptual groups: (i) early variables present at admission (GCS, mean arterial
104 pressure [MAP], pH, hematocrit, sodium, glucose, lactate, INR, DAI grade and associated radiological findings, history of
105 cardiopulmonary resuscitation [CPR]) and (ii) variables reflecting the hospital course (duration of ventilation, duration of
106 PICU and ward stay, nosocomial infection, blood transfusion, vasopressor support, surgery, day of MRI). The second
107 group was treated not as an independent prognostic marker in the primary sense, but as a reflection of injury severity and
108 clinical course, and this distinction was maintained throughout the Results and Discussion.

109 The study was approved by the Harran University Non-Interventional Clinical Research Ethics Committee (decision no.
110 HRÜ/24.05.21, 5th session, dated 29 April 2024).

111 Statistical analysis

112 All analyses were performed in Python (v3.12) using the SciPy, statsmodels, and scikit-learn libraries. The distribution of
113 continuous variables was assessed for normality using the Shapiro-Wilk test. Because most continuous variables were not
114 normally distributed, they are reported as median and interquartile range (IQR); normally distributed variables are reported
115 as mean $\pm$ standard deviation. Categorical variables are expressed as frequencies and percentages.

116 Two pre-specified early endpoints were analyzed: in-hospital mortality, and functional outcome at discharge dichotomized
117 using the Glasgow Outcome Scale (GOS) into favorable (GOS 4-5) and unfavorable (GOS 1-3). Between-group
118 comparisons of continuous variables used the independent-samples t-test when the normality assumption was met and the

119 Mann-Whitney U test otherwise. Differences among the three Adams DAI grades were examined using the Kruskal-Wallis
120 test. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test, as appropriate for expected
121 cell counts. Raw p-values are presented in Tables 2 and 3. To evaluate the risk of false positives from multiple
122 comparisons, a Benjamini-Hochberg false discovery rate (FDR) correction was applied as a sensitivity analysis for each
123 outcome family, and q-values are reported in a separate column. For comparisons involving three or more categories (e.g.,
124 the association of DAI grade and trauma mechanism with mortality), results were confirmed using Monte Carlo-based
125 exact p-values because of sparse cell counts.

126 Admission/early variables associated with each endpoint on univariable analysis were entered into binary logistic
127 regression models (OR, 95% CI); hospital-course variables were excluded from multivariable models. DAI grade was
128 modeled as ordinal and, because of collinearity with corpus callosum/brainstem involvement, was not combined with these
129 in the same model. For favorable outcome, a parsimonious model pre-selected one variable per domain (GCS, glucose,
130 DAI grade); for mortality, only univariable estimates are reported given the events-per-variable constraint. Discriminative
131 ability was assessed by ROC/AUC, with the optimal GCS cut-off determined by the Youden index [20]; 95% CIs for AUC,
132 sensitivity, and specificity used 2000-replicate bootstrap resampling, and the Brier score summarized overall prediction
133 error. These ROC findings are secondary/exploratory, being derived and tested in the same dataset with only 8 mortality
134 events, and should not be interpreted as a validated prediction tool. Holm-corrected Dunn post hoc comparisons followed
135 significant Kruskal-Wallis tests across DAI grades, and the ordinal-effect assumption for DAI grade was tested via a
136 categorical sensitivity analysis (grades 2 and 3 vs. grade 1; Table 5). Because of complete or near-complete separation for
137 some mortality variables, univariable mortality ORs were calculated using Firth penalized logistic regression. Two-sided
138 $p < 0.05$ was considered significant.

139 Results

140 Sixty-eight pediatric patients with radiologically confirmed DAI met the inclusion criteria (46 male, 67.6%; median age 6.0
141 years, IQR 2.0-12.0). Median admission GCS was 7.0 (IQR 5.0-11.0). Adams DAI grade distribution was 27 (39.7%), 27
142 (39.7%), and 14 (20.6%) for grades 1, 2, and 3, respectively; inter-rater agreement for DAI grade was high (exact
143 agreement 90.1%, linear weighted kappa = 0.87, 95% CI 0.80-0.94). In-hospital mortality was 8/68 (11.8%); at discharge,
144 34/68 patients (50.0%) achieved favorable functional outcome (GOS 4-5) and 34 (50.0%) had unfavorable outcome (GOS
145 1-3). Full baseline, clinical, and hospital-course characteristics are presented in Table 1.

146 Factors associated with mortality (Table 2). Patients who died had significantly lower admission GCS (median 5.0 vs. 8.0)
147 and MAP, and higher glucose and lactate. Brainstem involvement, higher DAI grade, vasopressor support, CPR history,

148 and blood transfusion were significantly more frequent in the non-survivor group; duration of ventilation and ward stay
149 also differed significantly between groups (see Table 2 for detailed values).

150 Factors associated with functional outcome (Table 3). In the favorable outcome group, admission GCS and MAP were
151 higher, and glucose and lactate were lower (all $p<0.001$). Brainstem and corpus callosum involvement, higher DAI grade,
152 vasopressor support, duration of ventilation/PICU stay, and nosocomial infection were significantly associated with
153 unfavorable outcome; pupillary deficit, CPR history, and blood transfusion also reached significance (see Table 3 for
154 details).

155 Sensitivity analysis for outcome overlap. Because the unfavorable outcome group (GOS 1-3) includes deaths, a comparison
156 restricted to the 60 survivors, comparing poor (GOS 2-3) with good (GOS 4-5) outcome, was additionally performed.
157 Duration of ventilation, PICU stay, GCS, vasopressor support, day of MRI, DAI grade, nosocomial infection, corpus
158 callosum involvement, lactate, glucose, MAP, and seizure remained significant among survivors; in contrast, CPR history,
159 admission pH, surgery, blood transfusion, pupillary deficit, and INR did not reach significance. This suggests that the
160 association of the latter variables in the primary analysis may be largely driven by the mortality component.

161 Clinical and laboratory findings by DAI grade are presented in Table 4. As Adams grade increased, admission GCS and
162 MAP declined progressively, while glucose, lactate, duration of ventilation, and PICU stay increased (all $p<0.05$). Age, pH,
163 hematocrit, sodium, INR, ward stay, and day of MRI did not differ significantly among grades. On Holm-corrected Dunn
164 post hoc comparisons, the difference in GCS and duration of ventilation was significant between all three grade pairs; the
165 difference in MAP and lactate was mainly driven by grade 1 versus grades 2/3 (with no significant difference between
166 grades 2 and 3), and PICU stay differed significantly only between grades 1 and 3.

167 Regression and discriminative ability are presented in Tables 5 and 6 and Fig. 1. In Firth penalized univariable analysis, the
168 variables most strongly associated with mortality were brainstem involvement, DAI grade, and blood transfusion; the
169 variables most strongly associated with favorable outcome were corpus callosum involvement, DAI grade, and duration of
170 ventilation. In the multivariable model (for favorable outcome; pseudo- $R^2 = 0.42$), admission GCS and DAI grade
171 remained independently associated, while glucose remained borderline; in the sensitivity analysis in which DAI grade was
172 modeled categorically, this association remained significant for grade 2 but did not reach significance for grade 3.

173 Admission GCS discriminated mortality with an AUC of 0.810 and favorable outcome with an AUC of 0.834; a cut-off of
174 ≤ 5 predicted mortality with 75% sensitivity and 80% specificity. DAI grade and glucose also showed moderate
175 discriminative ability (AUC 0.75-0.87).

176 Trauma mechanism (Table 7). The most common mechanism was road traffic accidents (55.9%), followed by falls
177 (25.0%). Trauma mechanism groups did not differ significantly in mortality or favorable functional outcome.

Variable	Median [IQR] / n (%)	Min-Max
Age (years)	6.0 [2.0-12.0]	1.0-17.0
Admission GCS	7.0 [5.0-11.0]	3.0-14.0
Admission MAP (mmHg)	72.6 [66.6-83.3]	36.6-96.3
Heart rate (bpm)	120.5 [100.0-136.2]	72.0-164.0
Admission pH	7.3 [7.2-7.4]	7.0-7.5
Hematocrit (%)	33.1 [29.8-38.1]	23.0-48.3
Sodium (mmol/L)	139.0 [136.0-141.0]	129.0-183.0
Glucose (mg/dL)	206.5 [145.5-295.2]	90.0-390.0
Lactate (mmol/L)	2.6 [1.9-3.4]	1.1-11.5
INR	1.2 [1.1-1.4]	0.9-2.5
Ventilation (days)	5.0 [1.0-13.2]	0.0-61.0
PICU stay (days)	15.0 [8.8-29.0]	2.0-119.0
Ward stay (days)	3.0 [1.0-6.0]	0.0-48.0
Day of MRI	5.0 [2.0-7.0]	1.0-16.0
Male sex	46 (67.6%)	-
History of CPR	16 (23.5%)	-
Seizure	11 (16.2%)	-
Pupillary deficit	27 (39.7%)	-
Blood transfusion	30 (44.1%)	-
Vasopressor support	31 (45.6%)	-
Corpus callosum involvement	39 (57.4%)	-
Brainstem involvement	14 (20.6%)	-
Hemispheric white matter	59 (86.8%)	-
Hypertonic therapy	64 (94.1%)	-
Surgery	14 (20.6%)	-
Additional trauma	58 (85.3%)	-
Nosocomial infection	23 (33.8%)	-

179 Continuous variables: median [IQR]. Categorical variables: n (%). Normality assessed by Shapiro-Wilk test. The highest sodium value
180 (183 mmol/L) is a genuine admission value, not a post-hypertonic-therapy measurement; a sensitivity analysis excluding this single
181 outlier did not change the association of sodium with mortality or functional outcome (see Limitations, in Discussion).

Variable	Death (n=8)	Survivor (n=60)	p	Test	q (FDR)
Ward stay (days)	0.0 [0.0-0.0]	3.0 [2.0-6.0]	<0.001	MWU	<0.001
DAI grade (1/2/3)	0/2/6	27/25/8	<0.001	Chi-square	0.003
Ventilation (days)	19.5 [15.8-28.8]	4.5 [1.0-7.5]	<0.001	MWU	0.004
Brainstem involvement	6 (75%)	8 (13%)	<0.001	FET	0.004
Vasopressor support	8 (100%)	23 (38%)	0.001	FET	0.006
Admission GCS	5.0 [4.5-5.2]	8.0 [6.0-11.2]	0.004	MWU	0.021

Variable	Death (n=8)	Survivor (n=60)	p	Test	q (FDR)
Admission MAP (mmHg)	57.5 [52.5-62.2]	73.3 [70.0-83.3]	0.005	MWU	0.022
Glucose (mg/dL)	287.0 [247.5-306.8]	199.5 [140.0-285.0]	0.013	MWU	0.045
CPR history	5 (62%)	11 (18%)	0.015	FET	0.045
Blood transfusion	7 (88%)	23 (38%)	0.018	FET	0.050
Lactate (mmol/L)	4.2 [2.9-4.7]	2.5 [1.9-3.2]	0.021	MWU	0.054
Pupillary deficit	6 (75%)	21 (35%)	0.051	FET	0.119
Age (years)	11.5 [6.5-15.2]	5.0 [2.0-12.0]	0.102	MWU	0.209
Nosocomial infection	5 (62%)	18 (30%)	0.109	FET	0.209
INR	1.4 [1.2-1.7]	1.2 [1.1-1.4]	0.112	MWU	0.209
Corpus callosum involvement	7 (88%)	32 (53%)	0.125	FET	0.219
Sodium (mmol/L)	140.5 [137.0-146.0]	138.5 [136.0-141.0]	0.160	MWU	0.264
PICU stay (days)	20.5 [15.8-28.8]	12.5 [7.8-29.0]	0.219	MWU	0.328
Admission pH	7.2 [7.2-7.3]	7.3 [7.2-7.4]	0.223	MWU	0.328
Day of MRI	3.5 [2.8-4.2]	5.0 [2.0-7.0]	0.275	MWU	0.384
Hematocrit (%)	30.5 [28.5-37.7]	33.6 [29.9-38.1]	0.561	MWU	0.748
Additional trauma	8 (100%)	50 (83%)	0.593	FET	0.755
Heart rate (bpm)	119.5 [100.8-136.5]	120.5 [100.0-136.2]	0.849	MWU	1.000
Male sex	6 (75%)	40 (67%)	1.000	FET	1.000
Seizure	1 (12%)	10 (17%)	1.000	FET	1.000
Hemispheric white matter	7 (88%)	52 (87%)	1.000	FET	1.000
Hypertonic therapy	8 (100%)	56 (93%)	1.000	FET	1.000
Surgery	1 (12%)	13 (22%)	1.000	FET	1.000

183 Continuous variables: median [IQR]; categorical variables: n (%). MWU, Mann-Whitney U test; FET, Fisher's exact test; q, p-value
184 after Benjamini-Hochberg FDR correction. Bold rows q<0.05.

185 **Table 3. Factors associated with functional outcome**

Variable	Good (n=34)	Poor (n=34)	p	Test	q (FDR)
Ventilation (days)	1.0 [0.0-4.5]	12.5 [5.2-24.8]	<0.001	MWU	<0.001
Vasopressor support	5 (15%)	26 (76%)	<0.001	Chi-square	<0.001
Admission GCS	11.0 [7.2-12.0]	6.0 [5.0-7.0]	<0.001	MWU	<0.001
PICU stay (days)	9.0 [7.0-13.8]	27.0 [16.8-34.8]	<0.001	MWU	<0.001
DAI grade (1/2/3)	23/8/3	4/19/11	<0.001	Chi-square	<0.001
Nosocomial infection	4 (12%)	19 (56%)	<0.001	FET	0.001
Lactate (mmol/L)	2.2 [1.8-2.6]	3.1 [2.6-4.4]	<0.001	MWU	0.001
Admission MAP (mmHg)	79.9 [70.3-84.3]	69.5 [56.6-75.7]	<0.001	MWU	0.002
Glucose (mg/dL)	170.0 [129.0-211.2]	268.0 [196.2-303.0]	<0.001	MWU	0.002
Corpus callosum involvement	12 (35%)	27 (79%)	<0.001	Chi-square	0.002
Day of MRI	4.0 [2.0-5.8]	6.0 [4.0-7.8]	0.002	MWU	0.006
Ward stay (days)	3.5 [2.0-6.0]	1.5 [0.0-4.0]	0.004	MWU	0.010
Blood transfusion	9 (26%)	21 (62%)	0.007	Chi-square	0.016
CPR history	3 (9%)	13 (38%)	0.009	FET	0.017

Variable	Good (n=34)	Poor (n=34)	p	Test	q (FDR)
Pupillary deficit	8 (24%)	19 (56%)	0.013	Chi-square	0.025
Admission pH	7.3 [7.3-7.4]	7.3 [7.2-7.3]	0.024	MWU	0.041
INR	1.2 [1.1-1.3]	1.3 [1.1-1.4]	0.025	MWU	0.041
Brainstem involvement	3 (9%)	11 (32%)	0.033	FET	0.052
Seizure	2 (6%)	9 (26%)	0.045	FET	0.066
Sodium (mmol/L)	138.0 [136.0-140.0]	139.0 [137.0-142.0]	0.068	MWU	0.096
Additional trauma	26 (76%)	32 (94%)	0.083	FET	0.111
Surgery	4 (12%)	10 (29%)	0.132	FET	0.168
Heart rate (bpm)	115.0 [100.0-134.2]	125.5 [102.0-138.8]	0.217	MWU	0.265
Age (years)	5.0 [2.0-11.5]	7.0 [2.2-13.0]	0.295	MWU	0.344
Hematocrit (%)	33.6 [31.0-36.0]	32.5 [28.9-38.9]	0.787	MWU	0.857
Male sex	24 (71%)	22 (65%)	0.795	Chi-square	0.857
Hemispheric white matter	30 (88%)	29 (85%)	1.000	FET	1.000
Hypertonic therapy	32 (94%)	32 (94%)	1.000	FET	1.000

Good = GOS 4-5 (at discharge), Poor = GOS 1-3 (at discharge). MWU, Mann-Whitney U test; FET, Fisher's exact test; q, p-value after Benjamini-Hochberg FDR correction. Bold rows q<0.05.

Table 4. Clinical and laboratory findings across Adams DAI grades

Variable	Grade 1	Grade 2	Grade 3	p	Test
Age (years)	7.0 [3.0-13.0]	5.0 [2.0-12.0]	8.0 [2.8-10.0]	0.343	K-W
Admission GCS	11.0 [7.5-12.0]	7.0 [6.0-8.0]	5.0 [3.0-6.5]	<0.001	K-W
Admission MAP (mmHg)	83.3 [72.4-84.7]	70.0 [55.0-73.6]	71.2 [58.7-76.7]	0.001	K-W
Heart rate (bpm)	110.0 [94.0-125.0]	126.0 [103.0-139.0]	130.5 [110.0-137.5]	0.044	K-W
Admission pH	7.3 [7.3-7.4]	7.3 [7.2-7.3]	7.3 [7.1-7.3]	0.289	K-W
Hematocrit (%)	34.0 [31.0-37.0]	34.0 [29.5-38.7]	31.0 [28.9-37.2]	0.740	K-W
Sodium (mmol/L)	138.0 [135.5-140.5]	139.0 [137.0-142.0]	138.0 [136.2-139.0]	0.415	K-W
Glucose (mg/dL)	167.0 [122.0-210.5]	235.0 [178.5-300.5]	252.0 [199.0-301.2]	0.011	K-W
Lactate (mmol/L)	2.1 [1.7-2.8]	2.9 [2.2-3.5]	3.4 [2.5-4.4]	0.007	K-W
INR	1.2 [1.1-1.3]	1.2 [1.1-1.4]	1.3 [1.2-1.4]	0.336	K-W
Ventilation (days)	1.0 [0.5-5.0]	6.0 [2.5-12.5]	19.5 [5.2-30.5]	<0.001	K-W
PICU stay (days)	10.0 [7.0-19.0]	16.0 [9.0-29.0]	28.5 [13.2-54.8]	0.008	K-W
Ward stay (days)	3.0 [2.0-6.0]	3.0 [1.0-6.0]	0.0 [0.0-4.5]	0.053	K-W
Day of MRI	4.0 [2.0-6.5]	6.0 [3.0-7.0]	4.5 [3.2-6.8]	0.382	K-W

Continuous variables: median [IQR]; K-W, Kruskal-Wallis test. Bold rows p<0.05. The grade-wise distribution of mortality, functional outcome, and radiological involvement is presented in Tables 2 and 3 and is not repeated here to avoid duplication. On Holm-corrected Dunn post hoc testing: GCS and duration of ventilation differed significantly between all three grade pairs (all pairwise p<0.05); the difference in MAP and lactate was mainly driven by grade 1 versus grades 2/3 (no significant difference between grades 2 and 3); PICU stay differed significantly only between grades 1 and 3.

Variable	OR	95% CI	p
Univariable — Mortality (Firth penalized logistic regression)			
Age (years)	1.12	0.98-1.28	0.107
Admission GCS	0.68	0.49-0.95	0.022
Admission MAP (mmHg)	0.94	0.90-0.99	0.016
Glucose (mg/dL)	1.01	1.00-1.02	0.028
Lactate (mmol/L)	1.37	0.99-1.90	0.061
Pupillary deficit	4.78	0.99-23.01	0.051
CPR history	6.76	1.49-30.77	0.013
Blood transfusion	7.98	1.25-50.87	0.028
Brainstem involvement	16.06	3.05-84.50	0.001
Corpus callosum involvement	4.38	0.69-27.98	0.118
DAI grade	9.06	2.18-37.60	0.002
Ventilation (days)	1.07	1.02-1.12	0.008
Univariable — Favorable outcome (OR>1 favors good outcome)			
Age (years)	0.95	0.87-1.04	0.292
Admission GCS	1.68	1.32-2.14	<0.001
Admission MAP (mmHg)	1.08	1.03-1.13	0.001
Glucose (mg/dL)	0.99	0.98-0.99	<0.001
Lactate (mmol/L)	0.43	0.25-0.74	0.002
Pupillary deficit	0.24	0.09-0.69	0.008
CPR history	0.16	0.04-0.62	0.008
Blood transfusion	0.22	0.08-0.62	0.004
Brainstem involvement	0.20	0.05-0.81	0.024
Corpus callosum involvement	0.14	0.05-0.42	<0.001
DAI grade	0.18	0.07-0.42	<0.001
Ventilation (days)	0.74	0.62-0.88	<0.001
Multivariable — Favorable outcome (pseudo-R² = 0.42)			
Admission GCS	1.49	1.15-1.94	0.003
Glucose (mg/dL), per 50 mg/dL increase	0.66	0.43-1.01	0.055
DAI grade (ordinal, per grade)	0.36	0.13-0.99	0.048
Sensitivity analysis — DAI grade categorical (reference: Grade 1; pseudo-R² = 0.46)			
Admission GCS	1.56	1.18-2.06	0.002
Glucose (mg/dL)	0.99	0.98-1.00	0.096
Grade 2 (vs Grade 1)	0.11	0.02-0.58	0.009
Grade 3 (vs Grade 1)	0.20	0.03-1.42	0.107

195 OR, odds ratio; CI, confidence interval. Bold rows $p < 0.05$. In the primary model, DAI grade was modeled as an ordinal variable; the
 196 sensitivity analysis below repeats the same model with DAI grade modeled categorically (grade 1 as reference). Because of the small
 197 number of mortality events ($n=8$) and near-complete separation for some variables, univariable mortality ORs were calculated using
 198 Firth penalized logistic regression, which reduces small-sample bias; wide confidence intervals for some variables (e.g., brainstem
 199 involvement, DAI grade) should nonetheless be interpreted cautiously. Favorable-outcome models (more balanced event count, 34/34)
 200 were calculated using standard logistic regression.

201 **Table 6. Discriminative ability (ROC/AUC)**

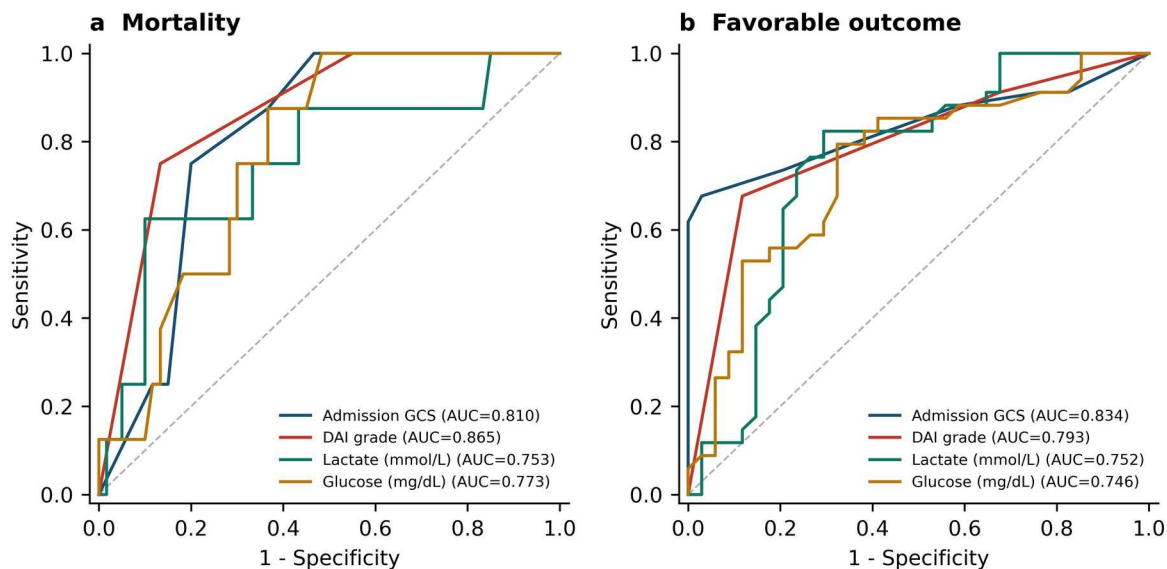
Endpoint	Admission marker	AUC	Bootstrap 95% CI
Mortality	Admission GCS	0.810	0.687-0.911
Mortality	DAI grade	0.865	0.750-0.951
Mortality	Lactate (mmol/L)	0.753	0.534-0.940
Mortality	Glucose (mg/dL)	0.773	0.636-0.901
Favorable outcome	Admission GCS	0.834	0.722-0.929
Favorable outcome	DAI grade	0.793	0.686-0.894
Favorable outcome	Lactate (mmol/L)	0.752	0.630-0.870
Favorable outcome	Glucose (mg/dL)	0.746	0.619-0.861

202 *Confidence intervals calculated using 2000-replicate bootstrap resampling. Optimal admission GCS cut-off for mortality (Youden*
203 *index): GCS ≤5 (sensitivity 75% [bootstrap 95% CI 40-100%], specificity 80% [95% CI 69-90%]). The Brier score of the GCS-only*
204 *logistic model was 0.095; this score summarizes overall probabilistic prediction error and should not alone be taken as evidence of*
205 *calibration. This cut-off remains exploratory: it was both derived and tested in the same dataset and is based on only 8 mortality events;*
206 *no external validation was performed.*

207 **Table 7. Distribution of trauma mechanism and association with outcome**

Trauma mechanism group	n (%)	Death n (%)	Favorable outcome n (%)
Road traffic accident (occupant/pedestrian/motorcycle)	38 (55.9)	5 (13.2)	18 (47.4)
Fall (height/stairs)	17 (25.0)	2 (11.8)	10 (58.8)
Other (asphyxia, electrical injury, drowning, falling object)	13 (19.1)	1 (7.7)	6 (46.2)

208 *Mechanisms were grouped into three main categories because of small cell counts; the "other" category includes asphyxia, electrical*
209 *injury, drowning, and falling-object injury, some of which may involve a primarily hypoxic-ischemic rather than classic shear-type*
210 *mechanism; this distinction was not systematically assessed in this dataset (see Limitations, in Discussion). Trauma mechanism was not*
211 *significantly associated with mortality (chi-square $p=0.87$, Monte Carlo exact $p=0.898$) or favorable functional outcome (chi-square*
212 *$p=0.70$, Monte Carlo exact $p=0.795$).*



213

214 **Fig. 1** Receiver operating characteristic (ROC) curves for admission GCS, DAI grade, lactate, and glucose. *a* In-hospital

215 mortality. *b* Favorable functional outcome at discharge (GOS 4-5). AUC values correspond to those reported in Table 6.

216 GCS, Glasgow Coma Scale; DAI, diffuse axonal injury; AUC, area under the curve

217 Discussion

218 Şanlıurfa, according to the Turkish Statistical Institute's (TURKSTAT) 2024 birth statistics, has the highest total fertility
 219 rate in Turkey at 3.28, and is the only province nationwide exceeding a rate of 3 children [21]. This demographic structure
 220 results in a pediatric population, and consequently a pediatric trauma burden, that is markedly above the national average in
 221 the region. Şanlıurfa Training and Research Hospital, where this study was conducted, is the only institution with a
 222 pediatric intensive care unit serving this large pediatric population, and therefore provides a cohort representing a
 223 substantial proportion of regional pediatric DAI cases. The demographic findings in our study (68% male predominance,
 224 median age 6.0 years) are broadly consistent with previous pediatric DAI series and with pediatric TBI data reported from
 225 the Middle East and North Africa region [2,6,8].

226 This study is a relatively comprehensive example among single-center series with a high level of clinical detail that jointly
 227 evaluate admission GCS, MRI-based Adams grade, and early metabolic parameters (glucose, lactate) in pediatric DAI.
 228 Admission GCS was strongly associated with early functional outcome at discharge. MRI-based DAI grade showed an
 229 independent association in the primary ordinal model; however, in the categorical sensitivity analysis, estimates were
 230 uncertain, particularly for grade 3 (see Table 5). It is therefore more cautious to state that the two variables carry
 231 contextually complementary information rather than that DAI grade adds independent prognostic value beyond GCS. This
 232 finding differs from corrected analyses in some pediatric series reporting that the independent contribution of DAI grade is
 233 lost once added to core clinical variables (such as GCS) [15]; this difference may stem from our study's endpoint being

234 discharge GOS, whereas the comparator study assessed six-month outcome, and may indicate that the added value of DAI
235 grade over GCS differs between the early and long-term periods. Complementary evidence in the literature also indicates
236 that admission GCS alone may not be sufficient: the GCS-Pupil (GCS-P) score, formed by adding pupillary reactivity to
237 GCS, has been shown to be more strongly associated with mortality and functional outcome than GCS alone [22], and the
238 BIG score, combining base deficit, INR, and GCS, has been reported to show a similar advantage [23]. The association of
239 pupillary deficit with poor outcome in univariable analysis in our cohort (Table 3) suggests that testing GCS-P or similar
240 composite scores specifically in pediatric DAI could be valuable in future studies.

241 In Table 2, which evaluated factors associated with mortality, lower admission GCS and lower mean arterial pressure
242 (MAP), together with higher glucose and lactate levels, were prominent among patients who died. This finding is
243 consistent with literature supporting a role for systemic hypoperfusion and the stress response in secondary brain injury:
244 lactate, as a product of anaerobic metabolism, is an indirect marker of tissue hypoperfusion and hypoxia, while
245 hyperglycemia is described as a mechanism arising from the stress response that is thought to aggravate secondary injury
246 by impairing cerebral autoregulation [9,10]. Fu et al., in a cohort of 213 pediatric TBI patients, showed that admission
247 lactate independently predicted mortality and had greater predictive value than glucose [9]. Similarly, Chong et al. reported
248 that early hyperglycemia was associated with mortality in pediatric TBI [10]. The association between low MAP and
249 mortality is consistent with current guidelines that identify maintenance of cerebral perfusion pressure as a priority goal in
250 the management of severe pediatric TBI [24]; however, because our age range was wide (1-17 years), the lack of age-
251 normalization of raw MAP values is a limitation. The prominence of blood transfusion requirement in mortality is
252 consistent with literature reporting that hemorrhage/coagulopathy is associated with poor prognosis in pediatric TBI [17],
253 although this association is also most likely a reflection of injury severity rather than causal. Admission glucose and lactate
254 levels may provide complementary information for early risk stratification; however, their independent prognostic value
255 requires confirmation in larger prospective cohorts, since in the multivariable model only GCS and DAI grade remained
256 independently significant, glucose remained borderline, and lactate did not enter the model. This finding is also consistent
257 with a multicenter Asian cohort of 305 pediatric TBI patients, which reported that early hyperglycemia remained
258 independently associated with unfavorable functional outcome after adjustment, while lactate and acidosis lost significance
259 after the same adjustment [25]; this suggests that glucose and lactate may carry independent prognostic weight to differing
260 degrees in pediatric TBI. Similarly, brainstem involvement, vasopressor requirement, blood transfusion, and infection
261 should be interpreted not as individual "causes of mortality" but as clinical process indicators associated with the severity
262 of injury and systemic illness [2].

263 In Table 3, which examined factors associated with functional outcome, corpus callosum and brainstem involvement,
264 higher DAI grade, prolonged ventilation and intensive care stay, and nosocomial infection were significantly associated
265 with unfavorable outcome. Corpus callosum and brainstem involvement are conceptually closely linked to DAI grade (the

Adams classification is based on these locations). The prognostic importance of lesion depth (superficial hemispheric lesions versus corpus callosum/brainstem) has also been demonstrated in adult series [2,13]; Skandsen et al., in a prospective MRI cohort of 106 patients with moderate-to-severe TBI, showed that prognosis was adversely affected only by brainstem-located lesions [13]. However, lesions within the brainstem itself have also been reported to be non-homogeneous: Abu Hamdeh et al. showed that lesions in the substantia nigra and mesencephalic tegmentum were associated with worse long-term outcome compared with other brainstem locations [14], and Izzy et al. reported that not all brainstem microbleeds carry the same prognostic weight [26]; this more refined sub-classification lies beyond the resolution of the current Adams grading system. Indeed, Moe et al. argued that the use of the Adams classification on clinical MRI often relies on inconsistent and poorly defined criteria, and that MRI-based grading may therefore not perfectly reflect clinical severity and functional outcome [27]; this further underscores the importance of the detailed description, in our Methods section, of how DAI grade was derived from MRI localization findings (corpus callosum/brainstem) in the present study. Lang et al., in a single-center series of 56 pediatric patients with severe TBI-DAI, reported that early fever and extensive DAI involvement on MRI were associated with unfavorable long-term outcome [12]. The association of nosocomial infection and prolonged ventilation/PICU stay with unfavorable outcome is probably because these variables are not prognostic causes in themselves but rather reflect the severity of the underlying injury and a prolonged critical illness course. Furthermore, given that the unfavorable outcome group (GOS 1-3) also includes deaths, a sensitivity analysis restricted to survivors showed that the association of CPR history, blood transfusion, pupillary deficit, and INR with unfavorable outcome lost significance, whereas the association of GCS, DAI grade, corpus callosum involvement, ventilation/PICU duration, nosocomial infection, MAP, glucose, and lactate was preserved. This finding indicates that the association of the first group of variables in the primary analysis may be largely driven by the mortality component, whereas the second group's associations with these variables are preserved even among survivors only.

The progressive decline in GCS and MAP, the rise in glucose and lactate, and the prolongation of ventilation/intensive care duration with increasing Adams DAI grade (Table 4), together with the accompanying increase in mortality and worsening of functional outcome (Tables 2-3), confirm that the grade is a clinically consistent indicator of injury severity; this finding is consistent with the original histopathological description by Adams et al. and with adult cohort data supporting the prognostic value of MRI-based DAI grading [1,3,13]. The Rotterdam CT score has also been reported to be associated with mortality in pediatric neurotrauma series [28]; our findings support that MRI-based DAI grading may serve as a complementary assessment tool in DAI-predominant pediatric cases. Notably, however, a recent national database study reported that the effect of Grade III DAI on mortality in pediatric patients was more limited than expected [8], and another pediatric series reported that DAI grade did not provide significant additional contribution to a core clinical model [15]; this has been partly attributed to the greater neuroplasticity potential of the pediatric brain. The markedly high mortality observed in grade 3 patients in our cohort (43%) suggests that this debated relationship may vary according to population,

sample size, and outcome timing (in-hospital versus long-term), and that the issue requires clarification through larger-scale studies with standardized follow-up.

The independent association of admission GCS and DAI grade with favorable outcome suggests that jointly evaluating these parameters may aid clinical decision-making, paralleling the approach used in adult TBI prognostic scores based on admission characteristics [11]. Admission GCS discriminated mortality with an AUC of 0.810 (Table 6, Fig. 1); however, the wide confidence intervals - particularly for sensitivity - reflect the small number of mortality events (n=8), and because the cut-off was both derived and tested in the same dataset, performance estimates may be optimistic. We therefore present this ROC finding as a secondary, exploratory observation rather than a validated prediction model; further development for clinical use would require a TRIPOD-consistent design with external validation. Machine-learning models based on admission laboratory values have shown high accuracy in predicting pediatric TBI outcome [29], suggesting a foundation for future multicenter model development building on our cohort's findings.

These findings apply to early/in-hospital risk stratification rather than permanent neurodevelopmental prognosis, as long-term pediatric DAI series show that even severe-appearing cases can improve markedly over months to years [12,16]. This study has several additional limitations. The single-center, retrospective design limits the generalizability of the findings. In the absence of a systematic post-discharge follow-up protocol, late mortality and neurodevelopmental outcomes could not be assessed in this study. Because of the small number of events in the mortality group (n=8) and near-zero or complete separation for some categorical variables, univariable mortality odds ratios were calculated using Firth penalized logistic regression; nonetheless, the confidence intervals for some variables (e.g., brainstem involvement, DAI grade) remain wide and should be interpreted descriptively. The same small event count is also the principal reason for the wide confidence intervals of the ROC/AUC findings. Because MRI confirmation was a requirement for diagnosis, patients who were too unstable to be transported for MRI or who died before MRI could be obtained may not have been included in the cohort; this potential selection/survivor bias may have caused the reported mortality rate to be underestimated. Trauma mechanism was not significantly associated with mortality or functional outcome in this cohort (Table 7); however, the small subgroup cell counts may have limited the power to detect clinically meaningful differences. Finally, the lack of age-normalization of raw MAP values is a limitation; because systolic and diastolic blood pressure were not recorded separately in the dataset, standard pediatric hypotension definitions based on age-specific systolic blood pressure percentiles (e.g., the $70+2\times\text{age}$ formula) could not be applied in this study, and this distinction is recommended for future studies.

Conclusions

This study characterizes the clinical, biochemical, and radiological features of 68 pediatric DAI patients from a five-year period at the region's only pediatric intensive care unit, in a region with Turkey's highest fertility rate and correspondingly

high pediatric trauma burden. The sample size is relatively large among single-center pediatric DAI series combining detailed clinical, metabolic, and MRI-based data. Lower admission GCS was strongly associated with unfavorable early outcome, and higher DAI grade showed an independent association in the primary model, though categorical sensitivity estimates for grade 3 remained uncertain. Admission GCS can support urgent bedside risk assessment, while MRI-based DAI grading may offer complementary information once imaging is feasible; admission hyperglycemia, elevated lactate, and hemodynamic instability were also associated with poor outcome. These findings offer a distinct contribution to pediatric DAI literature relevant to resource-limited, high-trauma-burden settings, and warrant confirmation in multicenter, prospective studies with standardized follow-up and external validation.

List of abbreviations

ADC, apparent diffusion coefficient; AUC, area under the curve; CI, confidence interval; CPR, cardiopulmonary resuscitation; DAI, diffuse axonal injury; DWI, diffusion-weighted imaging; FDR, false discovery rate; FET, Fisher's exact test; FLAIR, fluid-attenuated inversion recovery; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; HIMS, hospital information management system; INR, international normalized ratio; IQR, interquartile range; K-W, Kruskal-Wallis test; MAP, mean arterial pressure; MRI, magnetic resonance imaging; MWU, Mann-Whitney U test; OR, odds ratio; PICU, pediatric intensive care unit; ROC, receiver operating characteristic; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SWI, susceptibility-weighted imaging; TBI, traumatic brain injury; TURKSTAT, Turkish Statistical Institute.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Harran University Non-Interventional Clinical Research Ethics Committee (decision no. HRÜ/24.05.21, 5th session, dated 29 April 2024), which waived the requirement for individual informed consent given the retrospective, de-identified nature of the study design. The study was performed in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos).

Availability of data and materials

356 The datasets used and/or analysed during the current study are available from the corresponding author on reasonable
357 request.

358 **Competing interests**

359 The authors declare that they have no competing interests.

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362 **Authors' contributions**

363 Conception or design of the work: BE. Data collection: MK, SE, İY. Data analysis and interpretation: AB, EP. Drafting the
364 article: AB. Critical revision of the article: BE, YB. All authors contributed to the conception and design of the study,
365 acquisition or interpretation of data, and drafting or critical revision of the manuscript. All authors have read and approved
366 the final version of the manuscript.

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