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Tripartite Stratification of the Glasgow Coma Scale in Children with Severe Traumatic Brain Injury and Mortality: An Analysis from a Multi-Center Comparative Effectiveness Study

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Abstract

The Glasgow Coma Scale (GCS) score has not been validated in children younger than 5 years and the clinical circumstances at the time of assignment can limit its applicability. This study describes the distribution of GCS scores in the population, the relationship between injury characteristics with the GCS score, and the association between the tripartite stratification of the GCS on mortality in children with severe traumatic brain injury (TBI). The first 200 children from a multi-center comparative effectiveness study in severe TBI (inclusion criteria: age 0–18 years, GCS ≤8 at the time of intracranial pressure [ICP] monitoring) were analyzed. After tripartite stratification of GCS scores (Group A, GCS 3; Group B, GCS 4 - 5; and Group C, GCS 6 - 8), analyses of variance and chi-square testing were performed. Mean age was 7.61 years ±5.33 and mortality was 19.1%. There was no difference in etiology or type/mechanism of injury between groups. However, groups demonstrated differences in neuromuscular blockade, endotracheal intubation, pre-hospital events (cardiac arrest and apnea), coagulopathy, and pupil response. Mortality between groups was different (42.2% Group A, 22.6% Group B, and 3.8% Group C; $p < 0.001$), and adding pupil response improved mortality associations. In children younger than 5 years of age, a similar relationship between GCS and mortality was observed. Overall, GCS score at the time of ICP monitor placement is strongly associated with mortality across the pediatric age range. Development of models with GCS and other factors may allow identification of subtypes of children after severe TBI for future studies.

Keywords: comparative effectiveness research; Glasgow Coma Scale (GCS) score; pediatric neurocritical care; pediatric traumatic brain injury; secondary injuries

Introduction

It is more than 40 years since the Glasgow Coma Scale (GCS) score was developed for assessing impaired consciousness after severe traumatic brain injury (TBI).[1] This score is now accepted throughout the world as a simple, objective and easy-to-use scale that allows for reproducible assessments of a patient's condition over time and between caregivers.[2] The three component domains to the scale are eye-opening (E, scored 1-4), verbal response (V, scored 1-5), and motor response (M, scored 1-6; Table 1). Although the GCS is the most widely used assessment tool for children and adults with TBI, modifications are needed for the youngest children for whom current V- and M-response scales may not be developmentally appropriate.[3] In fact, children younger than 5 years were not included in the early development of the GCS score.[2] Some modified versions of the GCS score have been described for children,[4–8] yet none have gained universal acceptance as reliable and validated clinical instruments.[2]

Our interest is in improving the outcomes of children with severe traumatic brain injury (TBI) through focused clinical research and

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Table 1. Glasgow Coma Scale Score

	Description	*Score*
Eye opening (E)	Spontaneous	4
	To speech	3
	To pain	2
	None	1
Verbal response (V)	Oriented	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	None	1
Motor response (M)	Obeys commands	6
	Localizes to pain	5
	Withdraws to pain	4
	Flexion to pain	3
	Extension to pain	2
	None	1
Total score	**E + V + M**	**3 to 15**

randomized controlled trials (RCTs).[9,10] The GCS score is the *de facto* classification system of severity in TBI,[2] with scores for severe TBI (GCS ≤8), moderate TBI (GCS 9-12), and mild TBI (GCS 13-15) firmly established in the literature. While having some utility in identifying patients for RCTs of treatment in severe TBI, it is clear that GCS score ≤8 includes a number of clinical phenotypes.[11] Moreover, administration of medications and/or ongoing clinical events (recovery from seizures, resuscitation from shock, etc.) may temporarily alter the GCS score and affect the assignment of illness severity as a result of these transitory events. Since the E- and V-responses may be difficult to assess,[12–14] some of the variation in assessment of coma may be reduced by using the M-response of the GCS rather than the entire score. Alternatively, other investigators have proposed that inclusion of pupil reactivity improves the performance of the GCS at lower total scores in both adults and children.[2,15,16] In children, this test may improve the performance of the GCS in those who have suffered concurrent TBI and hypoxic-ischemic injury[17]; it seems that this phenomenon is particularly relevant when considering those presenting with scores 3 to 5 versus ≥6. Based on these previous studies that used stratified GCS scores, we speculated that dividing the 6-point scale in pediatric severe TBI (GCS scores 3 to 8) to hierarchical tripartite divisions of GCS (3, 4-5, 6-8) would lead to a robust association with mortality.

The Approaches and Decisions in Acute Pediatric TBI (ADAPT) trial[10] is an on-going, international, observational comparative effectiveness research (CER) study that can aid in addressing some of the limitations of the GCS score. This study is testing six hypotheses regarding therapies for intracranial hypertension, secondary injuries, and metabolic support using propensity scores and other statistical tools used in CER studies. For inclusion in the study, children must have total GCS score ≤8 at the time of intracranial pressure (ICP) monitor placement. Hence, children within the ADAPT trial have GCS scoring performed and prospectively recorded by clinicians who have determined that the child requires invasive ICP monitoring and ICP-directed therapies—a situation that is unique in clinical studies. Moreover, because testing of ADAPT's primary hypotheses will require collection of and correction for many covariates, including characteristics of the injury, demographics of the subjects, and events that occurred before ICP monitor placement, these variables are available for an analysis on the relationship between GCS score and important outcomes such as mortality.

For this report, we have analyzed data from the first 200 children enrolled into the ADAPT trial to test the hypotheses that: 1) stratifying the GCS into a tripartite score will demonstrate associations with mortality; 2) this relationship between the tripartite GCS score will be consistent across the entire pediatric age spectrum (including children <5 years of age); 3) the performance of the overall GCS score and that of the M-response alone to predict mortality will be similar; and 4) addition of variables such as pupil response, pre-hospital cardiac arrest, and others will strengthen the association between GCS and mortality.

Methods

As briefly mentioned above, the ADAPT trial is an observational CER study funded by a cooperative agreement with the United States National Institute of Neurological Disorders and Stroke (NINDS; U01 NS 081041).[10] This international study has recruitment sites in the U.S., United Kingdom, Spain, the Netherlands, India, South Africa, Australia, and New Zealand. All participating centers have obtained Institutional Human Research Review Board (IRB or equivalent) ethics approval for enrolling pediatric patients, and the University of Pittsburgh received IRB approval to coordinate the study. Importantly, all of the clinical sites have allowed data collection of standard therapies to be collected prior to informed consent, followed by obtaining informed consent for patient outcome assessments. Therefore, the cohort represents consecutive children meeting inclusion/exclusion criteria at the clinical sites. The ADAPT trial will recruit 1000 pediatric patients, and the first 200 enrolled (February 22, 2014-December 22, 2014) make up the cohort available for this analysis.

The full inclusion criteria for the study are: age 0–18 years, diagnosis of TBI, placement of an ICP monitor at the study site, and GCS score ≤8 at the time of monitor placement. Site personnel were instructed to utilize the version of the GCS score in Table 1 for their assessment of the child's mental status. Children were deemed ineligible for enrollment if there was no documented GCS score recorded before ICP monitor insertion. Importantly, some children had GCS determinations early during the resuscitation procedures—sometimes before endotracheal intubation and other procedures had been performed. On the other hand, other subjects had received sedatives or neuromuscular blocking agents prior to the GCS assessment, which may impact on the E-, V- or M-responses. Centers were instructed to give the most accurate score available to the research team. In some instances, this meant that sites enrolled children with GCS = 3 because the examination was hampered by sedatives, neuromuscular blockers, or both. The sole exclusion criterion was a diagnosis of pregnancy (done as part of the site's routine practices).

For this analysis, data derived from events that occurred prior to arrival at the study hospital were defined as the ''pre-hospital phase of care'' and those that occurred after arrival at the study hospital but prior to insertion of the ICP monitor were defined as the ''resuscitation phase of care.'' In addition to the GCS score at the time of ICP monitor insertion, other variables used in this analysis include: patient demographic characteristics (i.e., age, sex, race, primary language); injury details (i.e., cause, type, and mechanism of injury); severity of illness or injury-related scores (i.e., Pediatric Risk of Mortality [PRISM] III score,[18] Abbreviated Injury Scale [AIS] score,[19] and Injury Severity Score [ISS][20]); pre-hospital events and resuscitation events, including cardiac arrest, hypoxia, and hypotension among others; medications administered; and laboratory results. The definitions of all variables are provided in the Supplementary Table 1 (see online supplementary material at www.liebertpub.com). Coagulation tests were stratified, with prothrombin time (PT) >15 sec and partial thromboplastin time

(PTT) ≥32 sec considered abnormal. The primary outcome for this analysis was death within 12 months of ICP monitor insertion and the cause of death was recorded.

Tripartite stratification of the GCS and data analysis

In this analysis, the GCS was stratified into three parts (tripartite) and patients were assigned to groups based on categories that have been identified in the literature (Group A, GCS score 3; Group B, GCS scores 4-5; Group C, GCS scores 6- 8).[2,15–17] In a parallel analysis, children younger than 5 years of age also were stratified by GCS scores as previous manuscripts describing the utility of GCS score had excluded such children. The demographic and clinical characteristics of these three groups are reported as means and standard deviations for continuous variables and percentages for discrete variables. Analyses of variance were used to test the equality of the means across the groups for continuous variables and the chi-square test was used to compare percentages for discrete variables. When significant differences were identified ($p < 0.05$), *post hoc* pairwise comparisons were carried out (using *t*-test for continuous variables and chi-square for discrete variables) with a Bonferroni correction for multiple comparisons (i.e., $p < 0.05/3 = p < 0.017$). Of note, as these analyses were exploratory in nature and no adjustments for multiple tests were applied, results must be interpreted within this context.

When test assumptions were not met, the non-parametric Kruskal-Wallis test was used to compare between-group means and Fisher's exact test was used to compare the distributions of percentages. The non-parametric Mann-Whitney *U* test was used for *post hoc* comparisons of the three pairwise comparisons of GCS group (with a Bonferroni correction) when overall tests were significant. The association of GCS group with mortality after recruitment into the ADAPT trial was assessed with a Cox proportional hazards model. To control for confounding effects, a multi-variable Cox proportional hazards model was used to assess the independent association of GCS group on risk of death. Covariates included in the model were those characteristics that were significantly imbalanced across the groups, with the exception of the neurological measures, which were excluded because of their collinearity with GCS (due to paralysis). Cox proportional hazards models and the Akaike Information Criterion (AIC) were used to investigate the fit of the model with using only the M-response, incorporating pupil reactivity with GCS, and incorporating cardiac arrest with GCS.

Results

Demographic information stratified by tripartite division of the GCS is summarized in Table 2. The mean age was 7.61 years ±5.33, with 41.5% of subjects younger than 5 years. Subjects were predominantly male (62%) and the overall mortality was 19.1%. With regard to etiology, 88% of subjects had a closed-head injury, 17% had suffered definite or ''probable'' abuse, and 96.9% were not under the influence of drugs or alcohol at the time of injury.

In the whole population, the median GCS score at the time a decision was being made about ICP monitoring placement was 6. The distribution of patients within groups A, B, and C was 32.5%, 15.5%, and 52%, respectively. The AIS and ISS scores confirmed that the body-pattern of injuries in these subjects predominantly involved the head, with ISS scores of 27.4 ± 11.9. There was no significant difference in total ISS or head AIS scores between the GCS groups. There was no significant difference in etiology (including suspicion of abuse), type, or mechanism of injury between the GCS groups.

Neurological examination findings at the time of GCS score assignment are summarized in Table 3. Overall, 9% of subjects were pharmacologically paralyzed at the time of assessment of GCS score—28.6% of all patients in Group A and none of the subjects in the other two groups. Children in Group A also were more likely to have an endotracheal tube in place (Group A 93.7% vs. Group B 74.2% vs. Group C 78.6%; $p = 0.017$ and 0.010 for Group A vs. Group B, and Group A vs. Group C, respectively). However, the proportion of children in each group who were sedated at the time of the assessment was similar (Group A 61.9% vs. Group B 54.8% vs. Group C 66.3%). Pupil response—divided into four categories—varied between GCS groups, with Group A demonstrating a greater incidence of bilateral, fixed, and dilated pupils (Group A 39.1% vs. Group B 16.1% vs. Group C 7.7%; $p = 0.053$ and $p < 0.001$ for Group A vs. Group B, and Group A vs. Group C, respectively). Other potential differences noted in the neurological examination were not interpretable because a large proportion of the assessments were not performed during the resuscitation phase of care (Table 3).

Pre-hospital and injury score information is summarized in Table 4. Overall, 15.6% of subjects had apnea and 8.5% suffered cardiac arrest before arrival to a study hospital. Apnea was more common in Group A, compared with Group C (28.1% vs. 8.7%; $p = 0.001$), while cardiac arrest was less common in Group C compared to Group A and B (1.0% vs. 18.8% vs. 12.9%, $p < 0.001$ and $p = 0.012$ for Group A vs. Group C, and Group B vs. Group C, respectively). Of note, other common secondary injuries (e.g., hypotension, hypoxia, aspiration, seizures, etc.) were not different between the groups during the pre-hospital phase of care.

During the resuscitation phase of care, the only specified secondary injury that was different between groups was hyperthermia (Group C 17.3% vs. Group A 0%; $p < 0.001$; Table 5). In this phase of care, a greater proportion of patients in Group C received anticonvulsants (17.2% vs. 32.3% vs. 52.9%; $p < 0.001$ and $p = 0.044$ for Group A vs. Group C, and Group B vs. Group C, respectively).

Laboratory analyses demonstrated differences in hematological variables assessed. Overall, abnormal PT and PTT values were observed in 32.8% and 28.1% of subjects (Table 5). On group comparisons, there were several significant associations identified. Specifically, i) Group A demonstrated a decreased platelet count, compared with Group C ($243 \times 10^3/\text{mm}^3 \pm 87$ vs. $291 \times 10^3/\text{mm}^3 \pm 100$; $p = 0.003$); ii) a higher proportion of children in Group A demonstrated abnormal PT values, compared with Group C (50.0% vs. 30.8%; $p = 0.021$); and iii) a higher proportion of children in Groups A and B demonstrated abnormal PTT values, compared with Group C (45.3% vs. 29.0% vs. 17.3%; $p < 0.001$ and $p = 0.003$, respectively).

Tripartite stratification of the GCS and mortality

While the overall mortality was 19.1%, the mortality in each group differed significantly (42.2% vs. 22.6% vs. 3.8%; unadjusted hazard ratio [HR] 14.181 and 6.101, $p < 0.001$ for Group A vs. Group C and Group B vs. Group C, respectively; Table 6). After adjustment for multiple covariates, the HR remained significantly different (HR 11.16 and 5.789, $p = 0.031$ for Group A vs. Group C and Group B vs. Group C, respectively). A measure of severity of illness, PRISM III score, also was different between groups (21.5 ± 11.0 vs. 19.7 ± 8.45 vs. 14.0 ± 7.5; $p < 0.001$ for both Group A vs. Group C and Group B vs. Group C). The tripartite analysis was performed for children younger than 5 years of age (comprising 83 children). For children in Group A, the association between GCS and mortality was similar for children in both age strata (HR 16.4 for subjects <5 years vs. 14.2 for subjects ≥5 years).

Table 2. Demographic and Injury Measures by GCS Groups

Measure	*Total* n = *200*	*GCS groups* A (3) n = *65*	B (4, 5) n = *31*	C (6-8) n = *104*	p *value*
Age	7.61 ± 5.33	7.64 ± 5.37	7.02 ± 5.24	7.77 ± 5.37	0.8153
Sex					0.3138
Female	76 (38.0)	26 (40.0)	8 (25.8)	42 (40.4)	
Male	124 (62.0)	39 (60.0)	23 (74.2)	62 (59.6)	
Race					0.3973
White	129 (64.5)	45 (69.2)	21 (67.7)	63 (60.6)	
Black	44 (22.0)	11 (16.9)	7 (22.6)	26 (25.0)	
Other	17 (8.5)	4 (6.2)	1 (3.2)	12 (11.5)	
Unknown	10 (5.0)	5 (7.7)	2 (6.5)	3 (2.9)	
Weight (kg)	31.7 ± 23.1	30.1 ± 21.9	31.5 ± 23.2	32.7 ± 23.9	0.8173
Primary language					0.5609
English	178 (89.4)	58 (90.6)	27 (87.1)	93 (89.4)	
Spanish	14 (7.0)	4 (6.3)	4 (12.9)	6 (5.8)	
Other	7 (3.5)	2 (3.1)	0 (0.0)	5 (4.8)	
Cause of injury					0.4903
Motor vehicle	101 (51.0)	34 (54.0)	19 (61.3)	48 (46.2)	
Accidental fall	32 (16.2)	7 (11.1)	5 (16.1)	20 (19.2)	
Homicide/assault	38 (19.2)	15 (23.8)	4 (12.9)	19 (18.3)	
Other	27 (13.6)	7 (11.1)	3 (9.7)	17 (16.3)	
Type of injury					0.5496
Closed	176 (88.0)	57 (87.7)	26 (83.9)	93 (89.4)	
Penetrating	15 (7.5)	6 (9.2)	2 (6.5)	7 (6.7)	
Blast	1 (0.5)	0 (0.0)	1 (3.2)	0 (0.0)	
Crush	8 (4.0)	2 (3.1)	2 (6.5)	4 (3.8)	
Mechanism of injury					0.6610
Acceleration/Deceleration	26 (13.3)	9 (14.5)	5 (16.1)	12 (11.7)	
Direct impact/Fall	150 (76.5)	45 (72.6)	23 (74.2)	82 (79.6)	
Penetrating	12 (6.1)	4 (6.5)	1 (3.2)	7 (6.8)	
Other	8 (4.1)	4 (6.5)	2 (6.5)	2 (1.9)	
Likelihood injury due to abuse					0.5741
No concern	155 (77.5)	48 (73.8)	25 (80.6)	82 (78.8)	
Possible	11 (5.5)	4 (6.2)	3 (9.7)	4 (3.8)	
Probable	12 (6.0)	5 (7.7)	2 (6.5)	5 (4.8)	
Definite	22 (11.0)	8 (12.3)	1 (3.2)	13 (12.5)	
Likelihood under the influence					0.2658
None	186 (96.9)	59 (93.7)	30 (96.8)	97 (99.0)	
Suspected	1 (0.5)	1 (1.6)	0 (0.0)	0 (0.0)	
Confirmed	5 (2.6)	3 (4.8)	1 (3.2)	1 (1.0)	
Transported to study hospital from:					0.5492
Scene of injury	112 (56.0)	31 (47.7)	20 (64.5)	61 (58.7)	
Home	76 (38.0)	29 (44.6)	10 (32.3)	37 (35.6)	
Other hospital	12 (6.0)	5 (7.7)	1 (3.2)	6 (5.8)	

GCS, Glasgow Coma Scale.

However, for Group B, the risk of mortality was greater in children younger than 5 years, compared with Group C (HR 9.3 for subjects <5 years vs. 4.9 for subjects ≥5 years).

The ability of other variables (i.e., M-response of the GCS score, pupillary responses, cardiac arrest) in place of or along with the overall GCS score to improve the prediction of mortality in this hypothesis-generating analysis was assessed using a goodness-of-fit testing model using Akaike Information Criterion (AIC) scores. The fit of the model of the M-response alone, total GCS alone, tripartite stratification of the GCS alone, tripartite stratification of the GCS with pupil reactivity for those with a GCS of 3, and tripartite stratification of the GCS with cardiac arrest was assessed. The fit was similar utilizing only the M-response (AIC = 353.278), GCS total score (AIC = 353.278), the tripartite stratification (AIC = 352.734), and the tripartite stratification with pre-hospital cardiac arrest (AIC = 352.734). However, the fit improved when pupil reactivity was added to the tripartite score (AIC = 317.665).

Discussion

In this study in which the GCS score was used to determine whether a surgical procedure and ICP-directed therapies were necessary for treatment of a child with severe TBI, we found that a tripartite hierarchical stratification of the GCS meaningfully

Table 3. Neurological Examination Measures by GCS Groups

Measure	Total n = 200	GCS groups (total score) A (3) n = 65	B (4, 5) n = 31	C (6-8) n = 104	Probability values Overall	Pairwise comparisons A vs. B	A vs. C	B vs. C
Status								
Paralyzed	**18 (9.2)**	**18 (28.6)**	**0 (0.0)**	**0 (0.0)**	**<0.0001**	**<0.001***	**<0.001***	**NA**
Sedated	123 (63.1)	39 (61.9)	17 (54.8)	67 (66.3)	0.4963			
Intubated	163 (82.7)	59 (93.7)	23 (74.2)	81 (78.6)	0.0179	0.017	0.010*	0.603
Pupil(s) fixed					**<0.0001**	**0.053**	**<0.001***	**0.144**
Both	38 (19.1)	25 (39.1)	5 (16.1)	8 (7.7)				
Either	24 (12.1)	5 (7.8)	7 (22.6)	12 (11.5)				
Neither	123 (61.8)	30 (46.9)	17 (54.8)	76 (73.1)				
Unable to assess/Unknown	14 (7.0)	4 (6.3)	2 (6.5)	8 (7.7)				
Gaze					**<0.0001**	**0.002***	**<0.001***	**0.442**
Normal	3 (1.5)	2 (3.1)	1 (3.2)	0 (0.0)				
Abnormal	19 (9.5)	6 (9.4)	3 (9.7)	10 (9.6)				
Not tested	148 (74.4)	33 (51.6)	26 (83.9)	89 (85.6)				
Paralyzed	18 (9.0)	18 (28.1)	0 (0.0)	0 (0.0)				
NA	11 (5.5)	5 (7.8)	1 (3.2)	5 (4.8)				
Corneal					**<0.0001**	**<0.001***	**<0.001***	**0.065**
Normal	22 (11.1)	14 (21.9)	4 (12.9)	4 (3.8)				
Abnormal	24 (12.1)	4 (6.3)	7 (22.6)	13 (12.5)				
Not tested	122 (61.3)	22 (34.4)	18 (58.1)	82 (78.8)				
Paralyzed	18 (9.0)	18 (28.1)	0 (0.0)	0 (0.0)				
NA	13 (6.5)	6 (9.4)	2 (6.5)	5 (4.8)				
Cough					**<0.0001**	**0.004***	**<0.001***	**0.657**
Normal	31 (15.6)	7 (10.9)	4 (12.9)	20 (19.2)				
Abnormal	30 (15.1)	12 (18.8)	6 (19.4)	12 (11.5)				
Not tested	110 (55.3)	23 (35.9)	20 (64.5)	67 (64.4)				
Paralyzed	18 (9.0)	18 (28.1)	0 (0.0)	0 (0.0)				
NA	10 (5.0)	4 (6.3)	1 (3.2)	5 (4.8)				
Gag					**<0.0001**	**0.003***	**<0.001***	**0.041**
Normal	24 (12.1)	4 (6.3)	4 (12.9)	16 (15.4)				
Abnormal	29 (14.6)	14 (21.9)	8 (25.8)	7 (6.7)				
Not tested	118 (59.3)	24 (37.5)	18 (58.1)	76 (73.1)				
Paralyzed	18 (9.0)	18 (28.1)	0 (0.0)	0 (0.0)				
NA	10 (5.0)	4 (6.3)	1 (3.2)	5 (4.8)				
Swallow					**<0.0001**	**<0.001***	**<0.001***	**1.000**
Normal	2 (1.0)	1 (1.6)	0 (0.0)	1 (1.0)				
Not tested	169 (84.9)	41 (64.1)	30 (96.8)	98 (94.2)				
Paralyzed	18 (9.0)	18 (28.1)	0 (0.0)	0 (0.0)				
NA	10 (5.0)	4 (6.3)	1 (3.2)	5 (4.8)				

GCS, Glasgow Coma Scale; NA, not assessed.

reflects important characteristics and circumstances of injury, resuscitation, and pre-hospital or early therapies. We confirmed previous work that associated worse GCS score with higher mortality in children with severe TBI,[13,14,16,17,21,22] and our data show that the M-response performs similarly to the total score, as previously described.[11–14] We also provide evidence that GCS scoring in children younger than 5 years of age—who were not included in the early work that developed the GCS[1,2]—demonstrates the same relationship with mortality seen in older patients, albeit with some differences in those with GCS scores 4 or 5. Lastly, the addition of pupil response to the tripartite division of GCS ≤8 improved mortality prediction.

Tripartite stratification of GCS ≤8

In pediatric TBI, the total GCS score not only provides an overview for clinicians deciding about a pathway of care[23] but also a means to classify patients in research studies and RCTs.[24] In the current report, we simplified the 6-point scale for the currently defined severe TBI definition (GCS score 3 to 8) into three groups and found this approach to be highly informative of categorization of severity of TBI that may affect patient care, as well as the design of RCTs. First, in our cohort of children derived from large academic pediatric centers, we found that approximately one-third of children had a GCS score of 3 and approximately one-half had GCS scores between 6 and 8. Given the significant difference in mortality, the current assumption that these children react similarly in response to standard or experimental treatments appears dubious. Second, children in this cohort largely suffered from isolated TBI from a closed-head trauma with minimal influence of alcohol or illicit drug use. This emphasizes that the GCS score was unlikely to have been influenced by patient-based medication use. However, by the time of decision-making about ICP monitoring, clinicians do

Table 4. Prehospital Measures/Injury Scores by GCS Groups

		GCS groups (total score)			*Probability values*			
						Pairwise comparisons		
Measure	*Total* n = *200*	*A (3)* n = *65*	*B (4, 5)* n = *31*	*C (6-8)* n = *104*	*Overall*	*A vs. B*	*A vs. C*	*B vs. C*
Abbreviated Injury Score								
Head	4.30 ± 0.83	4.33 ± 0.89	4.42 ± 0.76	4.25 ± 0.81	0.4343			
Face	0.95 ± 1.07	0.88 ± 1.03	1.00 ± 1.00	0.98 ± 1.11	0.7436			
Neck	0.20 ± 0.64	0.19 ± 0.50	0.13 ± 0.43	0.22 ± 0.77	0.7235			
Thorax	0.96 ± 1.41	1.09 ± 1.61	0.84 ± 1.39	0.91 ± 1.29	0.7420			
Abdomen	0.49 ± 1.06	0.48 ± 0.94	0.55 ± 1.12	0.48 ± 1.12	0.8249			
Spine	0.38 ± 0.98	0.69 ± 1.45	0.23 ± 0.62	0.24 ± 0.62	0.1393			
Upper extremities	0.49 ± 0.85	0.42 ± 0.71	0.39 ± 0.72	0.56 ± 0.95	0.7198			
Lower extremities	0.66 ± 1.04	0.64 ± 0.98	0.48 ± 0.81	0.72 ± 1.13	0.7401			
External	0.56 ± 0.86	0.58 ± 0.92	0.61 ± 0.67	0.53 ± 0.87	0.5134			
Injury Severity Score	27.4 ± 11.9	29.6 ± 13.0	27.0 ± 9.31	26.2 ± 11.8	0.4285			
Apnea					**0.0073**	**0.256**	**0.001***	**0.391**
Yes	31 (15.6)	18 (28.1)	4 (12.9)	9 (8.7)				
No/Unknown	150 (75.4)	39 (60.9)	23 (74.2)	88 (84.6)				
Suspected	18 (9.0)	7 (10.9)	4 (12.9)	7 (6.7)				
Aspiration					0.0519			
Yes	5 (2.5)	3 (4.7)	2 (6.5)	0 (0.0)				
No/Unknown	164 (82.4)	53 (82.8)	22 (71.0)	89 (85.6)				
Suspected	30 (15.1)	8 (12.5)	7 (22.6)	15 (14.4)				
Cardiac arrest					**0.0001**	**0.823**	**<0.001***	**0.012***
Yes	17 (8.5)	12 (18.8)	4 (12.9)	1 (1.0)				
No/Unknown	175 (87.9)	49 (76.6)	26 (83.9)	100 (96.2)				
Suspected	7 (3.5)	3 (4.7)	1 (3.2)	3 (2.9)				
Hypotension					0.0698			
Yes	26 (13.1)	11 (17.2)	7 (22.6)	8 (7.7)				
No/Unknown	165 (82.9)	50 (78.1)	22 (71.0)	93 (89.4)				
Suspected	8 (4.0)	3 (4.7)	2 (6.5)	3 (2.9)				
Hypoxia					0.3107			
Yes	13 (6.5)	6 (9.4)	3 (9.7)	4 (3.8)				
No/Unknown	159 (79.9)	49 (76.6)	22 (71.0)	88 (84.6)				
Suspected	27 (13.6)	9 (14.1)	6 (19.4)	12 (11.5)				
Seizure					0.9791			
Yes	28 (14.1)	9 (14.1)	4 (12.9)	15 (14.4)				
No/Unknown	151 (75.9)	49 (76.6)	23 (74.2)	79 (76.0)				
Suspected	20 (10.1)	6 (9.4)	4 (12.9)	10 (9.6)				
Hyperthermia					1.0000			
Yes	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.0)				
No/Unknown	198 (99.5)	64 (100)	31 (100)	103 (99.0)				
Hypothermia					0.0853			
Yes	16 (8.0)	10 (15.6)	2 (6.5)	4 (3.8)				
No/Unknown	174 (87.4)	52 (81.3)	27 (87.1)	95 (91.3)				
Suspected	9 (4.5)	2 (3.1)	2 (6.5)	5 (4.8)				
Hyperventilation					0.1081			
Yes	6 (3.0)	2 (3.1)	3 (9.7)	1 (1.0)				
No/Unknown	191 (96.0)	61 (95.3)	28 (90.3)	102 (98.1)				
Suspected	2 (1.0)	1 (1.6)	0 (0.0)	1 (1.0)				

GCS, Glasgow Coma Scale.

have to contend with the problem of patient assessment being limited by procedures and medications administered by medical providers (endotracheal tube placement, use of pharmacological sedation, and neuromuscular blockade). Here, the tripartite simplification of GCS ≤8 may also help our thinking about patient recruitment to RCTs of interventions. In the two less severe strata (GCS 4-5 and GCS 6-8), there was similar use of endotracheal tube intubation (~76%) and sedatives (~60%) but virtually no use of neuromuscular blockade. In contrast, in the lowest strata of GCS scores (i.e., GCS = 3), there appears to be at least two unique clinical contexts to account for the unresponsive clinical examination. Clearly, a substantial portion of our cohort received neuromuscular blockade affecting their GCS assessment, while others were unresponsive due solely to their brain injury. A more substantive assessment of the larger cohort within ADAPT may glean significant differences between these two patient populations.

Third, children with a GCS score of 3 may be differentiated by the presence of bilateral fixed and dilated pupils and history of apnea or cardiac arrest—clinical features that occurred infrequently

TABLE 5. RESUSCITATION MEASURES/LABORATORY VALUES BY GCS GROUPS

Measure	Total n = 200	GCS groups (total score) A (3) n = 65	B (4, 5) n = 31	C (6-8) n = 104	Probability values Overall	Pairwise comparisons A vs. B	A vs. C	B vs. C
Complications								
Cardiac arrest	11 (5.5)	7 (10.9)	1 (3.2)	3 (2.9)	0.0826			
Hypotension	59 (29.6)	21 (32.8)	9 (29.0)	29 (27.9)	0.7914			
Hypoxia	8 (4.0)	2 (3.1)	2 (6.5)	4 (3.8)	0.7822			
Seizure	30 (15.1)	7 (10.9)	6 (19.4)	17 (16.3)	0.4891			
Hyperthermia	**21 (10.7)**	**0 (0.0)**	**3 (9.7)**	**18 (17.3)**	**0.0024**	**0.036**	**<0.001***	**0.404**
Hypothermia	52 (26.5)	21 (34.4)	8 (25.8)	23 (22.1)	0.2232			
Hyperventilation	45 (23.0)	14 (22.6)	8 (25.8)	23 (22.3)	0.9184			
Medications								
Anticonvulsant	**76 (38.2)**	**11 (17.2)**	**10 (32.3)**	**55 (52.9)**	**<0.0001**	**0.097**	**<0.001***	**0.044**
Hypertonic saline	85 (42.7)	23 (35.9)	14 (45.2)	48 (46.2)	0.4107			
Mannitol	50 (25.1)	14 (21.9)	7 (22.6)	29 (27.9)	0.6418			
Barbiturate	12 (6.0)	2 (3.1)	2 (6.5)	8 (7.7)	0.5011			
Fluids (mL/kg)								
In	56.8 ± 79.0	44.9 ± 43.3	63.6 ± 49.8	62.3 ± 99.8	0.0898			
Out	28.2 ± 58.5	19.5 ± 26.8	25.6 ± 29.7	34.2 ± 75.9	0.7412			
Labs								
Hemoglobin (gm/dL)	11.0 ± 2.02	10.9 ± 2.15	11.1 ± 1.89	11.0 ± 1.98	0.9148			
Platelets ($\times 10^3$/mm^3)	**272 ± 99.7**	**243 ± 86.6**	**271 ± 113**	**291 ± 99.9**	**0.0118**	**0.271**	**0.003***	**0.365**
WBC ($\times 10^3$/mm^3)	17.3 ± 7.23	16.2 ± 6.60	18.5 ± 7.84	17.7 ± 7.40	0.2988			
Sodium (mEq/L)	141 ± 5.70	142 ± 6.62	141 ± 7.10	140 ± 4.54	0.2408			
PT (sec)					**0.0418**	**0.498**	**0.021**	**0.170**
≥15	76 (38.2)	32 (50.0)	12 (38.7)	32 (30.8)				
<15	88 (44.2)	21 (32.8)	11 (35.5)	56 (53.8)				
Unknown/NA	35 (17.6)	11 (17.2)	8 (25.8)	16 (15.4)				
PTT (sec)					**<0.0001**	**0.275**	**<0.001***	**0.003***
≥32	56 (28.1)	29 (45.3)	9 (29.0)	18 (17.3)				
<32	112 (56.3)	23 (35.9)	13 (41.9)	76 (73.1)				
Unknown/NA	31 (15.6)	12 (18.8)	9 (29.0)	10 (9.6)				
INR					0.0801			
≥1.5	35 (17.6)	17 (26.6)	5 (16.1)	13 (12.5)				
<1.5	131 (65.8)	35 (54.7)	19 (61.3)	77 (74.0)				
Unknown/NA	33 (16.6)	12 (18.8)	7 (22.6)	14 (13.5)				
pH					**0.0180**	**0.511**	**0.046**	**0.004***
≥7.25	111 (55.8)	34 (53.1)	13 (41.9)	64 (61.5)				
<7.25	38 (19.1)	16 (25.0)	11 (35.5)	11 (10.6)				
Unknown/NA	50 (25.1)	14 (21.9)	7 (22.6)	29 (27.9)				
PaO_2 (mm Hg)					0.1545			
≥60	123 (61.8)	46 (71.9)	17 (54.8)	60 (57.7)				
<60	16 (8.0)	3 (4.7)	5 (16.1)	8 (7.7)				
Unknown/NA	60 (30.2)	15 (23.4)	9 (29.0)	36 (34.6)				
pCO_2 (mm Hg)					0.2152			
<30	19 (9.5)	8 (12.5)	6 (19.4)	5 (4.8)				
≥30	85 (42.7)	26 (40.6)	10 (32.3)	49 (47.1)				
≥45	46 (23.1)	16 (25.0)	8 (25.8)	22 (21.2)				
Unknown/NA	49 (24.6)	14 (21.9)	7 (22.6)	28 (26.9)				
HCO_3 (mEq/L)					0.2688			
≥18	133 (66.8)	42 (65.6)	19 (61.3)	72 (69.2)				
<18	18 (9.0)	8 (12.5)	5 (16.1)	5 (4.8)				
Unknown/NA	48 (24.1)	14 (21.9)	7 (22.6)	27 (26.0)				

GCS, Glasgow Coma Scale; NA, not assessed.

in the other upper ranges of our GCS scores in our study. In a previous attempt to better stratify children into clinical trials, the two most recent RCTs of hypothermia in this population used GCS = 3 and bilateral fixed and dilated pupils as a reason for exclusion from trial recruitment,[25,26] with the presumption that this cohort may not benefit from the therapy. Our data support that this combination of factors does represent an increased risk of mortality in these children and supports the presumption that these children may have unique characteristics that should be considered when planning interventional trials. At the other end of the spectrum, children with coma after TBI but showing some responsiveness (i.e., GCS 6-8) have relatively little mortality in our cohort and also

Table 6. Mortality Measures by GCS Groups

		GCS groups (total score)			Unadjusted†			Adjusted*		
Measure	*Total* N = *200*	*A (3)* n = *67*	*B (4, 5)* n = *32*	*C (6-8)* n = *101*	*3 HR*	*4,5 HR*	p	*3 HR*	*4,5 HR*	p
Died	38 (19.1)	27 (42.2)	7 (22.6)	4 (3.8)	14.181	6.106	<0.0001	11.16	5.789	0.0306
Days survived	210 ± 172	141 ± 171	204 ± 163	254 ± 162						
Cause of death										
System trauma	5 (13.5)	3 (11.5)	1 (14.3)	1 (25.0)						
Increased ICP	25 (67.6)	19 (73.1)	4 (57.1)	2 (50.0)						
Medical complications	2 (5.4)	2 (7.7)	0 (0.0)	0 (0.0)						
Other	5 (13.5)	2 (7.7)	2 (28.6)	1 (25.0)						
Other causes										
Diffuse axonal injury	1 (20.0)	0 (0.0)	0 (0.0)	1 (100)						
Hypoxic brain injury	1 (20.0)	0 (0.0)	1 (50.0)	0 (0.0)						
Intracranial hemorrhage	1 (20.0)	1 (50.0)	0 (0.0)	0 (0.0)						
Traumatic brain injury	2 (40.0)	1 (50.0)	1 (50.0)	0 (0.0)						

†Reference category: 6-8.

*Adjusted for pre-hospital apnea and cardiac arrest, hyperthermia complications, anticonvulsant, platelets, prothrombin time, partial thromboplastin time, pH, highest and lowest temperature, pupillary reflexes, lowest pH, highest pCO_2 (mm Hg), highest glucose (mg/dL), highest partial thromboplastin time (in seconds), and Pediatric Risk of Mortality [PRISM] III. Note: Neurological measures were not included due to collinearity with baseline GCS.

GCS, Glasgow Coma Scale; HR, hazard ratio; ICP, intracranial pressure.

may have unique responses to therapies. Further analysis of our larger cohort may make these characteristics more apparent.

Mortality, GCS ≤8, and the tripartite stratification

Previous reports—with less well-described methods for how the GCS was assessed—have shown that lower GCS score is not only associated with increased risk of mortality,[15] but that there is a linear relationship between GCS score and mortality rate in children with pediatric TBI.[16] Our data shows that hierarchical tripartite stratification of the GCS ≤8 in pediatric TBI maintains this relationship with mortality. In this regard, we confirmed similar performance using only the M-response rather than the total GCS score.[11–14] One reason why the M-response should perform so well is the high rate of endotracheal tube intubation in our population (83%), and the obvious difficulty in assessing the V-response. Within our comprehensive assessment of pre-hospital and resuscitation factors related to GCS and mortality, we found that measures of function of the hematopoetic system also were associated with the tripartite distribution of GCS scores. At the lowest GCS scores, children demonstrated lower platelet counts and a greater incidence of abnormal PT and PTT values. While coagulation disturbances are well described in children with severe TBI[27–29] and consistent with activation of the extrinsic, or tissue factor, pathway based on the cascade model of hemostasis,[30–32] our study is the first to fully describe the relationship between these variables within the tripartite GCS stratification. We speculate that these variables may play a future role in identifying unique characteristics along with the GCS and other variables presented in this cohort.

With regard to the youngest children who were excluded from studies that developed the GCS score, we found a relationship between GCS score and mortality in our tripartite system that is relatively similar to those of the older children for those presenting with the lowest GCS scores. Of significance, the hazard ratio for young children with GCS 4-5 was twice as high as the older cohort. This finding may represent a limitation of the GCS to accurately differentiate or gauge severity of TBI in the very youngest patients.[3] Alternatively, added mortality risk in the youngest patients with severe TBI may be related to different systemic response or disturbance in homeostasis in response to equivalent degrees of neurologic injury in the very young.[33]

Last, the improved performance in our outcome model when pupillary examination was included confirms findings in two previous studies.[15,16] We added to this observation with the tripartite separation of GCS ≤8. That is, at the lower end of the spectrum (GCS = 3, Group A) the presence of bilateral fixed and dilated pupils is an important differentiator, which is much less likely to occur in the other upper ranges of our GCS scores.

Limitations

Although our report has several significant strengths, including the multi-center nature of the study, the linkage of GCS scoring assessment with the need for ICP-directed therapies, and the well-characterized collection of potential confounders, there are limitations in our work. First, as a multi-center, international study, we are dependent upon accurate reporting of GCS scores by dozens of personnel at over 50 institutions worldwide. As such, we were unable to assess the reliability of individual GCS scores of subjects within the study. Instead, we must rely on the fact that all personnel at the various institutions would be quite reticent to place an invasive monitor into the brain of an injured child, and have done their best to reliably document the GCS score that prompted the decision. Second, in this analysis, we used mortality as our outcome of choice rather than other tests of neuropsychological or other outcomes. We did this for a number of reasons. The overall purpose of the ADAPT trial is to test the effect of therapies on outcomes at 6 months, specifically Glasgow Outcome Scale-Extended for Pediatrics (GOS-E Peds).[24] Because of this overall plan, we would not compromise the primary goals of the study and thus did not use this outcome for this manuscript. Secondly, we believed that an analysis of mortality was a necessary first step toward determining the relationship between GCS and outcomes. Another limitation of our work is the relatively small sample size. Despite this being one of the larger reports in the field, it is possible that some of the modifiers tested may perform better with a larger number of patients. To

address these limitations, we believe a future analysis of our overall cohort with these covariates and their relationship with GOS-E Peds may be informative.

Conclusion

In our cohort of patients, children undergoing ICP monitoring have generally suffered from closed-head trauma with little evidence of illicit drugs or alcohol affecting their mental status assessment. Our tripartite score within the severe TBI cohort demonstrated that mortality within these strata were quite disparate. This tripartite stratification of the GCS and the addition of pupil responses performed well as a hypothesis-generating model of mortality. It is possible that other factors may add to this predictive nature of the model when a larger cohort is assessed. This tripartite stratification warrants further validation and consideration as a factor for minimization of allocation bias in future RCTs in severe pediatric TBI.

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