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Reith, F.C.M., Lingsma, H.F., Gabbe, B.J. et al. (3 more authors) (2017) Differential effects of the Glasgow Coma Scale Score and its components: an analysis of 54,069 patients with traumatic brain injury. *Injury*, 48 (9). pp. 1932-1943. ISSN 0020-1383

<https://doi.org/10.1016/j.injury.2017.05.038>

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Differential effects of the Glasgow Coma Scale Score and its Components: an analysis of 54 069 patients with traumatic brain injury.

Keywords: Components, Floor and Ceiling effects, Glasgow Coma Scale Score, GCS, Prognosis, TBI

Running title: Differential effects of the GCS Score and its components

Abstract

1 Introduction

2 The Glasgow Coma Scale (GCS) is important in the assessment of clinical severity and prediction of
3 outcome after traumatic brain injury (TBI). The relevance of the sum score has been extensively
4 studied, but the influence of the components seldom addressed. We aimed to investigate the
5 contribution of the GCS components to the sum score, floor and ceiling effects of the components,
6 and their prognostic effects.

7 Methods

8 Data on adult TBI patients were gathered from three data repositories: TARN (n=50064), VSTR
9 (n=14062), and CRASH (n=9941). Data on initial hospital GCS-assessment and discharge mortality
10 were extracted. A descriptive analysis was performed to identify floor and ceiling effects. The relation
11 between GCS and outcome was studied by comparing case fatality rates (CFR) between different
12 component-profiles adding up to identical sum scores using Chi²-tests, and by quantifying the
13 prognostic value of each component and sum score with Nagelkerke's R² derived from logistic
14 regression analyses across TBI severities.

15 Results

16 In the range 3 to 7, the sum score is mainly determined by the motor component, as the verbal and eye
17 components show floor effects at sum scores 7 and 8, respectively. In the range 8-12, the verbal and
18 eye components become more relevant. The motor, eye and verbal scores reach their ceiling effects at
19 sum 13, 14 and 15, respectively. Significant variations were exposed in CFR between different
20 component-profiles despite identical sum scores, except in sum scores 6 and 7. Regression analysis
21 showed that the motor score had highest R² values in severe TBI patients, whereas the other
22 components were more relevant at higher sum scores. The prognostic value of the three components
23 combined was consistently higher than that of the sum score alone.

24 Conclusion

25 The GCS-components contribute differentially across the spectrum of consciousness to the sum score,
26 each having floor and ceiling effects. The specific component-profile is related to outcome and the
27 three components combined contain higher prognostic value than the sum score across different TBI
28 severities. We, therefore, recommend a multidimensional use of the three-component GCS both in
29 clinical practice, and in prognostic studies.

30

31 Introduction

32 The Glasgow Coma Scale (GCS) has been widely adopted both in clinical practice and health care
33 research as an instrument for assessing the (depressed) level of consciousness[1]. GCS assessment
34 involves recording responsiveness in three domains: the eye opening, motor and verbal responses to
35 speech and (if not responding) to a stimulus. Formal clinimetric analysis of the GCS was not
36 performed upon its introduction in 1974. Later studies reported floor and ceiling effects of the
37 components, but these have never been definitively established in large patient numbers [2,3]. Soon
38 after the introduction of the GCS, a numerical score was assigned for each of these responses
39 allowing for import of clinical data into a data bank[4]. The component scores (shaping the GCS
40 *scale*) should be differentiated from the derived *sum score*, i.e. the summation of the numeric values
41 of the three components. The sum score was initially used in research settings only, but is increasingly
42 used in clinical practice as a replacement for the description of the three responses. Application of the
43 sum score as a classification system to define clinical severity of patients with traumatic brain injury
44 (TBI) is widely adopted, distinguishing mild (sum score 13-15), moderate (sum score 9-12) and
45 severe (sum score ≤ 8) TBI. Over time, the sum score was moreover included in various clinical
46 stratification and outcome prediction scores, such as Acute Physiology and Chronic Health Evaluation
47 (APACHE) II [5], Revised Trauma Score (RTS) [6], Trauma and Injury Severity Score (TRISS) [7],
48 and adopted in several guidelines such as the National Trauma Triage Protocol [8] and severe TBI
49 guidelines [9]. Summing of the components, however, brings along consequences not foreseen at the
50 time its introduction, including loss of information on the scores of the individual components and
51 uncertainty about how to deal with untestable components. The information comprised by the sum of
52 the three components might be less than that contained in the components separately [10–12].
53 Teasdale et al. advocate in a more recent report to use the scale in the management of individual
54 patients, and to restrict use of the sum score for summarizing information on groups of patients [1].

55 The prognostic value of the sum score has been extensively studied in patients with TBI. The sum
56 score appeared to relate to various outcome measures, including case fatality rate, the Glasgow
57 Outcome Scale (GOS), the Disability Rating Scale (DRS) and the Rancho Los Amigos Levels of
58 Cognitive Function Scale (LCFS) (modest correlation only) [13]. Lower sum scores have been shown
59 to be associated with poorer outcome, and an inverse, approximately linear relation between mortality
60 and sum score is reported in patients with TBI [1]. However, fatality rates may differ for patients with
61 different combinations of the three component scores despite similar sum scores [14–16]. This raises
62 questions about the relative contribution of the GCS components to the sum score, how these
63 contributions may change across the broad spectrum of severity (i.e. sum score 3 to 15), and
64 differentially influence the relation of the sum score with outcome.

65 This study aimed to explore how the GCS components contribute to the sum score across injury
66 severity levels, to identify floor and ceiling effects of the components, to investigate how the
67 component-profile might affect the association of sum scores with outcome and to investigate the
68 relation of each component and sum score with outcome across different TBI severity levels.

69

70 **Methods**

71 We performed a retrospective observational study. The STROBE statement was used to guide the
72 reporting of this study [17].

73

74 *Patient population and Datasets*

75 Data on patients with TBI were accessed from two trauma registries: Trauma Audit and Research
76 Network (TARN) and Victorian State Trauma Registry (VSTR); and one randomized clinical trial
77 with very broad inclusion criteria, which as such can be considered a ‘large pragmatic trial’:
78 Corticosteroid Randomization After Significant Head Injury (CRASH) (see Table 1). Consent
79 procedures and IRB approvals are described for the studies separately.

80 Trauma Audit and Research Network (TARN): TARN is a hospital-based trauma registry in England
81 and Wales that includes patients with trauma resulting in immediate admission to hospital for more
82 than 3 days, critical care admission and/or transfers for critical care, or death after admission. The
83 injuries of each trauma case are coded using the abbreviated injury scale (AIS) dictionary [18]. The
84 central TARN database retains no patient identifiers. Approval for research on this anonymised data
85 set has been issued by the UK Health Research Authority (PIAG sections 251) [19]. For the current
86 study, we selected patients of > 15 years of age enrolled between 1988 and 2014 with TBI, defined as
87 having any AIS-head score, resulting in a dataset of 50064 patients. The outcome measure is survival
88 to discharge or 30 days post injury (whichever is earliest), which was available in 100%.

89 Victorian State Trauma Registry (VSTR): The VSTR, established in 2001, is a statewide trauma
90 registry, which captures information about all major trauma patients from 138 health services in the
91 state of Victoria in Australia, whose principal diagnosis is injury, irrespective of age. Major trauma,
92 as defined by the VSTR, includes death, admission to an intensive care unit, an injury severity score
93 (ISS) >15, and urgent surgery (within 24 hours of admission and surgery involving intracranial,
94 intrathoracic, intra-abdominal injury or fixation of spinal or pelvic fractures) [20]. The VSTR records
95 patient and injury details as well as information about outcomes. Diagnoses are coded according to
96 the AIS 2008, and the ISS is calculated to provide an overall rating of the severity of the patient’s
97 injuries. Outcome assessment includes mortality at discharge and the Glasgow Coma Scale Extended
98 (GOSE) at six months, derived via telephone interview. The VSTR uses an opt-out consent process,
99 where all eligible patients are provided with a letter and brochure explaining the purpose of the
100 registry, the data collected, and what the data are used for, but also how to have their data removed
101 from the registry if they wish to. The opt-off rates are less than 1.0 % [21]. Data of patients of over 15
102 years of age, presenting with any AIS head code, except for minor superficial injuries, that occurred

103 between July 2001 and July 2013 was extracted, resulting in 14062 cases. AIS-Head severity score
104 was ≥ 3 in 77%. Mortality at discharge was available in 14062 patients (100%).

105 Corticosteroid Randomization After Significant Head Injury (CRASH): CRASH was a randomized
106 controlled trial with broad inclusion criteria studying the effect of corticosteroids on death and
107 disability after TBI. CRASH was conducted in both high- and low/middle-income countries. The
108 multicentre research ethics committee gave approval for the trial to be conducted using a “consent
109 waiver” [22]. CRASH enrolled 10 008 patients suffering TBI with a GCS score of 14 or less, within
110 8hours of injury between 1999 and 2005. Outcome at six months was assessed by a simple postal
111 questionnaire version of the GOS and also 14-day mortality was collected. A total of 9941 patients
112 were ≥ 16 years old and were selected for inclusion in this study. Fourteen-day mortality was
113 available in 99% of patients.

114 Characteristics of these datasets are summarized in Table 1. The data sources were chosen based on
115 the availability of patients having a broad spectrum of TBI severities (good spread of GCS scores) in
116 adult patients alongside well-characterized injury descriptions and outcomes. The outcome examined
117 in this analysis is mortality at discharge, as this time point was consistently present across the data
118 sets. In CRASH, we considered 14-day mortality a suitable approximation for discharge mortality, as
119 in a previous study it was shown that the median length of stay was 11 days (IQR: 5-27) [23]. The
120 inclusion of three different databases contributes to broad applicability by including a wide range of
121 patients and permits exploration of contextual factors, including different clinical settings and
122 geographic influences.

123

124 ***Statistical methods***

125 *Analysis of the contribution of the GCS components to the sum score*

126 Patients with both GCS component scores and sum score obtained after arrival in hospital were used
127 for analyses. Analyses included descriptive analysis of the components of the GCS and its sum score
128 and their interrelations. The relation between the median GCS component score and the sum score is
129 presented graphically. The different component profiles adding up to identical sum scores were
130 explored and displayed graphically. Results were explored in each data set separately and in the
131 merged datasets.

132

133 *Analysis of associations of the GCS and sum score with outcome*

134 *a. Analysis of case fatality rates in subgroups with varying GCS component-compositions*

135 We compared the case fatality rates (CFR) among patients with different GCS components-profiles
136 adding up to identical sum scores by using the Chi squared test. For this analysis we selected only the
137 components-profile groups for which at least five deaths could be expected by taking into account the
138 overall mortality for all patients with an identical sum score. Patients with known GCS component
139 scores, sum score and outcome, were included for this analysis. We examined data from each
140 database separately followed by a combined analysis.

141 *b. Prognostic value of the GCS differentiated by TBI severity level*

142 The relations between the CFR and the GCS components and sum score, respectively, were explored
143 using univariate logistic regression models. We tested for non-linear relations by adding a quadratic
144 term to the regression model (polynomial regression). From these regression models, the
145 Nagelkerke's R^2 [24] was derived to quantify the prognostic value of GCS components and the sum
146 score. Nagelkerke's R^2 can be interpreted as an approximation of the percentage variability in
147 outcome that is explained by the GCS components [25]. To examine whether one of the GCS
148 components alone added predictive value above that of the other two components (or in other words:
149 to correct for correlation between the components), we plotted differences in Nagelkerke's R^2 values
150 of the model including all three components, when the one component was included and excluded
151 from the model. These partial R^2 values reflect the 'added prognostic value', or the 'uncorrelated
152 prognostic value' of a component. Moreover, the prognostic values (R^2) of both the combination of
153 the three components (EMV) and of the sum score were analysed, and the goodness of fit (LR chi2)
154 of both models were compared using the chi2-test. To control for TBI severity, the analyses were
155 performed both in subpopulations according to TBI severity based on the GCS, and in all patients.
156 Results are plotted in bar plots, with the open bars presenting the unadjusted R^2 and the hatched bars
157 presenting the partial (uncorrelated) R^2 values for the components. The results are differentiated by
158 data source.

159 Data analysis was conducted using R software for statistical computing and graphics (version 3.1.3)
160 (R Foundation for Statistical Computation, Vienna, Austria).

161 **Results**

162 A total of 74067 adult patients with TBI (CRASH n=9941; TARN n=50064; VSTR n=14062) were
163 included. The sum score was reported in 65568 (89%) patients, but the frequency of specific sum
164 scores varied between datasets, reflecting different populations (Fig. 1). The eye, motor and verbal
165 scores were each reported in 73% of patients. Of the total patient population, 54069 (73%) patients
166 had complete data on both the eye, motor, verbal (EMV) profile and the sum score. Of these 54069
167 patients, 54040 (99.9%) patients had available data on discharge mortality.

168

169 *Contribution of the GCS components to the sum score: floor and ceiling effects*

170

171 The composition of the sum score upon admission was analysed in the individual data sets and in the
172 combined data sets of 54069 cases in which both the GCS and sum score data were present. Fig. 2
173 presents the graphical composition of the mean GCS component score across the entire spectrum of
174 severity (sum score 3-15). Results as shown were consistent across the individual data sets.

175 In the sum score range 3 to 7, a steady increase in the mean motor score is observed (from 1 to 5 on
176 the six category score), whereas the eye and verbal scores remain low. Consequently, in the majority
177 of patients with sum scores ranging from 3 to 7, the sum score reflects changes in the motor response
178 only.

179 The motor component shows a plateau phase from sum scores 7 through 12. In this range, the sum
180 score is mainly influenced by both the verbal and eye components. From sum score 12 to 13, the
181 motor score again influences the sum score and accordingly reaches its ceiling effect at sum score 13.
182 The floor and ceiling effects of the eye response are reached at sum score 8 and 14, respectively. The
183 floor and ceiling effects of the verbal response are found at sum score 7 and 15.

184 When the three components are evaluated separately, mathematically a total of 120 possible
185 combinations of the three components can occur, as the sum scores 4 to 14 can be made up of
186 different GCS component-profiles. Although, some profiles are clinically not feasible, we identified
187 all 120 different combinations in the data sets. However, some profiles were much more prevalent
188 than others (see Fig. 3).

189

190 *Analysis of associations of the GCS and sum score with outcome*

191

192 *a. Analysis of case fatality rates in patients with varying GCS component-compositions*

193 We investigated whether significant variations in CFR were present between different component-
194 profiles with identical sum scores (Fig. 3). Considering all data together (N=54040), significant
195 differences in CFR were found between different component-profiles of all identical sum scores
196 ranging from 4 to 14 ($p < 0.01$), except for sum scores 6 ($p = 0.48$) and 7 ($p = 0.07$) (Table 2). Across the
197 three datasets, results showed similar trends, although significant different fatality rates were
198 confirmed for fewer sum scores due to smaller numbers in the separate datasets.

199 *b. Prognostic value of the GCS differentiated by TBI severity level*

200 We examined the prognostic value of each GCS component and the sum score and how these
201 relations might change across different levels of TBI severity: mild: sum 13-15, moderate: sum 9-12,
202 severe sum 3-8. Univariate logistic regression analyses identified decreasing case fatality rates with
203 increasing scores of either the components or sum score in all data sets.

204 Fig. 4 shows the relative prognostic value of the components and sum score expressed as
205 Nagelkerke's R^2 values for each data set. In CRASH and TARN we identified increasing R^2 values
206 with increasing TBI severity. In mild and moderate TBI the prognostic values of all components were
207 lower. In VSTR, however, R^2 values did not increase much in patients with severe TBI. An
208 exploratory analysis in VSTR, in which we excluded TBI patients who suffered from extra cranial
209 injuries (i.e. selecting isolated TBI patients ($n = 2967$)), showed clearly higher R^2 values: not only in
210 patients with severe TBI, but also across all severities.

211 In all data sets, the motor score had the highest prognostic value (partial R^2) in patients with severe
212 TBI compared to the other components. However, in patients with less severe TBI its prognostic
213 effect was lower. Both the eye and verbal components held prognostic value at different TBI severity
214 levels, but prognostic effects differed between data sets. In every data set, the verbal component
215 showed highest R^2 of all components among patients with mild TBI.

216 The prognostic value of the three components combined (E+M+V) in the logistic regression models
217 was consistently higher than the R^2 of the sum score across different severities. This can be related to
218 the observation that different EMV-compositions with identical sum scores carry a different mortality
219 risk. In all data sets and across all TBI severities, the goodness of fit (LR χ^2) was significantly
220 higher for the E+M+V-model compared to the model including the sum score only ($p < 0.001$). Only in
221 patients with severe TBI derived from VSTR database, the sum score model and E+M+V-model had
222 a similar goodness of fit ($p = 0.13$).

223

224 **Discussion**

225 This pooled analysis of individual patient data in 54069 patients with TBI has shown how the three
226 components of the GCS contribute to form the sum score at different levels of depressed
227 consciousness. We identified clear floor and ceiling effects. Moreover, the specific combinations of
228 components imply different clinical situations of patients and we demonstrated a significant impact on
229 the relation with outcome. These results underline the relevance of reporting each GCS component
230 over the sum score, both in individual clinical data as well as in prognostic models.

231

232 ***Floor and ceiling effects of the GCS components***

233 The three behavioral responses making up the GCS show a specific interaction early after
234 head injury across the full spectrum of consciousness (Fig. 2), and patterns appeared similar across
235 the different included data sets, despite differences in case mix. This descriptive analysis of the
236 component variables of the scale, results in better understanding of the clinimetric aspects of the GCS.
237 In patients having sum scores ranging from 13 to 15, reflecting mild TBI, the motor score is not
238 influencing the level of consciousness at all, as it reaches its maximum influence (ceiling effect) at
239 sum score 13. Of the patients having a sum score of 14, 73% showed impairment in the verbal
240 response (V4) as the eye response reached its ceiling effect at sum score 14. Clinically this
241 demonstrates that the majority of patients will be disoriented as a first sign of reduced consciousness.
242 In the patients with sum scores ranging from 8 to 12, first the verbal response (sum score 8), next the
243 eye (sum scores 9-10) and then again the verbal response (sum scores 11-12) will contribute to an
244 increasing sum score. At these levels of consciousness (sum score 8-12), the majority of patients are
245 localizing to painful stimuli (M5) and they show no alteration in their motor response (plateau phase).
246 In the patients with severely depressed consciousness (sum scores 3-7), the level of consciousness is
247 mostly influenced by the motor response only until it reaches a plateau phase at sum score 7, as the
248 floor-effects of both the verbal and eye response occur at sum score 7 and 8, respectively. Based on
249 this specific interaction pattern, the current definition of *severe TBI* (sum 3-8) may be challenged. As
250 there is a clear flattening of the influence of the motor score at the plateau phase occurring at sum
251 score 7, the range 3-7 might be more appropriate. Already in 2002, Jennett recognized that according
252 to the original definition of severe TBI as introduced by Jennett et al. in 1977, all patients with a sum
253 score of 7 were in coma, but only half of those with sum score 8 [26]. However, the current ‘3-8’
254 definition for *severe TBI* is so deeply embedded in clinical practice and research, that we do not
255 consider this difference large enough to warrant any change in current practice.

256

257 The interaction pattern as revealed in the current study relates only partially to those presented
258 by Bhatti et al. 1993 [2], who studied the mathematical foundation of the GCS. They concluded that
259 the motor component of the GCS was dominant at the lower end of the sum score, the verbal
260 component dominated between sum scores 8 and 10, and the eye component at the higher end. Results
261 shown in their study are, however, based on an unknown number of cases and only 15 most relevant
262 GCS component-profiles were selected for analysis. Peters 2010 published the relative distribution of
263 each component within the modified GCS sum score and showed how in the range of 3 to 8 the eye
264 and verbal scales are typically at minimum values. In children admitted to the intensive care unit,
265 often having a sum score of 8 or less, the motor score alone would therefore be anticipated to
266 distinguish between poor and good outcome [3]. Other studies have suggested that the eye and verbal
267 components can be omitted without compromising the predictive accuracy of the GCS as the motor
268 score accounts for almost all the predictive power, both in adults as in children[14,27–33]. However,
269 the current study illustrates how different levels of the sum score are influenced by each component of
270 the scale. It shows how the relative contribution of the motor score diminishes after it reaches a
271 plateau phase at sum score 7 and how the verbal and eye components have increasing relevance in
272 patients with less depressed levels of consciousness. The influence of each component is also
273 reflected in their prognostic values across the spectrum of severity as shown in Figure 4. From this
274 perspective, the motor-score only approach could be justified in patients with *severe* TBI only, as was
275 also suggested by Teasdale et al. in 1979 [12]. The floor and ceiling effects are also relevant with
276 regard to clinical decision-making, as from our experience clinical decisions to undertake surgery are
277 often based on a decline in the motor score. This can be a misleading approach at the higher levels of
278 consciousness (i.e. in patients localizing to pain and obeying commands), considering clinical
279 evolution and outcome in these patients will mainly depend on changes in the eye and verbal
280 responses. In conclusion, the complex interaction pattern of the three components across the full
281 spectrum of consciousness necessitates a multidimensional approach to adequate assessment as
282 carried out by testing the three components of the scale.

283

284 ***GCS-component-profiles and prognosis***

285 The sum score comprises various clinical situations, reflected by different combinations of the
286 GCS components. Principal component analysis has previously shown that summation of the three
287 components implies a substantial loss of clinical information [10].

288 In this study all 120 possible GCS-component-profiles that are comprised in the 13 different
289 sum scores were identified. However, some of these are unlikely from a clinical perspective (f.e. no

290 eye opening, abnormal flexion to stimuli but normal verbal response, E1M3V5). These clinically
291 improbable combinations were not frequently encountered and presumably reflect errors in data entry.

292 The specific composition of components adding up to a certain sum score is relevant to
293 outcome as revealed by this study. Significantly different outcomes were identified among different
294 GCS-component-profiles with identical sum scores. This was demonstrated for every sum score
295 ranging from 4 to 14 ($p < 0.01$), except for sum scores 6 and 7. Similar findings have been reported in
296 other studies: In 1979 Teasdale et al. showed that in patients with severe TBI (sum score 8), outcome
297 was similar despite different component profiles[12]. Healey et al. included large patient numbers
298 reflecting a general trauma population, and confirmed significant differences in hospital discharge
299 survival rates except in patients with sum scores 6, 12 and 13[14]. Hirai et al. observed differences in
300 6-months GOS in patients with a sum score of 14 that underwent surgery for cerebral aneurysm
301 rupture [15]. And Teoh et al. included 1390 patients admitted to a general intensive care unit and
302 found significant different mortalities during ICU admission in patients with component-profiles
303 adding up to sum scores 7, 9, 11 and 14 [16]. Although these varying results are presumably related to
304 differences in patient population and outcome measures, they underline the relevance of reporting and
305 incorporating the three components rather than the sum score alone. The sum score does not equal the
306 sum of the GCS-components.

307

308 *The GCS, sum score and prognosis*

309 This study reveals how the three components hold varying degrees of prognostic value
310 (partial R^2) across different TBI severity levels. The prognostic values of the components may be
311 related to their floor and ceiling effects across the spectrum of consciousness as demonstrated in
312 figure 2. The higher prognostic value of the motor score in severe TBI patients diminishes at higher
313 sum scores, whereas the eye and verbal scores have relative higher R^2 values in less severe TBI
314 patients. Nevertheless, R^2 values were relatively low for all three components in patients with mild
315 TBI, reflecting overall low mortality in this population group and as such a limited value of the GCS
316 in terms of predicting mortality. The results of the regression analyses showed, moreover, that
317 reporting the sum score only, implies a loss in prognostic information. The prognostic value of the
318 three components combined (E+M+V) was higher ($R^2 = 21.1\%$, 21.6% and 26.8% in TARN, VSTR
319 and CRASH) than the R^2 of the sum score ($R^2 = 20.2\%$, 20.5% and 26.3% , respectively). This finding
320 was consistent across TBI severity levels.

321 Various other studies have explored the importance of the GCS components versus the sum
322 score in outcome prediction and reported conflicting results. Teasdale et al. reported the average
323 reduction in entropy or uncertainty as presented by the information influence coefficient, which is a

324 measure of the amount of information that is lost when using the sum score instead of the three
325 components for predicting outcome. The sum score performed less compared to the three components
326 combined and they concluded that it is of importance to convey maximum information by considering
327 each component separately[12]. Healey et al., using fractional polynomial models, showed that the
328 eye score did not add predictive value, and, although the verbal score did add little predictive value,
329 advocated a motor-score only approach[14]. Gill et al. used the area under receiver operating
330 characteristic curves (AUC) to calculate the predictive ability of the emergency department GCS and
331 showed that the components alone as well as two simplified 3-point scores showed similar test
332 performances compared to the sum score for prediction[34]. Moore et al. showed good discrimination
333 for the sum score, whereas the eye component did not add predictive value to the combination of the
334 motor and verbal component. Using the three components separately, rather than the sum, did not
335 improve the predictive model. They concluded that there is no need to use each component separately,
336 and instead only the sum score is needed to accurately predict mortality[35]. Lesko et al. explored the
337 prognostic value of the GCS by logistic regression models deriving the AUC, the classifications
338 accuracy and Nagelkerke R^2 from each model. They found that the sum score had similar prognostic
339 value as the motor or the verbal score, or any combinations of the three components. They, however,
340 do not support omission of the eye and verbal scores in clinical practice, as they recognize the added
341 value of these scores in more moderate degrees of injury[30].

342 The available evidence base prevents drawing clear conclusions regarding the predictive
343 ability of the three components and the sum score. A likely explanation for the conflicting results can
344 be found in an interaction with the type of patient population, the TBI severity, the type of outcome
345 measure, and the time of GCS and outcome assessment. In the current study, the associations of the
346 GCS with early mortality in the patients with severe TBI were less pronounced in VSTR compared to
347 the other data sources. We hypothesized that the presence of major extra-cranial injuries in this patient
348 population had an influence on the relation with outcome, irrespective of the neurologic condition.
349 Indeed, the R^2 values increased in the isolated TBI population, mainly in the patients with severe TBI.
350 In a previous study capturing data from ‘International Mission on Prognosis and Clinical Trial Design
351 in TBI’ (IMPACT), TARN and CRASH, the effect of major extra-cranial injuries was found to be an
352 important prognostic factor in TBI patients, although the effect varied by population[36]. Osler et al.
353 recently suggested in this journal that the sum score is a stronger predictor in trauma for patients with
354 TBI compared to those without TBI[37]. This again accentuates limitations of the sum score in
355 prognostication with a potential differentiating effect for the presence of TBI. The conflicting findings
356 in the literature, as well as the varying results in the different data sets as presented in this study
357 underline the relevance of incorporating the three components separately and the need for
358 multidimensional approaches to prognostication. Moreover, they illustrate that incorporation of the

359 sum score in trauma triage protocols and general scoring systems may be relatively crude and carries
360 limitations.

361

362 ***Strengths and limitations of this study***

363 We performed a detailed analysis of the GCS and its effect on case fatality from three different data
364 sources with a total of 54069 cases, thereby accounting for differences in patient populations, and
365 inclusion criteria. Various limitations should, however, be acknowledged. First, we excluded cases in
366 which data points were missing, and only performed complete case analysis. We anticipated this not
367 to be a potential selection bias, as we considered it likely that the missing values were randomly
368 missing due to logistical reasons. Also, imputation of missing data was not considered of added value,
369 since the sum of imputed component scores would not strictly match the actual sum score. Moreover,
370 as we studied a considerable amount of data, deriving satisfying error estimates was not considered
371 problematic. Second, the outcome measure used in this data analyses was restricted to early mortality,
372 reflecting the confined content of the main data source employed (see table 1). Third, we did not
373 adjust for other possible prognostic factors in the prognostic analysis as the primary interest of these
374 analyses was in the GCS: we aimed to compare the different components of the GCS in terms of the
375 variance in outcome they explain. Also, we recognize that case fatality rate in patients with sum score
376 15 is rather high (10%). This finding is driven by the results of the largest dataset in this study, which
377 included patients with systemic injuries in addition to TBI. Finally, we recognize that the actual R^2
378 values as presented in this study are relatively low, suggesting that the components, taken in isolation,
379 will predict poorly. This emphasizes that outcome prediction in TBI necessitates a multidimensional
380 approach[38].

381

382 **Conclusions and clinical relevance of this study**

This research shows how the eye, motor and verbal components, each carrying unique clinical information, have floor and ceiling effects in their contribution to form the sum score across different levels of consciousness. The specific sequence of scoring of the components is, moreover, essential with regard to clinical practice and in determining the short-term outcome in patients with head injury. Finally, the three components combined show consistently higher prognostic value compared to the sum score across different severity levels. Consequently, summing the GCS does not equal the sum of its parts, but rather implies a considerable loss of information. Moreover, the relation of the GCS with outcome seems context dependent. We, therefore, endorse a multidimensional use of the three-component Glasgow Coma Scale, both in clinical practice for assessing and follow up of patients with acute TBI and in general trauma stratification and prognostic models.

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