**Title:** Limited contribution of the GCS verbal component in predicting mortality among encephalopathic inpatients without mechanical ventilation.

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**Abstract**

**Background and Objectives:** The utility of the Glasgow Coma Scale (GCS) in intubated patients is limited due to its reliance on language function evaluation. The Full Outline of UnResponsiveness (FOUR) Score was designed to circumvent the shortcoming of language assessment in the GCS, instead adding evaluations of brainstem reflexes (FOUR B) and specific respiratory patterns (FOUR R). We aimed to determine if the verbal component of the GCS (GCS V) among encephalopathic patients who are not intubated significantly contributes to mortality prediction. In addition, we aimed to assess the overall performance of the GCS vs. FOUR Score in the same cohort.

 **Methods: This is a prospective cohort study.** All consented patients ≥18 years admitted to the Internal Medicine service at Zambia’s UTH from October 3rd, 2017 to May 21st, 2018 with a GCS of ≤10 had simultaneous GCS and FOUR Score assessments performed. None of the patients were on mechanical ventilatory support. Patients’ demographic and clinical characteristics were presented as frequency with percentage, or mean with standard deviation, median, and mode. The predictive power of the GSC without Verbal component vs. total GCS vs. FOUR Score on mortality were estimated using the area under the receiver operating characteristic (AU-ROC).

  **Results:** 235 patients (50% women; mean age 47.5 years) were-enrolled. All patients were Black. Most patients were presumed to have either CNS infection (64; 27%), stroke (63; 27%), systemic infection (39; 16.6%) or metabolic encephalopathy (3; 14.5 %). In-hospital mortality was 83%. Mean (SD) for GCS V was 1.5 (0.5); total GCS was 6.9 (2.3); total FOUR Score was 10.2 (3.2). AU ROC for GCS Eye+Motor (0.662) vs. total GCS (0.641) vs. total FOUR Score (0.657) did not differ. Odds ratio mortality for GCS > 6 vs. < 6 was 0.32, 95% CI 0.14-0.72 (p 0.01); for FOUR Score >10 vs. <10 was 0.41, 95% CI 0.19-0.86 (p 0.02).

 **Discussion:** Absence of a verbal component of GCS had no significant impact on total GCS scale’s performance and either GCS or FOUR Score are acceptable scoring tools for mortality prediction in this patient population.

**Classification of Evidence: Class III**

**Introduction.**

Critically ill comatose patients constitute a large portion of hospital admissions leading to death. The mortality rate is directly linked to coma etiology as well as the ability to provide adequate medical support during the acute phase of illness.

Rapid standardized clinical assessment scoring systems have been developed to inform providers of illness severity, guide care, adjust risk, and predict outcomes in critically ill patients. The Glasgow Coma Scale (GCS) has been shown to be informative in predicting mortality in patients with traumatic brain injury (TBI) [1] and is widely used beyond TBI diagnosis [2]. In addition, it has become part of the serial bedside evaluation and is utilized as a communication tool for day-to-day and hour-to-hour assessments of clinical status in critically ill patients [3]. The main components of GCS evaluate patients’ language comprehension and verbal response (GCS V), eye response (GCS E), and gross motor abilities (GCS M) on a 15-point scale (range 3-15) where a score of 8 and below usually warrants intubation and mechanical ventilation [4] where such supportive care is readily available. Despite being the most widely used tool to communicate patients’ global neurological status, its accuracy and utility in intubated patients is limited due to the inability to fully assess the verbal component [5]. GCS V is also difficult to assess in patients receiving sedatives, analgesics and neuromuscular blocking agents. The extent of the GCS V subscore’s contribution in predicting mortality among encephalopathic patients is unclear. Attempts have been made to create imputation models to bypass the verbal component of the GCS where this assessment is naturally limited in intubated or deeply comatose patients [6], [7].

The [Full Outline of](http://www.northeastcenter.com/four-full-outline-of-unresponsiveness-score.htm) UnResponsiveness (FOUR) Score was designed to circumvent the shortcoming of language assessment in the GCS, instead adding evaluations of brainstem reflexes and specific respiratory patterns in critically ill patients [8]. FOUR Score is a 17-point scale (ranging from 0 - 16) assessing eye (FOUR E), motor (FOUR M), respiratory (FOUR R), and brainstem (FOUR B) responses [8]. The FOUR Score has been validated in various clinical settings [9] and compared to the GCS as a tool for predicting mortality in critically ill patients with etiologies such as intracerebral hemorrhage [10], aneurysmal subarachnoid hemorrhage [11], traumatic brain injury [12] and bacterial meningitis [13]. These studies were performed in major academic settings with full access to state of the art medical care, including Neuro-critical care specialized units, which contributed to relatively lower mortality comparing to resource-limited communities. Some of the reported patients were already intubated and receiving mechanical respiratory support at the time of GCS and FOUR Score assessments [9]. In addition, some studies applied strict selection criteria and excluded patients who were deemed too sedated, had psychiatric illnesses, alcoholism or drug addiction [10] or had a personal or family history of neuromuscular diseases [11].

In highly developed medical settings, most comatose patients will be intubated for airway protection and respiratory management. In contrast, a small minority of encephalopathic and comatose patients presenting to most hospitals in Sub-Saharan Africa are able to receive mechanical ventilatory support. In this resource-limited setting, artificial respiration is a scarce commodity with priority allocation often directed to post-operative cases or to patients with well-understood, potentially reversible requirements for mechanical respiratory support. Within the context of a study evaluating subclinical seizures among encephalopathic and comatose patients at the University Teaching Hospitals (UTH) Adult Hospital in Lusaka, Zambia [14] we assessed concomitant GCS and FOUR scoring systems with the aim to compare GCS without GCS V, total GCS and total FOUR Score performance in predicting mortality in those who were not and would not be receiving ventilatory support. The goal of this study was to specifically assess the predictive validity of GCS with and without the verbal score in the population where endotracheal intubation would not be an impediment in the verbal assessment. In addition, we aimed to assess performance of each individual and combination subscores in outcome prediction. Lastly, we developed combined scales encompassing verbal, eye, motor and brainstem components of GCS and FOUR Score to evaluate if complementing either scale with the missing subscores would improve the overall performance of either scoring system.

**Methods.**

*Study Population.* As part of a previously reported EEG study [14] approved by the University of Zambia Biomedical Research Ethics Committee (Assurance No. FWA00000338; IRB00001131 of IORG0000774 and University of Rochester Research Subject Review Board, No. RSRB0006766, all patients ≥18 years admitted to the Internal Medicine (IM) service at Zambia’s UTH from October 3rd, 2017 to May 21st, 2018 with a GCS of ≤10 and enrolled in the EEG study had simultaneous GCS and FOUR Score assessments performed [14]. None of the patients were on mechanical ventilator support. No other exclusion criteria were used to eliminate selection bias and maintain population homogeneity in regards to GCS scoring.

*Consent.* Proxy consent was required for participation in the study. Excluded patients either lacked proxy at the bedside and could not be consented or died prior to initiation of study procedures~~.~~ This would more likely be the case for patients coming from further areas with family unable to accompany them. Coma assessment scoring of the patients on the IM service was performed by a single medical student (CB), who at the time of the study had completed three years of graduate medical education at the University of Rochester School of Medicine, had received specific training in GCS and FOUR Score evaluations and successfully applied those scoring techniques during the supervised clinical rotations at the University of Rochester Medical Center. Given the large amount of screened patients, having an additional evaluator was not feasible for completion of this study. In addition, the data elements for similar assessments of either scale were cross checked to ensure accuracy of scoring technique and recording.

*Data elements.* Structured neurological exam findings were captured by CB. Patients were followed until discharge or death in the hospital. The patients’ functional outcome at discharge was captured using the Karnofsky scale where a score of zero equated to in-hospital mortality. All patients had simultaneous GCS and FOUR Score assessments and there were no missing data. Comatose patients with a mouthpiece for oral airway support, but without mechanical ventilation, were scored as FOUR R=1 and included in the analysis. The data were validated by CB and OS.

*Statistical analysis.* Demographic and clinical characteristics are presented as frequency with percentage, or mean with standard deviation, median, and mode. The predictive power of the Total GSC without GCS V (GCS M+GCS E), total GCS and FOUR Score, their respective subscores, and composite scales on mortality were estimated using the area under the receiver operating characteristic (AU-ROC) and compared using logistic regression for the binary mortality outcome. GCS and FOUR Score totals, their subscores, and composite scales were then dichotomized as below the mean vs. at or above the mean and included in bivariate logistic regression models to determine the odds of mortality for each measures at or estimated as odds ratios and 95% confidence intervals. Composite scales were calculated as 1) GCS Total + FOUR R + FOUR B (range 3-23) and 2) FOUR Score total + GCS V (range 0- 21). In addition, similar composite assessments were made for a select subset of patients with clinically identical eye and motor responses, excluding those with GCS M=4, and FOUR E=3 due to lack of equivalent matches in the other scoring system. This selected approach allowed assessment of GCS V contribution to the total FOUR Score performance as well as the contribution of FOUR R and FOUR B to the total GCS performance among patients with clinically similar motor and eye findings while retaining the original scoring parameters of either scale and limiting contribution bias of the matching subscores. All analyses were performed using SAS v9.4 software and p-values<0.05 were considered statistically significant.

**Results.**

During a predefined recruitment period, proxy consent was obtained for 235 out of 392 patients meeting eligibility criteria and enrolled in this study. Excluded patients either lacked proxy at the bedside and could not be consented or died prior to initiation of study procedures. Half of the enrolled patients were females and the mean age was 47.5 (SD 18.2) years. The overall mortality rate was 83%. Due to lack of local resources limiting diagnostic evaluations, the exact etiology of coma was unknown for many patients. Presumed etiology of coma are listed in Table 1. At best approximation, most patients had either CNS infection (64; 27%), stroke (63; 27%), systemic infection (39; 16.6%) or metabolic encephalopathy (3; 14.5 %). Nearly half of the patients were HIV positive. UTH serves urban and rural populations. All patients were Black. Total and individual subscore values for GCS and FOUR Score and their composite scores are presented in Table 1.

Performance of the GCS without the Verbal component (GCS E+ GCS M) did not differ from the total GCS (Fig. 1 A) (p value =0.08) When comparing performance of individual and combined GCS subscores against total GCS score, GCS M and GSC M+GCS E performed similarly to the total GCS. AU ROC for GCS E was statistically different from the total GCS (p=0.01) (Figure 1 A). Similarly, in comparison to a total FOUR Score, only FOUR M did not differ in its performance (Figure 1 B). On the contrary, individual FOUR E, FOUR B, FOUR R, or combined FOUR B + FOUR R were statistically different from a total FOUR Score value in mortality prediction (all p-values < 0.03).

ROC performance curves for GCS, FOUR Score, and their composite scores in predicting mortality are displayed in Figures 2 A and 2 B. Overall, total GCS and total FOUR Score assessment scales did not differ in their performance (p value=0.53) (Figure 2 A). The composites of total FOUR Score + GCS V, total GCS +FOUR R+FOUR B) performed similarly in mortality prediction among all patients (p value= 0.56), as well as in the subset of patients with clinically similar motor and eye findings (p value=0.22) (Figure 2 B). Based on AUC ROC, performance of Total GCS +FOUR R+ FOUR B (AUC=0.649) was not different than total GCS (AUC=0.641) (p-value=0.62) and performance of Total FOUR Score +GCS V (AUC=0.645) was not different than total FOUR Score (AUC=0.657) (p-value=0.21).

Comparison of mortality between the values either below or > the mean demonstrated significant association for total GCS, GCS M, GCS M+GCS E, total FOUR Score, FOUR M and FOUR R+FOUR B as well as composites for the entire cohort with the cut off values listed in Table 2. Odds ratio mortality for total GCS > 6 vs. < 6 was 0.32, 95% CI 0.14-0.72 (p 0.01); for FOUR Score >10 vs. <10 was 0.41, 95% CI 0.19-0.86 (p 0.02) (Table 2). For ninety-eight patients with equivalent clinical values for both eye and motor scores in the GCS and FOUR scoring systems, neither composite of GCS Total + FOUR R + FOUR B scores nor FOUR Total + GCS V at or above the mean had significantly different mortality odds ratios than scores below the mean in this subset of patients (p=0.28) (Table 2).

**Discussion.**

Assessment scales of patients with decreased level of consciousness are expected to be easy to administer and accurate in their metric performance. GCS has an established reputation and is a widely accepted scale across many centers. However, inability to assess verbal response in intubated patients is considered one of its deficiencies [3]. As the coma ensues, higher cortical functions, such as language, are typically affected first. Reith et al. [15] reported that the contribution of each subscore to a total GCS sum is different across the scoring spectrum: in the range of 3 to 7, the sum score is mainly determined by the motor component whereas the verbal and eye components become more relevant in the range of 8 to 12.

In our patient cohort, due to the resource-limited nature of this setting, none of the patients were on mechanical ventilation at the time of the assessment. As anticipated, with the inclusion criterion requiring total GCS value < 10, verbal response had the overall lowest scores with no patients having GCS V equal to 4 or 5 and only 3 (1.3%) patients having a GCS V value of 3 (Tables 1, 2). In this cohort, there was no difference in AU ROC for prediction of mortality between total GCS and its subscore without verbal component (GCS E+ GCS M) (Fig. 1 A) emphasizing limited contribution of verbal subscore in these encephalopathic and comatose patients. Similar to previously published studies [16], [17], our cohort identified the best predictive value for the motor component of either scale, underscoring the importance of this metric, which is easy to assess regardless of the use of mechanical ventilation.

Individual GCS Eye or Verbal responses had no significant impact on mortality prediction neither on AU ROC assessments, nor when evaluating association of mortality and values around the respective means. On the other hand, GCS motor score (values < 3), combination of GCS Eye with GCS Motor responses (values < 6), and the total GCS (values < 7) values had a significant predictive power for poor outcome (Table 2).

Brainstem dysfunction cannot be fully captured by GCS [18]. This limitation was overcome by the FOUR Score, which includes scoring of respiratory patterns (FOUR R) and brainstem reflexes (FOUR B). Among individual FOUR subscore analyses, as with GCS, the only individual component performing similarly on AU ROC assessment was the motor subscore. The values of FOUR M <2 showed significant association with poor outcome. When comparing values below and above the means, total FOUR Score (values <11) and a combined FOUR R + FOUR B score (values < 7) had a significant predictive association with mortality.

Few scales were reported to have combined cortical, brainstem and autonomic responses [4]. Neither combining GCS V assessment with total FOUR Score nor FOUR B and FOUR R assessments with total GCS values provided additive value over either scale in this cohort on the AU ROC comparisons. The imputational models did not improve prognostic accuracy in the comatose and encephalopathic patients.

**Key Results.**

Among encephalopathic and comatose patients, the verbal component of the GCS does not significantly influence the utility of the GCS for predicting mortality based upon AU ROC. Either GCS or FOUR score are reliable assessment tools in mortality prediction among encephalopathic and comatose patients. Combining GCS V and FOUR R and FOUR B with eye and motor exam does not improve the prognostic accuracy of either scale. The prognostic value of the isolated motor subscores of either GCS or FOUR scores was most predictive for mortality estimate.

**Limitations.**

This study was conducted in a resource-limited setting in sub-Saharan Africa, which facilitated evaluation of coma measures in the absence of ventilation. While this population allowed comparisons of GCS and FOUR Score in comatose adults who were not receiving ventilatory support, most patients had GCS V < 3, limiting statistical applicability for this individual subscore in assessment of mortality. Other individual item subscores with limited unfavorable ratings (e.g. FOUR B) may be underpowered to detect an association with mortality and are considered exploratory. Coma etiologies and outcomes among patients in higher income settings where ventilation is routinely available might indeed differ. Finally, this study misses comatose Zambian patients who could not survive without ventilation long enough to be evaluated and included in this analysis, so extrapolating the findings in this study to patients in more developed medical setting at this extremity of illness may not be valid.

**Disclosures.**

Peggy Auinger, MS, none.

Gretchen Birbeck, MD, MPH

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**Table 1**. Demographics, GCS and FOUR Score Values and Distribution

|  |  |
| --- | --- |
| Characteristics  | Mean (SD), Median, Mode  |
| Age  | 47.5 (18.2), 44, 37  |
| GCS Total  | 6.9 (2.3), 7, 10 |
|  GCS Eye Response (GCS E) | 2.5 (1.3), 2, 4 |
|  GCS Verbal Response (GCS V) | 1.5 (0.5), 1, 1 |
|  GCS Motor Response (GCS M) | 3.0 (1.5), 4, 4 |
|  Composite GCS Eye Response/Motor Response (GCS E+GCS M) | 5.5 (2.1), 6, 8 |
| FOUR Score Total  | 10.2 (3.2), 11, 12 |
|  FOUR Score Eye Response (FOUR E) | 1.5 (1.3), 1, 3 |
|  FOUR Score Motor Response (FOUR M) | 1.9 (1.4), 3, 3 |
|  FOUR Score Brainstem Reflexes (FOUR B) | 3.1 (1.3), 4, 4 |
|  FOUR Score Respiration Pattern (FOUR R) | 3.7 (0.8), 4, 4 |
|  Composite FOUR Score (FOUR B+FOUR R) | 6.8 (1.7), 8, 8 |
| Composite GCS Total + FOUR R + FOUR B  Entire cohort Subset with similar motor and eye clinical values (n=98) | 13.7 (3.5), 15, 1811.8 (3.9), 11, 9 |
| Composite FOUR Score Total + GCS V Entire cohort Subset with the similar motor and eye clinical values (n=98) | 11.6 (3.4), 12, 139.5 (3.6), 9, 7 |
| Females, n (%) | 118 (50%) |
| Mortality, n (%) | 195 (83%) |
| Presumed Etiology of coma, n (%) |  |
| Anemia  | 1 (0.4%) |
| Brain metastasis  | 1 (0.4%) |
| Cardiogenic Shock | 2 (0.9%) |
| Cerebral Malaria | 1 (0.4%) |
| CNS Infection (non-TB\* or unknown organism) | 43 (18.3%) |
| CNS Infection (TB) | 21 (8.9%) |
| CNS IRIS\*\* | 2 (0.9%) |
| CNS Lymphoma | 1 (0.4%) |
| DKA\*\*\* | 5 (2%) |
| Eclampsia | 1 (0.4%) |
| Hemorrhagic Stroke | 22 (9.3%) |
| Hepatic Encephalopathy | 8 (3.4%) |
| Hypovolemic shock | 1 (0.4%) |
| Ischemic stroke | 41 (17.4%) |
| Malaria | 3 (1.3 %) |
| Malnutrition  | 2 (0.9%) |
| Multiple Myeloma | 1 (0.4%) |
| Organophosphate Poisoning | 1 (0.4%) |
| PML\*\*\*\* | 3 (1.3 %) |
| PNEA\*\*\*\*\*/Psychogenic Coma | 1 (0.4%) |
| Renal Encephalopathy | 26 (11%) |
| Sepsis | 35 (14.9%) |
| Severe Anemia | 1 (0.4%) |
| Status Epilepitcus | 11 (4.7%) |
| Subarachnoid/Subdural/Epidural Hemorrhage | 1 (0.4%) |
| HIV status (known positive), n (%) | 109 (46.4%) |
| Known Preexisting Epilepsy, n (%)  | 1. 6%)
 |

**\*** TB Tuberculosis

**\*\*** IRIS Immune reconstitution inflammatory syndrome

\*\*\* DKA Diabetic ketoacidosis

**\*\*\*\*** PML Progressive multifocal leukoencephalopathy

**\*\*\*\*\*** Psychogenic Non-Epileptic Attacks

**Figure 1.** ROC Curves for Total and Subscores for GCS (A) and FOUR Score (B) and Mortality



**Figure 2.** ROC Curves for Mortality and (A) Total GCS and FOUR Score; (B) Composite GCS+ FOUR R + FOUR B and FOUR Score + GCS V for the entire cohort and for subset of patients with similar Motor and Eye Clinical Values.



**Table 2.** Odds Ratios for Associations between GCS and FOUR Score Totals, Subscores, and Composites vs. Mortality

|  |  |  |  |
| --- | --- | --- | --- |
|  | Odds Ratio | 95% CI | p-value |
| GCS Total |  |  |  |
| 7-10 vs 3-6 | 0.32 | 0.14-0.72 | 0.01 |
|  Eye Response |  |  |  |
|  3-4 vs 1-2 | 0.80 | 0.40-1.58 | 0.52 |
|  Verbal Response |  |  |  |
|  2 vs 1 | 0.97 | 0.49-1.93 | 0.93 |
|  3 vs 1 | \* |  |  |
|  Motor Response |  |  |  |
|  3-5 vs 1-2 | 0.20 | 0.08-0.54 | 0.001 |
|  Eye Response/ Motor Response Composite |  |  |  |
|  6-9 vs 2-5 | 0.26 | 0.12-0.57 | 0.001 |
| FOUR Score Total |  |  |  |
| 11-15 vs 0-10 | 0.41 | 0.19-0.86 | 0.02 |
|  Eye Response |  |  |  |
|  2-4 vs 0-1 | 0.80 | 0.40-1.58 | 0.52 |
|  Motor Response |  |  |  |
|  2-4 vs 0-1 | 0.20 | 0.08-0.54 | 0.001 |
|  Brainstem Reflexes |  |  |  |
|  4 vs 0-3 | 0.59 | 0.28-1.23 | 0.16 |
|  Respiration Pattern |  |  |  |
|  4 vs 0-3 | 0.31 | 0.07-1.38 | 0.12 |
|  Brainstem Reflexes/ Respiration Pattern Composite |  |  |  |
|  7-8 vs 0-6 | 0.44 | 0.20-0.95 | 0.04 |
| Composite GCS Total + FOUR R + FOUR B |  |  |  |
|  14-18 vs 3-13 Entire cohort 12-18 vs 3-11 Subset with similar motor and eye clinical values | 0.370.49 | 0.18-0.760.13-1.78 | 0.010.28 |
| Composite FOUR Score Total + GCS V |  |  |  |
|  12-17 vs 1-11 Entire cohort 10-17 vs 1-9 Subset with similar motor and eye clinical values | 0.430.49 | 0.21-0.880.13-1.78 | 0.020.28  |

\* Patients with GCS verbal response of 3 (n=3) too few to provide reliable odds ratio.