External validation of the Glasgow coma scale-pupils in low- to middle-income country patients with traumatic brain injury: Could “motor score-pupil” have higher prognostic value?

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ABSTRACT

Background: The objective of this study is to validate the admission Glasgow coma scale (GCS) associated with pupil response (GCS-P) to predict traumatic brain injury (TBI) patient's outcomes in a low- to middle-income country and to compare its performance with that of a simplified model combining the better motor response of the GCS and the pupilar response (MS-P).

Methods: This is a prospective cohort of patients with TBI in a tertiary trauma reference center in Brazil. Predictive values of the GCS, GCS-P, and MS-P were evaluated and compared for 14 day and in-hospital mortality outcomes and length of hospital stay (LHS).

Results: The study enrolled 447 patients. MS-P demonstrated better discriminative ability than GCS to predict mortality (AUC 0.736 × 0.658; P < 0.001) and higher AUC than GCS-P (0.736 × 0.704, respectively; P = 0.073). For hospital mortality, MS-P demonstrated better discrimination than GCS (AUC, 0.750 × 0.682; P < 0.001) and higher AUC than GCS-P (0.750 × 0.714; P = 0.027). Both scores were good predictors of LHS (r² = 0.084 [GCS-P] × 0.079 [GCS] × 0.072 [MS-P]).

Conclusion: The predictive value of the GCS, GCS-P, and MS-P scales was demonstrated, thus contributing to its external validation in low- to middle-income country.

Keywords: External validation, Glasgow coma scale, Motor score, Prognostic factor, Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is attributed to a cranial injury that generates a structural or physiological change in the brain. TBI is one of the main causes of mortality and morbidity, with
MATERIALS AND METHODS

Study design, patients, and population

This prospective study was conducted at the Hospital das Clínicas da Faculdade de Medicina de São Paulo (HCFMUSP), one of the largest hospitals in Latin America. Consecutive patients from the emergency department from 2012 to 2015 with TBI were included in the study. No missing data imputation was performed and only patients with full GCS or pupil data were included in the study. Patients under 14 years of age, with penetrating TBI, or coming from another hospital were excluded from the study. Chronic subdural hematomas were also excluded from the study. This research complied with the guidelines of the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement and the Declaration of Helsinki and was approved by the Research Ethics Committee of the HCFMUSP (Registry: 46831315300000068). Written consent was obtained by all participants or their legal representatives. None of the patients are identifiable in this research.

GCS-P and MS-P

The GCS-P score was calculated by subtracting 0, 1, or 2 points of the GCS when the pupils were bilaterally responsive, only one responsive, and bilaterally irresponsive, respectively (range, 1–15 points). The MS-P was calculated similarly, subtracting the pupillary evaluation of the highest motor response evaluated using the GCS, with a variation of 1–6 points. Scores were calculated based on hospital admission and the clinical picture was evaluated by the emergency team.

Outcome and variables of interest

Patients were followed throughout the hospital stay. The primary outcomes were short-term mortality, considered 14-day mortality, according to the literature used to evaluate acute outcomes of TBI. The secondary outcomes were in-hospital mortality and length of hospital stay (LHS).

Statistical analysis

Data are expressed as median (quartiles), absolute and relative frequencies, or mean and standard deviation (SD). For categorical variables, the Chi-square test was used. The predictive ability of GCS, GCS-P, and MS-P and its subscores to predict mortality outcomes was performed with logistical regression. The discriminative capacity of each logistic model was evaluated by calculating the area under the receiver operating characteristic (ROC) curve (AUC). An AUC or C statistic <0.60 reflects poor discrimination.
0.60–0.75, possibly helpful discrimination, and >0.75, clearly useful discrimination.[1] The cutoff for each score was chosen as the point that maximized the Youden index (sensitivity + specificity – 1).[31] To compare AUC, the nonparametric technique described by De Long et al. was used.[12] The calibration was evaluated using the Hosmer–Lemeshow test. P < 0.05 in the Hosmer–Lemeshow Chi-square test suggests poor calibration.[19] Overall performance was evaluated using the Brier score, ranging from 0 to 1.[16] A lower score indicates better model calibration. Spiegelhalter’s z statistic was used to test the significance of Brier scores; a significant result indicates poor calibration.[32] Discrimination, calibration, and Brier score were reported for the selected predictor variables of interest (GCS, GCS-P, and MS-P) as well as for a multivariate model that included sex, age, and computed tomography (CT)-based Marshall Classification of TBI in addition to the variables mentioned. These variables were selected on the assumption of the literature to be associated with the clinical outcome of patients with TB, which is part of the IMPACT score.[21]

Data were analyzed using STATA (StataCorp. 2017. *State Statistical Software: Release 15*. College Station, TX: StataCorp LLC.). ROC curves were performed using MedCalc version 19.1.3 (MedCalc Software bv; Ostend, Belgium; https://www.medcalc.org; 2020). All hypotheses were constructed as two-tailed, and P < 0.05 within a 95% CI was considered statistically significant.

RESULTS

Patient characteristics

There were a total of 447 patients enrolled. The mean (± SD) age was 40.0 ± 17.8 years (range, 13–99 years), 85.5% were male, and 64.2% were classified as severe TBI. Regarding outcome, 22.8% of the patients died in 14 days and 33.8% in follow-up time. The mean LHS was 25.7 ± 29.7 days and ranged from 1 to 232. The patient characteristics are presented in Table 1. The median GCS score was 6 (IQR 3–12), the median GCS-P score was 6 (IQR 3–12), and the median MS-P score was 5 (IQR 3–6). Baseline patient characteristics are summarized in Figure 1.

Prediction of 14-day mortality

The univariate logistic regression model shows that each GCS score increase was associated with a 12.9% reduction in the mortality risk at 14-days (OR 0.871 [95% CI 0.819–0.926]; P < 0.001), while in the GCS-P, each point on the scale was associated with a reduction of 15.3% (OR 0.847 [95% CI 0.769–0.900]; P < 0.001). Each point increase in MS-P was associated with a 37.4% reduction in 14-day mortality (OR 0.626 [95% CI 0.557–0.703]; P < 0.001).

Table 2 shows the discrimination, calibration, and overall AUC on all scales; for the 14-day mortality outcome, the highest AUC was obtained for MS-P (AUC = 0.790).

Table 2:

| Predictor Variable | AUC | P-value |
|--------------------|-----|---------|
| GCS                | 0.626| 0.001   |
| GCS-P              | 0.698| < 0.001 |
| MS-P               | 0.736| < 0.001 |

Prediction of in-hospital mortality

The univariate logistic regression model shows that each GCS score increase was associated with a 14.7% reduction in the odds of in-hospital mortality (OR 0.853 [95% CI 0.808–0.900]; P < 0.001), while in the GCS-P, each point on the scale was associated with a 16.2% reduction in the odds of in-hospital mortality (OR 0.838 [95% CI 0.795–0.884]; P < 0.001). Each point increase in MS-P was associated with a 39.7% reduction in the odds of mortality (OR 0.603 [95% CI 0.537–0.678]; P < 0.001).

The isolated Motor score presented AUC equal to 0.722, the addition of the pupillary response (MS-P) demonstrated a significant increase in its discriminative ability with AUC equal to 0.750 (P = 0.001). Figure 3a shows the ROC curves of the MS-P and its components. MS-P demonstrated better discrimination than GCS (AUC, 0.750 versus [vs.] 0.682, respectively; P < 0.001) and a greater AUC than the GCS-P; however, the difference was not statistically significant for this outcome (0.736 vs. 0.704; P = 0.073) [Figure 2b]. The ideal cutoff point for the GCS score to predict 14-day mortality was 4 (sensitivity, 57.84%; and specificity, 70.14%), five for GCS-P (sensitivity 66.67%; and specificity 66.09%), and three for MS-P (sensitivity 55.88%; and specificity 82.03%). Regarding the calibration and overall performance, all models were adequate. Furthermore, multivariate analysis showed an increase in AUC on all scales; for the 14-day mortality outcome, the highest AUC was obtained for MS-P (AUC = 0.790).

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Prediction of LHS

There were a total of 296 patients discharged alive that were included in the LHS prediction analysis. LHS was logarithmically transformed. Linear regression revealed that all scores were moderate predictors of LHS. The GCS-P showed a regression coefficient ($\beta$) of $-0.289$ (95% CI $-0.39$ to $-0.18$; $P < 0.05$), compared to $-0.280$ (95% CI $-0.39$ to $-0.17$; $P < 0.05$) for the GCS and $-0.268$ (95% CI $-0.10$ to $-0.44$; $P < 0.05$) for the MS-P. The determination coefficients ($R^2$) were 0.084, 0.079, and 0.072 for the GCS-P, GCS, and MS-P, respectively, thus demonstrating that the GCS-P explained a slightly greater variation in LHS in relation to the other scales. Details of the log LHS analysis for each of the scales are provided in Table 4.

DISCUSSION

The present study compared the predictive accuracy of GCS and GCS-P in a low- to middle-income country, which is
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In addition, the present study described a new score, MS-P, which is more accurate in assessing 14-day and in-hospital mortality. Accurate data for prognosis are important for determining appropriate health-care management in life-threatening cases and for proper communication with the patient. \(^1\) For patients with TBI, effective measures have a substantial potential to change patient outcomes \(s\). \(^{34,37}\) It is crucial to employ straightforward prognostic models that can be used in the clinical environment and include relevant information regarding the outcome. \(^{15,25}\) Both to justify decision-making

### Table 2: Discriminative ability, calibration and overall performance of all scales for predicting 14-day mortality and in-hospital mortality.

|                          | Discrimination - AUC (95% CI) | Calibration - H-L (P-value) | Overall Performance - Brier Score\(^1\) | 
|--------------------------|-------------------------------|-------------------------------|----------------------------------------|
|                          | Univariate | Multivariate\(^2\) | Univariate | Multivariate\(^2\) | Univariate | Multivariate\(^2\) | Univariate | Multivariate\(^2\) |
| **14-days mortality**    |            |                      |            |                      |            |                      |            |                      |
| GCS                      | 0.658 (0.612–0.702)           | 0.720 (0.676–0.762)           | 6.79 (0.339) | 7.60 (0.473) | 0.16          | 0.15          |
| GCS-P                    | 0.704 (0.659–0.746)           | 0.744 (0.701–0.784)           | 8.46 (0.231) | 9.78 (0.800) | 0.16          | 0.14          |
| MS                       | 0.698 (0.654–0.741)           | 0.754 (0.712–0.794)           | 1.04 (0.791) | 13.34 (0.100) | 0.15          | 0.14          |
| MS-P                     | 0.736 (0.693–0.777)           | 0.790 (0.749–0.827)           | 7.37 (0.117) | 12.65 (0.124) | 0.14          | 0.13          |
| **In-hospital mortality**|            |                      |            |                      |            |                      |            |                      |
| GCS                      | 0.682 (0.636–0.725)           | 0.762 (0.720–0.801)           | 9.51 (0.144) | 4.59 (0.799) | 0.20          | 0.17          |
| GCS-P                    | 0.714 (0.670–0.755)           | 0.778 (0.736–0.816)           | 6.82 (0.127) | 7.25 (0.509) | 0.19          | 0.16          |
| MS                       | 0.722 (0.678–0.763)           | 0.791 (0.750–0.828)           | 1.91 (0.591) | 9.08 (0.334) | 0.19          | 0.16          |
| MS-P                     | 0.750 (0.707–0.789)           | 0.813 (0.773–0.848)           | 7.73 (0.102) | 5.89 (0.658) | 0.18          | 0.15          |

\(^1\) Spiegelhalter test demonstrated a p-value of >0.05 for the Brier score, suggesting that the describes models had adequate calibration and overall performance. \(^2\) Multivariate model included sex, age, and Marshall CT class. AUC: Area under the curve, ETI: Endotracheal intubation, H-L: Hosmer Lemeshow test, GCS: Glasgow Coma scale, GCS-P: Glasgow Coma scale–pupil, MS-P: Motor score–pupil

Figure 1: Percentage of patients in each category of Glasgow coma scale (a), Glasgow coma scale–pupils (b), and motor score–pupils (c) and their sub-scores (d).
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and to facilitate risk communication in a manner that is easily understandable for everyone involved in patient care.[24,27,30,37]

Solla et al.[40] suggested, regarding the work of Brennan et al. and Murray et al., who described GCS-P, to report statistical analyses of scale discrimination such as AUC. In the present study, these data were described and corroborated the applicability and utility of GCS-P.[5,26,40] It is important to mention that there were some differences regarding the characteristics of the population of their studies, including the mean age.

The three scales demonstrated useful discriminative ability for 14-day and in-hospital mortality, considering that AUC was between 0.60 and 0.75, with emphasis on the MS-P score with the greatest AUC for these two outcomes (0.736 and 0.750, respectively). In addition to having good discrimination, the models presented adequate calibration.

It is not possible to make accurate comparisons regarding the precision of GCS-P in the primary population studied and in the sample of this study, because OR and AUC were not described in the studies mentioned above.[5,26] Nevertheless, it should be noted that differences between the populations studied, the combined data from the Corticosteroid Randomization after Significant Head Injury trial, and IMPACT studies reported mortality of 23.8%, while our study yielded an in-hospital mortality rate of 33.8%. Furthermore, the number of individuals with severe TBI was numerically higher in our population (64.2%) compared to 57% in the previous studies. This reflects the change in the epidemiology of TBI in high-income nations, where falls

Figure 2: Receiver operating characteristics curve for prediction of 14-day mortality by (a) motor score – pupil (MP-P) and its components, (b) Glasgow coma scale (GCS), Glasgow coma scale – pupil (GCS-P) and MS-P.

Figure 3: Receiver operating characteristics curve for prediction of in-hospital mortality by (a) motor score – pupil (MP-P) and its components, (b) Glasgow coma scale (GCS), Glasgow coma scale – pupil (GCS-P) and MS-P.
and older age are now the main contributors to TBI.\cite{35,36} Another important difference is that pupil reactivity was determined at different time periods in the IMPACT study, while in this study, it was obtained at admission.

The higher accuracy of the GCS-P in predicting 14-day and in-hospital mortality compared to the GCS is expected and can be explained as follows. First, pupil reactivity (an important component in the assessment of brainstem reflexes) has been demonstrated in several studies as a strong predictor of TBI-related mortality.\cite{19,22,28,29,43} Second, patients with GCS scores of 3 can be better stratified using the GCS-P, allowing a more accurate prediction of patient outcomes [Figure 1].

LHS is an important epidemiological data point, both to measure healthcare and to estimate the costs resulting from hospitalization for each pathology.\cite{2,20} Although patient admission assessment scores are commonly used to predict mortality and unfavorable outcomes after TBI, reports in the literature have demonstrated an association between these and patient length of stay in the ICU, as in the study by Okasha et al.\cite{29} This study is significant in that the scores described the impact on LHS, information that can be useful for managers and clinical practice.

Healey et al.\cite{17} demonstrated that motor score alone is a better predictor of mortality in relation to GCS since MS contains virtually all information about GCS itself and can be performed in intubated patients. In addition, MS has a linear relationship with mortality, while GCS has a non-linear function. The higher accuracy of the MS in relation to the other components of the scale was also demonstrated in several other studies.\cite{17,18,20,28,29,43} Thus, it is reasonable to use the best motor response associated with pupillary reactivity (i.e., MS-P), which, according to the AUC analysis in the present study, was superior for 14-day and in-hospital mortality prediction to both the GCS and GCS-P.

The prognosis of patients with TBI depends on several variables, which are considered during risk stratification, decision-making, and resource allocation.\cite{30} Several studies have shown that age and tomography findings are independent predictors of mortality.\cite{22,35} A multivariate analysis with sex, age, and Marshall Classification associated with the scales showed increased discrimination and a closer relationship between predicted and observed probabilities, as assessed using the Brier score. Therefore, the usefulness of GCS-P and MS-P was demonstrated both separately and in association with the variables commonly used in practice to stratify the risk in patients with TBI.

Lin et al.\cite{21} have also published a paper on external validation of the GCS-pupils score, reaching similar results. In their research, they were able to corroborate that the GCS-P score was superior regarding outcome prediction in comparison to the GCS. Regarding in-hospital mortality, GCS presented an AUC of 0.836, MS of 0.820, and a GCS-P of 0.847, while ours were 0.682, 0.722, and 0.714, respectively. Instead of measuring 14-day mortality, their study opted to evaluate 90-day mortality, with an AUC of 0.766 for GCS, 0.742 for MS, and 0.774 for GCS-P, while our 14-day results were 0.682, 0.722, and 0.714 respectively.

It is important to notice that there were significant epidemiological differences between these studies. The gender distribution in their study was almost 50/50, while our database included 85.5% males and 14.5% females, and their mean age was 65.5 compared to our 40. In this regard, our sample is more similar to the IMPACT database, which had a male proportion of 79% and a mean age of 35.7. Another noticeable difference is that Lin et al. used a database in a high IDH country, while our data were collected in a low to middle IDH country. These differences might explain why their study found significantly higher AUC values across all scores.

**Study limitations**

This is a single-center study, which may limit generalization to other groups. Nonetheless, it is worth mentioning that it is the largest Brazilian city, with a heterogeneous population. The city where the study was conducted receives a high flow of migration from other states of the country. Furthermore, as a tertiary hospital, high-severity patients with complex systemic trauma are commonly admitted. Nevertheless,
our work and results are a step toward filling an important information gap in the literature, as several authors have already reported that the GCS motor score is the best predictor of mortality.

This study was performed in a trauma center with a highly specialized and academic environment. However, this is not the reality of most hospitals in LMICs. For that reason, healthcare professionals should be properly trained for performing the necessary neurological tests and be able to obtain reliable data that can be used as described in this article.

Based on these findings, we encourage other researchers from numerous locations worldwide to evaluate and describe the accuracy of the MS associated with pupillary reactivity with respect to its predictive power. Furthermore, we suggest that authors from countries, in which the epidemiology of TBI is different from that of the present study, validate the GCS-P in their populations so that it is demonstrably a better predictor of GCS, is widespread, and routinely used in various centers.

We highlight the limitation of not having information on the sample's long-term results. The Glasgow outcome scale needs to be used to assess results in future investigations. However, the problem with long-term monitoring of TBI patients is not unique to our study and has been discussed in the literature. [2,29,38,42,46]

CONCLUSION

This study validated the usefulness of GCS-P in an LMIC population, thereby contributing to the process of its external validation. GCS-P had greater precision than GCS in predicting 14-day mortality and in-hospital mortality. Moreover, a new score (MS-P) that combines the best GCS motor response with pupillary reactivity was proposed. MS-P demonstrated clearly useful discrimination and higher AUC value than the GCS-P and the GCS for predicting mortality. Discrimination and calibration were also reported for a multivariate model, which included age, sex, and the Marshall CT classification in addition to validated scales. The multivariate model showed an increase in predictive ability compared to individual scales. Another contribution of this study was the evaluation of the relationship between the described scores and LHS, on which there are few reports in the literature, and is very useful for healthcare managers.

Data availability statement

The datasets generated for this study are available on request to the corresponding author.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Conflicts of interest

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