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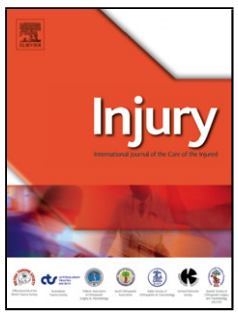

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Differential effects of the Glasgow Coma Scale Score and its Components: an analysis of 54 069 patients with traumatic brain injury.

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

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Abstract

Introduction

The Glasgow Coma Scale (GCS) is widely used in the assessment of clinical severity and prediction of outcome after traumatic brain injury (TBI). The sum score is frequently applied, but the differential

influence of the components infrequently addressed. We aimed to investigate the contribution of the GCS components to the sum score, floor and ceiling effects of the components, and their prognostic effects.

Methods

Data on adult TBI patients were gathered from three data repositories: TARN (n=50064), VSTR (n=14062), and CRASH (n=9941). Data on initial hospital GCS-assessment and discharge mortality were extracted. A descriptive analysis was performed to identify floor and ceiling effects. The relation between GCS and outcome was studied by comparing case fatality rates (CFR) between different component-profiles adding up to identical sum scores using Chi^2-tests, and by quantifying the prognostic value of each component and sum score with Nagelkerke's R^2 derived from logistic regression analyses across TBI severities.

Results

In the range 3 to 7, the sum score is primarily determined by the motor component, as the verbal and eye components show floor-effects at sum scores 7 and 8, respectively. In the range 8-12, the effect of the motor component attenuates and the verbal and eye components become more relevant. The motor, eye and verbal scores reach their ceiling-effects at sum 13, 14 and 15, respectively. Significant variations were exposed in CFR between different component-profiles despite identical sum scores, except in sum scores 6 and 7. Regression analysis showed that the motor score had highest R^2 values in severe TBI patients, whereas the other components were more relevant at higher sum scores. The prognostic value of the three components combined was consistently higher than that of the sum score alone.

Conclusion

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

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

Introduction

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

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

This study aimed to explore the contribution of the GCS components to the sum score across injury severity levels, to identify floor and ceiling effects of the components, to investigate how the

component-profile might affect the association of sum scores with outcome and to investigate the relation of each component and sum score with outcome across different TBI severity levels.

Methods

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

Patient population and Datasets

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

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

Victorian State Trauma Registry (VSTR): The VSTR, established in 2001, is a statewide trauma registry, which captures information about all major trauma patients from 138 health services in the state of Victoria in Australia, whose principal diagnosis is injury, irrespective of age. Major trauma, as defined by the VSTR, includes death, admission to an intensive care unit, an injury severity score (ISS) >15, and urgent surgery (within 24 hours of admission and surgery involving intracranial, intrathoracic, intra-abdominal injury or fixation of spinal or pelvic fractures) [20]. The VSTR records patient and injury details as well as information about outcomes. Diagnoses are coded according to the AIS 2008, and the ISS is calculated to provide an overall rating of the severity of the patient's injuries. Outcome assessment includes mortality at discharge and the Glasgow Coma Scale Extended (GOSE) at six months, derived via telephone interview. The VSTR uses an opt-out consent process, where all eligible patients are provided with a letter and brochure explaining the purpose of the registry, the data collected, and what the data are used for, but also how to have their data removed from the registry if

they wish to. The opt-off rates are less than 1.0 % [21]. Data of patients of over 15 years of age, presenting with any AIS head code, except for minor superficial injuries, that occurred between July 2001 and July 2013 was extracted, resulting in 14062 cases. AIS-Head severity score was ≥ 3 in 77%. Mortality at discharge was available in 14062 patients (100%).

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

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

Statistical methods

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

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

Analysis of associations of the GCS and sum score with outcome

a. Analysis of case fatality rates in groups with identical sum scores but varying GCS component-compositions

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

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

The relations between the CFR and the GCS components and sum score, respectively, were explored using univariate logistic regression models. We tested for non-linear relations on a logistic scale by adding a quadratic term to the regression model (polynomial regression) and comparing the 2-log likelihood ratio of both models using the chi^2 test, which is a measure of the goodness of fit. Non-linear relations were identified if the regression model that included the quadratic term had a significantly higher goodness of fit. Analyses were performed in each data set separately, and because of heterogeneity the data were not pooled. Statistical significance was met if p-values were < 0.05. Results are shown graphically by plotting the regression models using a logit scale for CFR.

From these regression models, the Nagelkerke's R^2 [24] was derived to quantify the prognostic value of GCS components and the sum score. To examine whether one of the GCS components alone added predictive value above that of the other two components (or in other words: to correct for correlation between the components), we plotted differences in Nagelkerke's R^2 values of the model including all three components, when the one component was included and excluded from the model. These 'partial R^2 values' reflect the 'added prognostic value', or the 'uncorrelated prognostic value' of a component. Moreover, the prognostic values (R^2) of both the combination of the three components (E+M+V) and of the sum score were analysed, and the goodness of fit (LR chi2) of both models were compared using the chi2-test. The Akaike information criterion (AIC) [25], a measure that corrects the likelihood ratio of the model for the number of parameters fitted, was also used to compare both models. A smaller AIC indicates a better model fit. To control for TBI severity, the analyses were performed both in subpopulations according to TBI severity based on the GCS, and in all patients. Results are plotted in bar plots, with the open bars presenting the unadjusted R^2 and the hatched bars presenting the partial (uncorrelated) R^2 values for the components. The results are differentiated by data source.

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

Results

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

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

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

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

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

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

Analysis of associations of the GCS and sum score with outcome

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

We investigated whether significant variations in CFR were present between different component-profiles with identical sum scores (Fig. 3). Considering all data together (N=54040), significant differences in CFR were found between different component-profiles of all identical sum scores 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 three data sets, results showed similar trends, although significant different fatality rates were confirmed for fewer sum scores due to smaller numbers in the separate data sets.

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

We examined the prognostic value of each GCS component and the sum score and how these relations might change across different levels of TBI severity: mild: sum 13-15, moderate: sum 9-12, severe sum 3-8. Univariate logistic regression analyses identified decreasing case fatality rates with increasing scores of either the components or sum score in all data sets. However, the non-linear regression models showed often a significant higher goodness of fit ($p<0.01$), except for the motor score in TARN ($p=0.23$) and the sum ($p=0.09$) and verbal score ($p=0.25$) in CRASH (Fig. 4). As such, the relation with case fatality on a logistic scale was not consistently linear across data sources, indicating that the results are population and data dependent.

Fig. 5 shows the relative prognostic value of the components and sum score expressed as Nagelkerke's R^2 values for each data set. In CRASH and TARN we identified increasing R^2 values with increasing TBI severity. In mild and moderate TBI the prognostic values of all components were lower. In VSTR, however, R^2 values did not increase much in patients with severe TBI. An exploratory analysis in VSTR, in which we excluded TBI patients who suffered from extra cranial injuries (i.e. selecting isolated TBI patients (n=2967)), showed clearly higher R^2 values: not only in patients with severe TBI, but also across all severities.

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

The prognostic value of the three components combined (E+M+V) in the logistic regression models was consistently higher than the R^2 of the sum score across different severities. In all data sets and across all TBI severities, the goodness of fit (LR chi^2) was significantly higher for the E+M+V-model compared to the model including the sum score only ($p<0.01$), except for patients with severe TBI

derived from VSTR database in which the sum score model and E+M+V-model had a similar goodness of fit (p=0.13). The AIC was, however, consistently lower for the E+M+V-model compared to the sum-model, indicating a better model fit (see Supplementary data). This finding can be related to the observation that different EMV-compositions with identical sum scores carry a different mortality risk.

Discussion

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

Floor and ceiling effects of the GCS components

The three GCS-components show a specific interplay early after head injury across the spectrum of consciousness (Fig. 2), and patterns appeared similar across the included data sets, despite differences in case mix. This descriptive analysis of the component variables of the scale, results in better understanding of the clinimetric aspects of the GCS. In most patients having sum scores ranging from 13 to 15, reflecting mild TBI, the motor score is not influencing the level of consciousness, as it reaches its maximum influence (ceiling effect) at sum score 13 in the majority of patients. Of the patients having a sum score of 14, 73% showed impairment in the verbal response (V4) as the eye response reached its ceiling effect at sum score 14. Clinically this demonstrates that the majority of patients will be disoriented as a first sign of reduced consciousness. In the patients with sum scores ranging from 8 to 12, first the verbal response (sum score 8), next the eye (sum scores 9-10) and then again the verbal response (sum scores 11-12) will contribute to an increasing sum score. At these levels of consciousness, the majority of patients are localizing to painful stimuli (M5) and they show no alteration in their motor response (motor plateau phase). In the majority of patients with severely depressed consciousness (sum scores 3-7), however, the level of consciousness is primarily influenced by the motor response until it reaches a plateau phase at sum score 7. The floor-effects of both the verbal and eye response only occur at sum score 7 and 8, respectively. Based on this specific pattern of interplay, the current definition of *severe TBI* (sum 3-8) may be challenged. As there is a clear flattening of the influence of the motor score at the plateau phase occurring at sum score 7, the range 3-7 might be more appropriate. Already in 2002, Jennett recognized that according to the original definition of severe TBI as introduced by Jennett et al. in 1977, all patients with a sum score of 7 were

in coma, but only half of those with sum score 8 [26]. However, the current '3-8' definition for *severe TBI* is so deeply embedded in clinical practice and research, that we do not consider this difference large enough to warrant any change in current practice.

The relevance of the three components

The interplay of the components as revealed in the current study relate only partially to those presented by Bhatty et al. in 1993 [2], who studied the mathematical foundation of the GCS. They concluded that the motor component of the GCS was dominant at the lower end of the sum score, the verbal component dominated between sum scores 8 and 10, and the eye component at the higher end. Results shown in their study are, however, based on an unknown number of cases and only 15 most relevant GCS component-profiles were selected for analysis. Peters published the relative distribution of each component within the 'modified GCS sum score' and showed how in the range of 3 to 8 the eye and verbal scales are typically at minimum values. In children admitted to the intensive care unit, often having a sum score of 8 or less, the motor score alone would therefore be anticipated to distinguish between poor and good outcome [3]. Other studies have suggested that the eye and verbal components can be omitted without compromising the predictive accuracy of the GCS as the motor score accounts for almost all the predictive power, both in adults as in children[14,27–33]. However, the current study illustrates how different levels of the sum score are influenced by each component of the scale. It shows how the relative contribution of the motor score diminishes after it reaches a plateau phase at sum score 7 and how the verbal and eye components have increasing relevance in patients with less depressed levels of consciousness. The influence of each component is also reflected in their prognostic values across the spectrum of severity as shown in figure 5. From this perspective, the motor-score only approach could be justified in patients with *severe* TBI only. The floor and ceiling effects are also relevant with regard to clinical decision-making, as from our experience clinical decisions to undertake surgery are often based on a decline in the motor score. This can be a misleading approach at the higher levels of consciousness (i.e. in patients localizing to pain and obeying commands), considering clinical evolution and outcome in these patients will largely depend on changes in the eye and verbal responses. In conclusion, the complex interplay of the three components across the full spectrum of consciousness necessitates a multidimensional approach to adequate assessment as carried out by testing the three components of the scale.

GCS-component-profiles and prognosis

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

In this study all 120 possible GCS-component-profiles that are comprised in the 13 different sum scores were identified. However, some of these are unlikely from a clinical perspective (f.e. no eye opening, abnormal flexion to stimuli but normal verbal response, E1M3V5). These clinically improbable combinations were not frequently encountered and presumably reflect errors in data entry.

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

The GCS, sum score and prognosis

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

VSTR and CRASH) than the R^2 of the sum score (R^2 = 20.2%, 20.5% and 26.3%, respectively) across TBI severity levels.

Other studies have explored the importance of the GCS components versus the sum score in outcome prediction and reported conflicting results. Teasdale et al. reported the average reduction in entropy or uncertainty as presented by the information influence coefficient, which is a measure of the amount of information that is lost when using the sum score instead of the three components for predicting outcome. The sum score performed less compared to the three components combined and they concluded that each component should be considered separately [12]. Healey et al. used fractional polynomial regression models to predict hospital discharge survival rates in a large general trauma population. They showed that the eye score did not add predictive value, and they, although the verbal score did add little predictive value, advocated a motor-score only approach[14]. Gill et al. used the area under receiver operating characteristic curves (AUC) to calculate the predictive ability of the emergency department GCS and showed that the components alone as well as two simplified 3-point scores showed similar test performances compared to the sum score for predicting discharge mortality [34]. Moore et al. showed good discrimination for the sum score, whereas the eye component did not add predictive value to the combination of the motor and verbal component. Using the three components separately, rather than the sum, did not improve the predictive model. They concluded that only the sum score is needed to accurately predict mortality[35]. Lesko et al. explored the prognostic value of the GCS by logistic regression models deriving the AUC, the classifications accuracy and Nagelkerke R^2 from each model. They found that the sum score had similar value in predicting survival at discharge as the motor or the verbal score, or any combinations of the three components. They, however, did not support omission of the eye and verbal scores in clinical practice, as they recognize the added value of these scores in more moderate degrees of injury[30].

A likely explanation for these conflicting results in the literature can be found in an interaction with the type of patient population, TBI severity, type of outcome measure, and the time of assessment. Also, the number of included patients could influence the results: the current study shows significant improvements in prognostication when using the three components rather than the sum score ($p<0.01$), however, the differences in the actual R^2 values are small, and this may explain that smaller studies did not find this, being underpowered to detect small effects. In the current study, the R^2 values in patients with severe TBI were less pronounced in VSTR compared to the other data sources. We hypothesized that the presence of major extra-cranial injuries in this patient population had an influence on the relation with outcome, irrespective of the neurologic condition. Indeed, the R^2 values increased in the isolated TBI population, mainly in the patients with severe TBI. In a previous study capturing data from ‘International Mission on Prognosis and Clinical Trial Design in TBI’ (IMPACT), TARN and CRASH, the effect of major extra-cranial injuries was found to be an important prognostic factor in TBI patients, although the effect varied by population[36]. Osler et al.

recently suggested in this journal that the sum score is a stronger predictor in trauma for patients with TBI compared to those without TBI[37]. This again accentuates limitations of the sum score in prognostication with a potential differentiating effect for the presence of TBI. The conflicting findings in the literature, as well as the varying results in the different data sets as presented in this study underline the relevance of incorporating the three components separately and the need for multidimensional approaches to prognostication. Moreover, they illustrate that incorporation of the sum score in trauma triage protocols and general scoring systems may be relatively crude and carries limitations.

Strengths and limitations of this study

We performed a detailed analysis of the GCS and its relation to case fatality, using a holistic approach. The study used data from three different sources resulting in a total of 54069 cases, thereby accounting for differences in patient populations and inclusion criteria. Various limitations should, however, be acknowledged. First, we excluded cases in which data points were missing. We anticipated this not to be a potential selection bias, as we considered it likely that the missing values were randomly missing due to logistical reasons. Also, imputation of missing data was not considered of added value, since the sum of imputed component scores would not strictly match the actual sum score. Moreover, as we studied a considerable amount of data, deriving satisfying error estimates was not considered problematic. Second, the outcome measure used in this data analyses was restricted to early mortality, reflecting the confined content of the main data source employed (see table 1). It is possible that the pattern of interplay in relation to quality of outcome in survivors may differ, for example with different floor and ceiling values. Third, we did not adjust for other possible prognostic factors in the prognostic analysis as the primary interest was in comparing the different components in terms of the variance in outcome they explain. Next, we recognize that CFR in patients with sum score 15 is rather high (10%). This finding is driven by the results of the largest dataset in this study, which included patients with systemic injuries in addition to TBI. Finally, as R^2 values derived from logistic regression models are more complex to interpret, the values as presented in this study should not be interpreted as absolute numbers, but rather as a visualization of the relative importance of the components and sum score in prediction. Also, the presented R^2 values are relatively low, suggesting that the components, taken in isolation, will predict poorly. This emphasizes that outcome prediction in TBI necessities a multidimensional approach[38].

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 the sum score across different levels of consciousness. Moreover, the specific composition of the components, adding up to similar sum scores, is 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 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.

Conflicts of interest statement

The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other (personal or professional) relationships or activities that could appear to have influenced the submitted work

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Figure legends

Figure 1

Caption:

Frequency diagrams of sum scores differentiated for each database

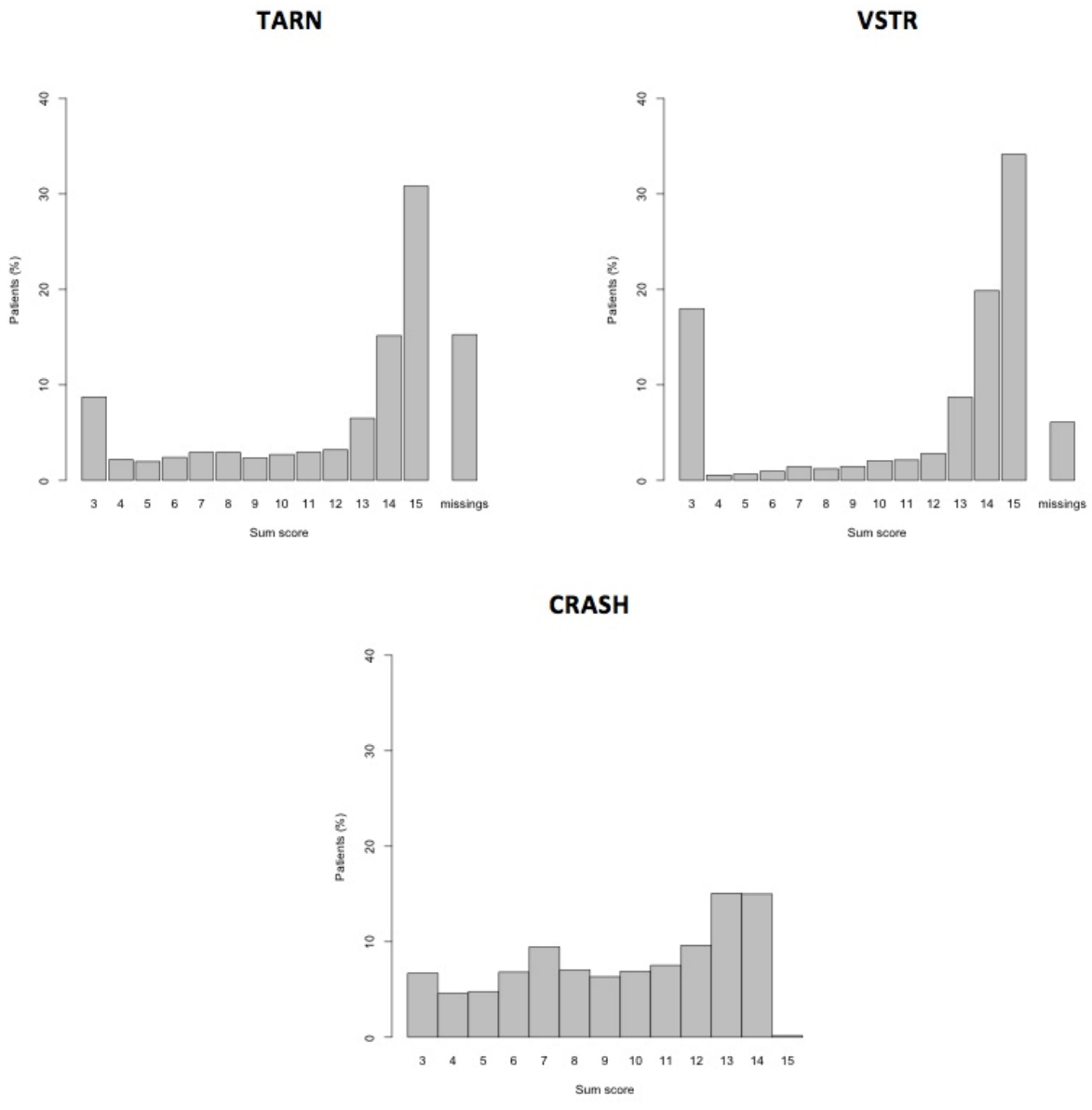

Figure 2

Caption:

Interplay of the GCS components and the sum score

Legend:

Floor effects of *motor*, *verbal* and *eye* components are reached at sum scores 1, 7 and 8, respectively. Ceiling effects are reached at sum score 13, 15 and 14, respectively. The motor score plateau phase is at sum score 7-12.

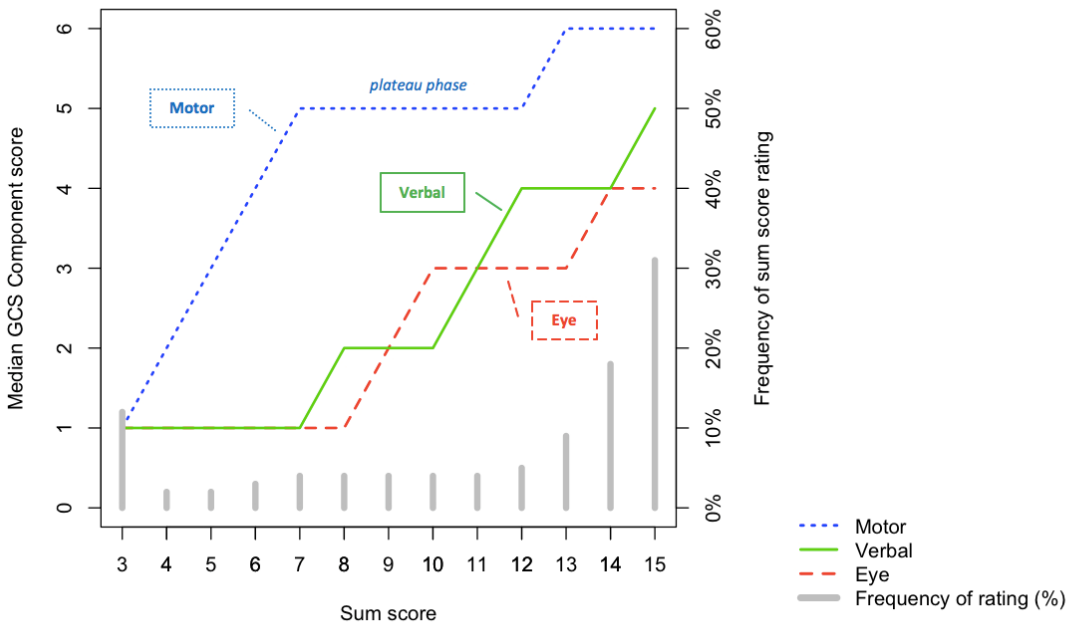

Figure 3

Caption:
Frequency of different GCS component profiles with identical sum scores (blue) and the accompanying case fatality rates (red).

Legend:

Blue bars: showing the total amount of patients (N) for each specific component-profile on a logarithmic scale. The component-profiles with identical sum scores are clustered. Component-profiles were excluded from analysis if N < at least 5 expected deaths

Red line: showing the case fatality rate (%) for each component-profile group.
* $p<0.05$, indicates a significant difference in case fatality rates between different component-profiles with identical sum scores

Horizontal brown dots: showing the mean weighted case fatality rate (%) for each sum score.

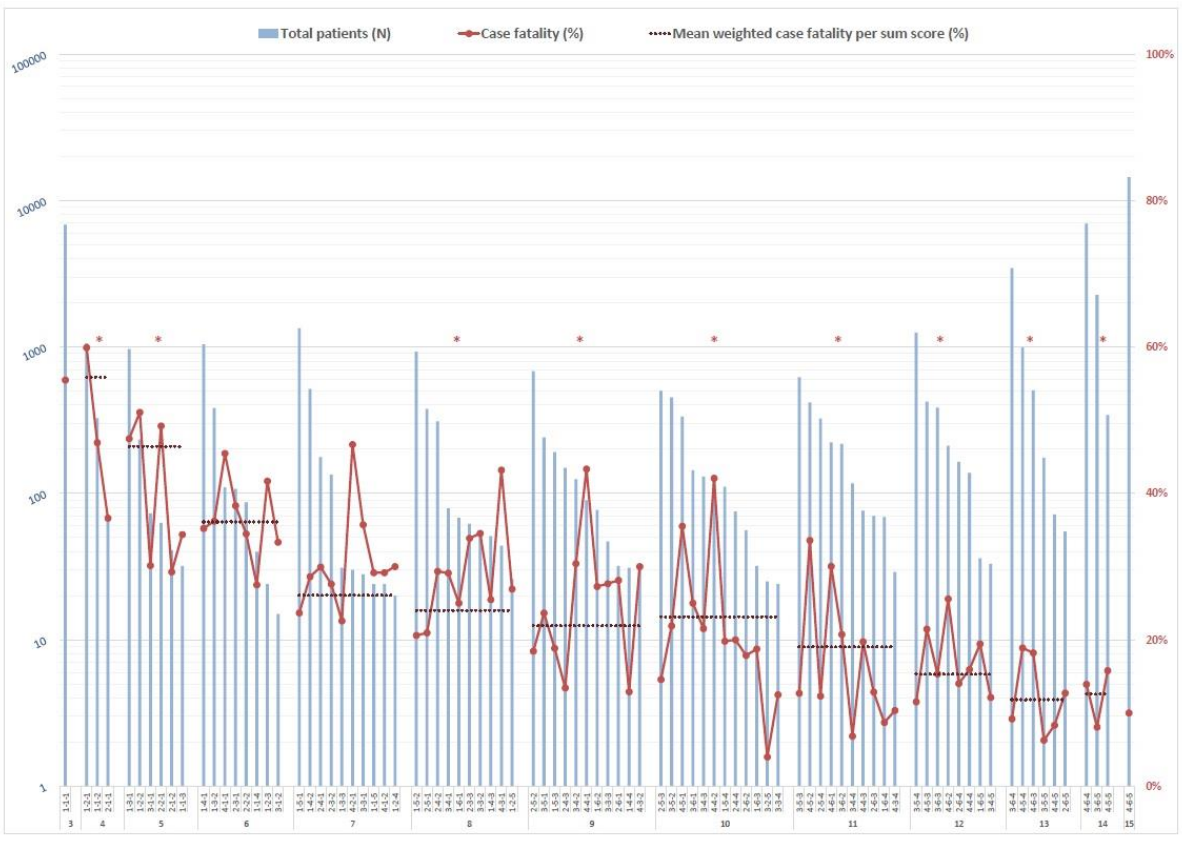

Figure 4

Caption:
The relation of the sum score and GCS components with logit CFR.

Legend:
Results of logistic regression analyses with accompanying 95% confidence intervals indicated by the polygons around the solid lines. Results are differentiated by data set. Non-linear relations on a logistic scale were revealed if the polynominal regression model showed a significant higher goodness of fit compared to the linear model ($p<0.01$).

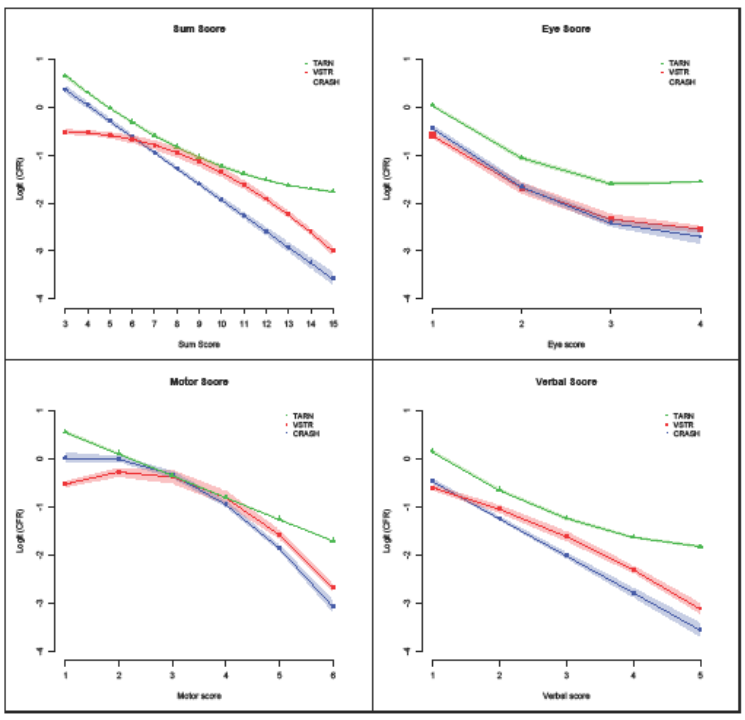

Figure 5

Caption:
Prognostic value of the GCS components and sum score expressed as Nagelkerke's R^2 values. Results are differentiated by data set

Legend:

Prognostic values are expressed as Nagelkerke's R^2 values derived from logistic regression models in the data sets. In case of non-linear relations (as revealed by previous analysis), quadratic terms were included in the regression models. The open bars give the R^2 values for the unadjusted association of each GCS component or sum score with mortality. The R^2 for E+M+V-model is derived from multivariate regression models. The hatched bars give the partial R^2 values (i.e. the uncorrelated prognostic value) of the components adjusting for the other two components.

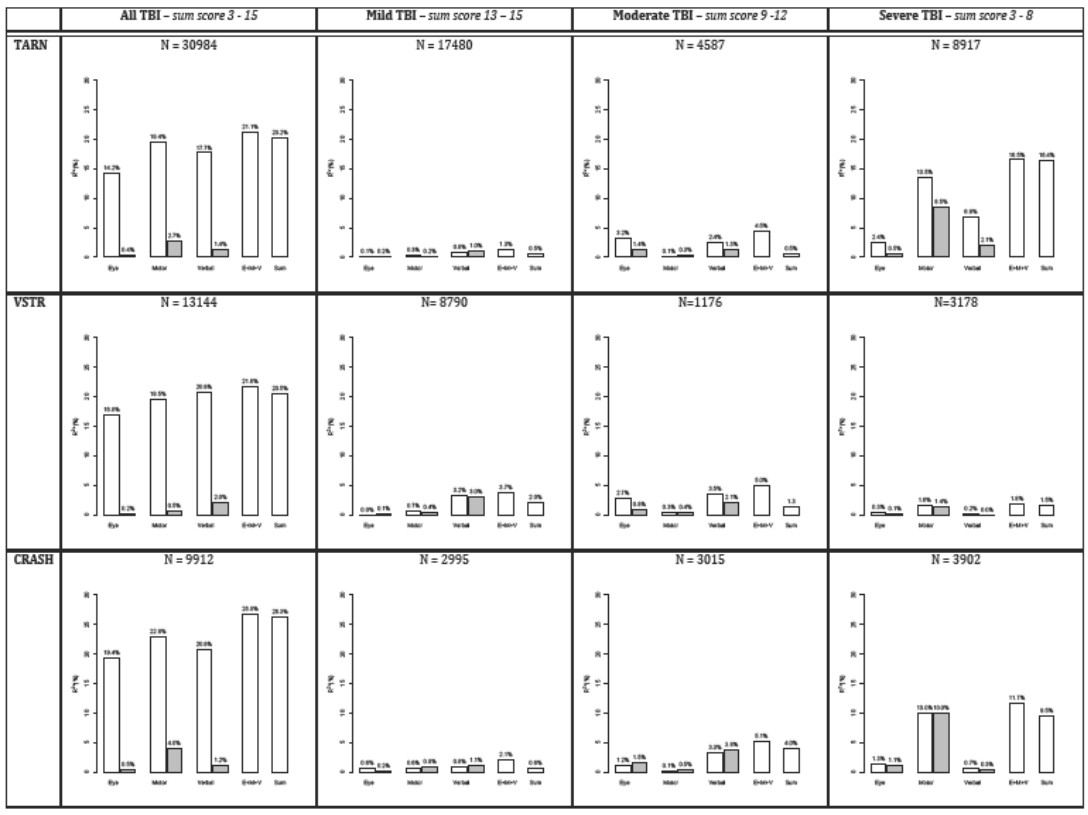

Table 1 Characteristics of included databases

Study	Study type	Setting and duration	Focus	Study population				Time window	GCS	Outcomes
				Patients (N)	Age (years)	Clinical severity	TBI definition based on:			
TARN	Registry	1989-ongoing England and Wales	Trauma	50064	All	Presence of at least one: - LOS ≥ 3 days - Admitted to intensive care - Inter-hospital transfer for specialist care - Dying after admission	Any AIS head code	All	At scene, ED admission	Mortality and GOS at discharge
VSTR	Registry	2001 – ongoing Victoria, Australia	Major trauma	14062	All	Presence of at least one: - Death after injury - Admission to ICU > 24h requiring mechanical ventilation - ISS>15 - Urgent surgery * - Serious injury to ≥ 2 body systems	Any AIS head code except minor superficial injuries	All	Pre-hospital, ED admission, Discharge	Mortality at discharge, GOSE, SF12, EQ-5D at 6, 12 and 24 months
CRASH	RCT	1999-2005, Multi-nation	TBI	9941	> 16	GCS ≤ 14	GCS	< 8 hours of injury	Admission	Death or disability at 2 weeks, Death or disability, GOS at 6 months

RCT: randomized clinical trial, Obs: observational, LOS: length of stay, TBI: Traumatic Brain Injury, GCS: Glasgow Coma Scale
** for intracranial, intrathoracic or intra-abdominal injury, or fixation of pelvic or spinal fractures*

Table 2 Discharge mortality for patients with different GCS-component-combinations adding up to similar sum scores. Groups with at least 5 expected deaths are shown.

GCS score	E	M	V	Patients		Deaths (N)	Fatality rate	Chi² + p-value
				N	%			
3	1	1	1	6847	100 %	3471	0.55	
4	1	2	1	1060	72.8 %	635	0.60	X-squared = 28.23, df = 2, p-value = < 0.01
	1	1	2	326	22.4 %	153	0.47	
	2	1	1	71	4.9 %	26	0.37	
5	1	3	1	969	68.7 %	460	0.47	X-squared = 17.15, df = 5, p-value = < 0.01
	1	2	2	233	16.5 %	119	0.51	
	3	1	1	73	5.2 %	22	0.30	
	2	2	1	63	4.5 %	31	0.49	
	2	1	2	41	2.9 %	12	0.29	
	1	1	3	32	2.3 %	11	0.34	
6	1	4	1	1042	57.1 %	367	0.35	*X-squared = 6.51, df = 7, p-value = 0.48*
	1	3	2	381	20.9 %	138	0.36	
	2	3	1	110	6.0 %	50	0.45	
	4	1	1	107	5.9 %	41	0.38	
	2	2	2	87	4.8 %	30	0.34	
	1	1	4	40	2.2 %	11	0.28	
	1	2	3	24	1.3 %	10	0.42	
	3	1	2	15	0.8 %	5	0.33	
7	1	5	1	1339	56.5 %	317	0.24	*X-squared = 15.83, df = 9, p-value = 0.07*
	1	4	2	517	21.8 %	148	0.29	
	2	4	1	177	7.5 %	53	0.30	
	2	3	2	134	5.7 %	37	0.28	
	1	3	3	31	1.3 %	7	0.23	
	3	3	1	30	1.3 %	14	0.47	
	4	2	1	28	1.2 %	10	0.36	
	1	1	5	24	1.0 %	7	0.29	
	4	1	2	24	1.0 %	7	0.29	
	1	2	4	20	0.8 %	6	0.30	
8	1	5	2	927	44.4 %	191	0.21	X-squared = 29.54, df = 9, p-value = < 0.01
	2	5	1	377	18.1 %	79	0.21	
	2	4	2	310	14.8 %	91	0.29	

	3	4	1	79	3.8 %	23	0.29	
	1	6	1	68	3.3 %	17	0.25	
	2	3	3	62	3.0 %	21	0.34	
	3	3	2	55	2.6 %	19	0.35	
	1	4	3	51	2.4 %	13	0.25	
	4	3	1	44	2.1 %	19	0.43	
	1	2	5	26	1.2 %	7	0.27	
9	2	5	2	683	38.7 %	126	0.18	X-squared = 47.44, df = 10, p-value = < 0.01
	3	5	1	241	13.6 %	57	0.24	
	1	5	3	191	10.8 %	36	0.19	
	2	4	3	149	8.4 %	20	0.13	
	3	4	2	125	7.1 %	38	0.30	
	4	4	1	90	5.1 %	39	0.43	
	1	6	2	77	4.4 %	21	0.27	
	3	3	3	47	2.7 %	13	0.28	
	1	4	4	32	1.8 %	9	0.28	
	2	6	1	31	1.8 %	4	0.13	
	4	3	2	30	1.7 %	9	0.30	
10	2	5	3	501	23.9 %	73	0.15	X-squared = 84.84, df = 11, p-value = < 0.01
	3	5	2	452	21.6 %	99	0.22	
	4	5	1	335	16.0 %	119	0.36	
	3	6	1	144	6.9 %	36	0.25	
	3	4	3	130	6.2 %	28	0.22	
	4	4	2	126	6.0 %	53	0.42	
	1	5	4	111	5.3 %	22	0.20	
	2	4	4	75	3.6 %	15	0.20	
	2	6	2	56	2.7 %	10	0.18	
	1	6	3	32	1.5 %	6	0.19	
	3	2	5	25	1.2 %	1	0.04	
	3	3	4	24	1.1 %	3	0.12	
11	3	5	3	622	27.9 %	79	0.13	X-squared = 120.15, df = 9, p-value < 0.01
	4	5	2	417	18.7 %	140	0.34	
	2	5	4	325	14.6 %	40	0.12	
	4	6	1	223	10.0 %	67	0.30	
	3	6	2	217	9.7 %	45	0.21	

	3	4	4	117	5.2 %	8	0.07	
	2	6	3	76	3.4 %	15	0.20	
	4	4	3	70	3.1 %	9	0.13	
	1	6	4	69	3.1 %	6	0.09	
	4	3	4	29	1.3 %	3	0.10	
12	3	5	4	1250	46.6 %	144	0.12	X-squared = 44.45, df = 7, p-value = < 0.01
	4	5	3	424	15.8 %	91	0.21	
	3	6	3	385	14.3 %	59	0.15	
	4	6	2	211	7.9 %	54	0.26	
	2	6	4	164	6.1 %	23	0.14	
	4	4	4	138	5.1 %	22	0.16	
	1	6	5	36	1.3 %	7	0.19	
	3	4	5	33	1.2 %	4	0.12	
13	3	6	4	3456	65.8 %	318	0.09	X-squared = 96.04, df = 5, p-value < 0.01
	4	5	4	990	18.8 %	187	0.19	
	4	6	3	505	9.6 %	92	0.18	
	3	5	5	175	3.3 %	11	0.06	
	4	4	5	72	1.4 %	6	0.08	
	2	6	5	55	1.0 %	7	0.13	
14	4	6	4	6961	72.7 %	969	0.14	X-squared = 56.19, df = 2, p-value = < 0.01
	3	6	5	2265	23.7 %	183	0.08	
	4	5	5	342	3.6 %	54	0.16	
15	4	5	6	14431	100 %	1445	0.10	