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REVIEW ARTICLE

The Full Outline of UnResponsiveness (FOUR) Score and Its Use in Outcome Prediction: A Scoping Systematic Review of the Adult Literature

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Abstract

Background: The Full Outline of UnResponsivness (FOUR) score is a neurological assessment score. Its theoretical benefit over preexisting scores is its evaluation of brainstem reflexes and respiratory pattern which may allow better assessment of patients with severe neurologic impairment.

Objective: Our goal was to perform a scoping systematic review on the available literature for FOUR score and outcome prediction in critically ill patients. The primary outcome of interest was patient global outcome, as assessed by any of: mortality, modified Rankin Score, Glasgow Outcome Score, or any other functional or neuropsychiatric outcome. Information on interobserver reliability was also extracted.

Methods: MEDLINE and five other databases were searched. Inclusion criteria were: humans, adults, and children; prospective randomized controlled trial; prospective cohort, cohort/control, case series, prospective, and retrospective studies. Two reviewers independently screened the results. Full texts for citations passing this initial screen were obtained. Inclusion and exclusion criteria were applied to each article to obtain final articles for review. Results on adult populations are presented here. Data are reported following the preferred reporting items for systematic reviews and meta-analyses guidelines.

Results: The initial search yielded 1709 citations. Of those used, 49 were based on adult and 6 on pediatric populations. All but 8 retrospective adult studies were performed prospectively. Patient categories included traumatic brain injury, intraventricular hemorrhage, intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke, general/combined neurology and neurosurgery, post-cardiac arrest, medicine/general critical illness, and patients in the emergency department. A total of 9092 adult patients were studied. Fourteen studies demonstrated good interobserver reliability of the FOUR score. Nine studies demonstrated prognostic value of the FOUR score in predicting mortality and functional outcomes. Thirty-two studies demonstrated equivalency or superiority of the FOUR score compared to Glasgow Coma Score in prediction of mortality and functional outcomes.

Conclusions: The FOUR score has been shown to be a useful outcome predictor in many patients with depressed level of consciousness. It displays good inter-rater reliability among physicians and nurses.

Keywords: FOUR score, Prognosis, Clinical scoring, Critical illness, Neurological illness

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Introduction

Clinical assessment of neurological status is a vital element in decision making, outcome prediction, and information sharing among medical professionals. Traditionally, the Glasgow Coma Scale (GCS) has been widely adopted to document and formally assess neurological status. This scale has been praised for its simplicity and ease of use among healthcare workers. However, a shortcoming of the GCS is its inaccuracy in certain patient populations, including those with severe neurological impairment. This population may include intubated patients, which are difficult to assess with the GCS due to their lack of verbal communication. Similarly, alteration of brainstem function and respiratory pattern are important clinical factors reflecting severity of impairment, which the GCS neither addresses nor attempts to quantify.

In 2005, Wijdicks et al. [1] devised a new coma score, the Full Outline of UnResponsiveness (FOUR) score, which addressed the pitfalls of the GCS. The benefit that the FOUR score has over preexisting systems is the inclusion of specific categories for eye movement, motor exam, brainstem reflexes, and respiratory pattern. Thus, the FOUR score provides a structured scoring system for aspects of brainstem function that can be assessed in all patients, including those unable to verbally communicate.

Since its inception, the FOUR score has been studied in a variety of settings and patient populations. Our goal was to perform a scoping systematic review of the existing literature on the application of the FOUR score within critically ill patients and its use in outcome prediction.

Methods

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers [2] was conducted. Data are reported following the PRISMA guidelines [3]. The PRISMA checklist is found in the supplementary material as "Appendix A." The search strategy was decided upon by the primary author (AA) and supervisor (FAZ).

Search Question, Population, Inclusion, and Exclusion Criteria

We aimed to answer the question: What literature is available for FOUR score and outcome prediction in critically ill patients? The primary outcome of interest was patient global outcome, as assessed by any of: mortality, modified Rankin Score (mRS), Glasgow Outcome Score (GOS), or any other functional or neuropsychiatric outcome.

Studies documenting interobserver variability were also included in order to provide context to the reliability of the FOUR score system.

Inclusion criteria were: humans, adults, and children; prospective randomized controlled trial, prospective cohort, cohort/control, case series, prospective and retrospective studies. Non-English studies and those involving animals were excluded. Ultimately, studies on pediatric populations were excluded as these results will be reported in a separate publication. The FOUR score was used as described in the original validation study by Wijdicks et al. [1] (Table 1).

Search Strategy

Six databases were searched from inception to September 2017: MEDLINE, BIOSIS, Scopus, Cochrane Libraries, Globalhealth, and Embase. Published meeting proceedings were included in the search. Following study selection, reference sections of each paper were examined to ensure relevant papers not captured by the initial search were included in the review. "Appendix B" of the supplementary materials highlights the search strategy implemented for each database.

Study Selection

A two-step review was performed. Two reviewers independently screened each resulting title and abstract from the initial search for inclusion. Full texts for citations passing this initial screen were obtained. Inclusion and exclusion criteria were applied to each article to obtain final articles for review. In cases of disagreement between the two reviewers, open discussion was done and a detailed review of the study in question was done to reach a consensus.

Data Collection

Data were extracted from the final list of articles and stored electronically. Data from adult populations were organized into the following categories based on patient pathology and setting by the primary author: patients in the emergency department, medicine and general critical illness patients, traumatic brain injury, intraventricular/intracerebral hemorrhage, subarachnoid hemorrhage, ischemic stroke and general neurology/neurosurgery patients. Data extracted included study country, design, objectives, outcomes, and conclusions made by the study authors. Data on interobserver reliability, if assessed, was also included, as was any information on prognostic ability of the FOUR score.

Quality of Evidence Assessment

Each study was evaluated for quality of evidence using the RTI Item Bank on Risk of Bias and Precision of Observational Studies [4]. This validated item bank is applicable to a variety of observational study designs and evaluates the risk of bias and internal validity of studies using a

Table 1 Neurological grading scales

Full Outline of UnResponsiveness Score		Glasgow Coma Scale	
Eye response		Eye opening	
E4	Eyelids open or opened, tracking or blinking to command	E4	Spontaneous
E3	Eyelids open but not tracking	E3	To verbal command
E2	Eyelids closed but open to loud voice	E2	To pain
E1	Eyelids closed but open to pain	E1	None
E0	Eyelids remain closed with pain		
Motor response		Verbal response	
M4	Thumbs-up, fist or peace sign	V5	Oriented
M3	Localizing to pain	V4	Confused
M2	Flexion response to pain	V3	Inappropriate words
M1	Extension to pain	V2	Incomprehensible sounds
M0	No response to pain or generalized myoclonus status	V1	None
Brainstem reflexes		Motor response	
B4	Pupil and corneal reflexes present	M6	Follows commands
B3	One pupil wide and fixed	M5	Localizes pain
B2	Pupil or corneal reflexes absent	M4	Withdraws from pain
B1	Pupil and corneal reflexes absent	M3	Flexion to pain
B0	Absent pupil, corneal and cough reflex	M2	Extension to pain
		M1	None
Respiration			
R4	Not intubated, regular breathing pattern		
R3	Not intubated, Cheyne–Stokes breathing		
R2	Not intubated, irregular breathing		
R1	Breathes above ventilator rate		
R0	Breathes at ventilator rate or apnea		

comprehensive list of itemized questions. "Appendix C" of the supplementary materials provides the tabulated results of the bias assessment for each study included in this scoping review.

Statistical Analysis

A meta-analysis was not performed due to the heterogeneity of data and study design within the studies; thus, a scoping review was performed.

Results

The initial search yielded 1709 citations. Of 55 articles selected for final review, 49 were based on adult populations and will be included in the results of this paper. Sixteen of these articles studied general medical and critical illness populations, 6 articles studied patients in an emergency department setting, 10 articles studied patients with traumatic brain injury, 3 articles studied patients with intracerebral or intraventricular hemorrhage, 1 article studied patients with subarachnoid hemorrhage, 2 articles studied patients with ischemic stroke, and 11 articles studied general neurology and neurosurgery patients. Forty-one of these articles were performed prospectively; the remainder of the articles were performed retrospectively. There were no randomized controlled trials performed in the literature. A total of 9092 adult patients were studied. Figure 1 displays the PRISMA [3] flow diagram of the search results and filtering processes.

Interobserver Reliability

Fourteen studies [1, 5–17] demonstrated good to excellent interobserver reliability of the FOUR score among raters. In general, a kappa value of 0.4 or less is considered poor, values of 0.4–0.6 are considered fair to moderate, values of 0.6–0.8 are considered good, and values above 0.8 are considered to have excellent inter-rater agreement. The lowest weighted kappa score found in the literature for the FOUR score was 0.68 [10], with the majority being at least 0.80. 3 of the 14 studies were done on patients in the emergency department [5–7], 6 on general medical and critical illness patients [8–13], and 5 on general neurology and neurosurgical patients [1,

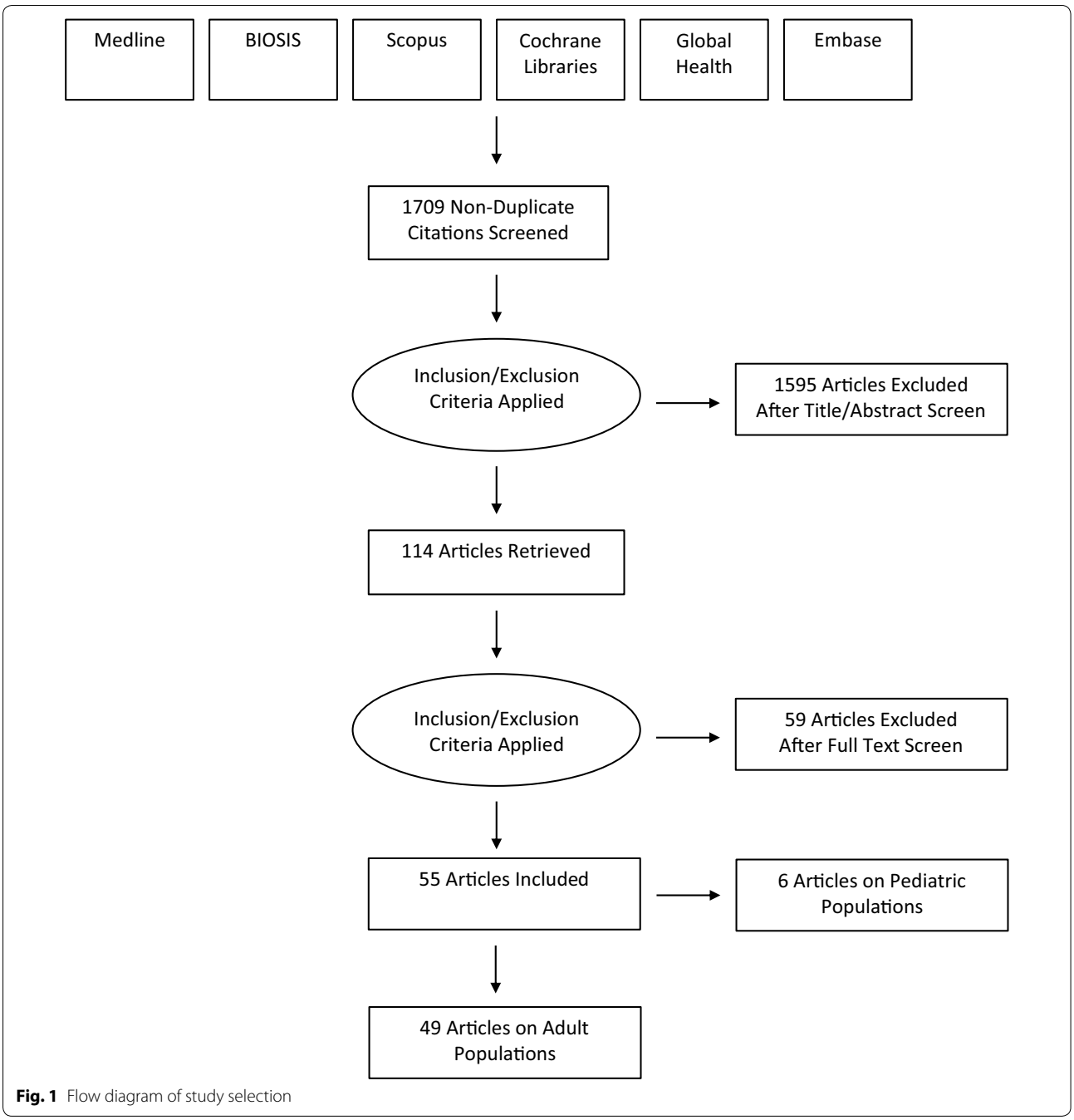

Fig. 1 Flow diagram of study selection

14–17]. No articles that studied interobserver reliability failed to demonstrate at least good reliability. "Appendix D" of the supplementary materials provides the tabulated results from those studies assessing interobserver reliability.

Prognostic Value When Used Alone

Nine studies [18–25] demonstrated prognostic value of the FOUR score in predicting mortality and functional outcomes. Four were based on general medicine and critical illness populations [18–21], whereas 5 were based on neurology and neurosurgery populations (including 2 on intracerebral hemorrhage patients [23, 24] and 2 on traumatic brain injury patients [25]).

In a neurological intensive care unit, Akavipat et al. [22] demonstrated the predictive value of the FOUR score in predicting poor outcome at discharge (AUC ROC = 0.88, 95% CI 0.82–0.92) and in-hospital mortality (AUC

ROC = 0.92, 95% CI 0.87–0.97). In medicine patients, Rohaut et al. [20] demonstrated the predictive value of the FOUR score in predicting 28-day mortality (*c*-index of 0.76, 95% CI 0.67–0.84). Other outcomes studied include admission to an intensive care unit [23], overt hepatic encephalopathy [18] and discharge to home or a rehabilitation facility [19]. "Appendix E" of the supplementary materials displays the tabulated results from these studies.

One study [26] examined the use of various weaning parameters (including the FOUR score) in predicting extubation failure in general neurology and neurosurgical patients. The authors found no significant difference in FOUR score between patients who failed extubation and those who were successfully extubated.

Prognostic Value When Compared to the GCS

Thirty-two studies [1, 6, 7, 9, 11, 12, 16, 25, 27–51] demonstrated equivalency or superiority of the FOUR score compared to GCS in the prediction of mortality and functional outcomes. Four of these studied patients in the emergency department [6, 7, 27, 30], 8 studied general medical and critical illness patients [9, 11, 12, 29, 31, 45, 48, 49], 11 studied traumatic brain injury patients [25, 34–36, 40–45, 47], and 10 studied other neurology/neurosurgery patients (6 studied general neurology and neurosurgical patients [16, 28, 33, 37, 49, 50], 2 studied ischemic stroke patients [38, 39], 1 studied intraventricular hemorrhage patients [32] and 1 studied aneurysmal subarachnoid patients [51]).

Table 2 displays the studies focusing on emergency department populations. Multiple authors demonstrated equal or superior prognostic value of the FOUR score in predicting mortality; for example, Eken et al. [30] showed AUC ROC = 0.788 for FOUR (95% CI 0.722–0.844) and AUC ROC = 0.735 for GCS (95% CI 0.655–0.797) in predicting in-hospital mortality ($p = 0.0001$). Similarly, Stead et al. [6] demonstrated OR = 0.67 for FOUR (95% CI 0.53–0.84) versus OR = 0.68 for GCS (95% CI 0.56–0.83) in predicting in-hospital mortality ($p < 0.001$).

Table 3 displays the studies on general medical/critically ill patients. Outcomes studied in this population include those in the intensive care unit (ICU) [49], in-hospital [6, 7, 27, 31] and 28-day mortality [45], successful extubation [45], the ability to become a potential organ donor [29], and other functional outcomes based on the GOS, modified Rankin Scale and Glasgow–Pittsburgh cerebral performance categories [9, 12, 45, 48]. All demonstrated equivalency or superiority of the FOUR score; for example, Wijdicks et al. [49] demonstrated AUC ROC = 0.742 (95% CI 0.694–0.790) for FOUR and AUC ROC = 0.715 for GCS (95% CI 0.663–0.768) in predicting in-ICU mortality ($p = 0.001$).

Table 4 outlines the studies on traumatic brain injury patients, while Table 5 highlights the other studies on neurology/neurosurgery patient populations. Values for AUC ROC were similar across studies in predicting in-hospital mortality; generally AUC ROC ≥ 0.80 [1, 34, 39, 40, 43, 44, 47]. Mortality was studied at various other time points [35, 46], along with functional outcome based on the GOS, the Karnofsy Performance Score, the Acute Physiology and Chronic Health Evaluation II score and the modified Rankin Scale [34, 36, 40, 41, 43, 44]. Again, all illustrate the equivalent or superior ability of the FOUR score to predict mortality and functional outcomes when compared to GCS.

One study [52] conducted in post-resuscitation encephalopathy patients studied the motor components of both the FOUR score and GCS to predict poor prognosis, and found a lower sensitivity of the FOUR score in outcome prediction (68.7% sensitivity for FOUR, 95% CI 41.4–88.9 vs. 87.5% sensitivity for GCS, 95% CI 61.6–92.6).

Quality of Evidence

Quality of evidence was assessed using the RTI Item Bank on Risk of Bias and Precision of Observational Studies [4]. Based on its itemized list of questions, there was an overall low risk of bias in the studies included in this review.

Discussion

We aimed to perform a scoping review of the FOUR score and its use in outcome prediction. The existing literature around the FOUR score generally demonstrates that it possesses prognostic value alone and in comparison with the GCS, as exemplified through 9 and 32 mainly prospective studies, respectively.

In predicting extubation failure, however, Ko et al. [26] failed to show predictive value for the FOUR score as well as all other weaning parameters they chose to study, including rapid shallow breathing index and spontaneous breathing trial. In neurology and neurosurgical patients, the ability to forcefully cough and actively clear secretions is of importance in successful extubation, and perhaps not specifically assessed by the FOUR score. However, the authors also had missing data regarding etiology of respiratory failure and inaccurate fluid balance, which may have contributed to their negative results. In contrast, Said et al. [45] published a pilot study among a general ICU population, and did show superiority of the FOUR score compared to GCS in predicting successful extubation at 14 days post-intubation.

In comatose patients post cardiopulmonary arrest, Topcuoglu et al. [52] examined the motor parts of the GCS and FOUR score in outcome prediction and showed

Table 2 Studies on patients in the emergency department examining the prognostic value of FOUR Score versus GCS

Citation	Country	Design	Outcome studied	FOUR result	GCS result
Baratloo 2016 Predictive value of GCS and FOUR Score on the Outcome of multiple trauma patients	Iran	Prospective cohort	In-hospital mortality, clinical diagnosis of brain death, or motor disability (grouped as "death or disability") at admission	AUC ROC = 0.93 95% CI 0.87–0.98	AUC ROC = 0.91 95% CI 0.85–0.97 ($p = 0.20$)
			"Death or disability" at the 6th h	AUC ROC = 0.96 95% CI 0.93–1.0	AUC ROC = 0.96 95% CI 0.91–1.0 ($p = 0.16$)
			"Death or disability" at the 12th h	AUC ROC = 0.96 95% CI 0.92–1.0	AUC ROC = 0.95 95% CI 0.90–1.0 ($p = 0.49$)
Eken 2009 Comparison of the FOUR Score Coma Scale and the GCS in an Emergency Setting population	Turkey	Prospective observational	In-hospital mortality	AUC ROC = 0.788 95% CI 0.722–0.844 ($p = 0.0001$)	AUC ROC = 0.735 95% CI 0.655–0.797 ($p = 0.0001$)
			3-month mortality	AUC ROC = 0.776 95% CI 0.709–0.834 ($p = 0.0001$)	AUC ROC = 0.726 95% CI 0.656–0.789 ($p = 0.0001$)
			Poor outcome (mRS of 3–6) at 3 months	AUC ROC = 0.751 95% CI 0.682–0.812 ($p = 0.0001$)	AUC ROC = 0.720 95% CI 0.650–0.784 ($p = 0.001$)
Matheesiriwat 2012 The FOUR score and GCS to evaluate the patients with intubation at emergency room	Thailand	Prospective observational	In-hospital mortality	OR = 0.865 95% CI 0.678–1.103	OR = 0.908 95% CI 0.569–1.447
Stead 2009 Validation of a New Coma Scale, the FOUR Score, in the emergency department	USA	Prospective observational	Survival at hospital discharge	OR = 0.67 95% CI 0.53–0.84 ($p < 0.001$)	OR = 0.68 95% CI 0.56–0.83 ($p < 0.001$)
			Functional outcome at hospital discharge (modified Rankin scale 3–6)	OR = 0.59 95% CI 0.26–0.71 ($p < 0.029$)	OR = 0.61 95% CI 0.41–0.92 ($p < 0.018$)

AUC area under the curve, *CI* confidence interval, *FOUR* full outline of unresponsiveness, *GCS* Glasgow Coma Scale, *ICC* intraclass correlation coefficient, *k* weighted kappa score, *OR* odds ratio, *ROC* receiver operating characteristic curve

a lower sensitivity of the FOUR motor component compared to the GCS motor component. When either scores were combined with specific magnetic resonance imaging (MRI) findings, sensitivity improved to 100%. It is important to note that in this study, the authors focus primarily on MRI findings, and specific details regarding how and when the FOUR score is measured, as well as the presence of potentially confounding factors (for example, sedating or paralyzing medications) is unclear.

Taking into consideration the shortcomings of these two studies, overall, the remainder of the present literature around the FOUR score displays its usefulness as a neurological assessment tool. While its accuracy in predicting extubation failure is not clearly established—again, perhaps as a result of the limitations described previously—multiple studies have shown it to hold prognostic significance in predicting mortality and functional outcomes in diverse patient populations, from general medicine patients to those with neurosurgical pathology.

Accurate neurological assessment is made imperfect by the presence of mental alteration caused by sedating medications, endotracheal intubation, and language barriers including patient dysphasia or dysarthria. These conditions make application of the GCS verbal score especially difficult, as it relies heavily on accurate comprehension, orientation and the ability of the patient to verbally respond to the rater. Raters will make adjustments to the GCS to account for the presence of such clouding factors, especially in the presence of endotracheal intubation, but these adjustments are non-standardized across institutions. The FOUR score bypasses this by not including a verbal score based on orientation or the ability of a patient to respond; a degree of comprehension is required to obey simple motor commands

Table 3 Studies on medicine and general critical illness patients examining the prognostic value of FOUR score versus GCS

Citation	Country	Design	Outcome studied	FOUR result	GCS result
Bruno 2011 Comparison of the FOUR and GCS in an intensive care unit population	Belgium	Prospective cohort	Poor outcome at 3 months (GOS of 3 or less)	AUC ROC = 0.70 OR = 0.83 95% CI 0.73–0.95 ($p = 0.002$)	AUC ROC = 0.68 ($p = 0.67$) OR = 0.82 95% CI 0.71–0.95 ($p = 0.007$)
De Groot 2011 Donor conversion rates depend on the assessment tools used in the evaluation of potential organ donors	USA, Netherlands	Retrospective chart review	Donor conversion rate using three different definitions to identify IBD: IBD-FOUR definition IBD-GCS definition IBD-Organ procurement transplantation network definition	76 patients identified using IBD-FOUR definition The highest donor conversion rate was noted in the IBD-FOUR definition (36.5%)	104 patients identified using IBD-GCS definition 107 patients identified using the IBD-OPTN definition
Fugate 2010 The FOUR Score Predicts Outcome in Patients after Cardiac Arrest	USA	Prospective observational	In-hospital mortality	FOUR ≤ 8: Sensitivity = 90.5 Specificity = 91.1 PPV = 90.5 NPV = 91.1 ($p < 0.0001$)	GCS ≤ 6: Sensitivity = 90.6 Specificity = 86.7 PPV = 86.4 NPV = 90.7 ($p < 0.0001$)
Gujjar 2013 Full Outline of UnResponsiveness score and Glasgow Coma Scale in medical patients with altered sensorium: Inter-rater reliability and relation to outcome	Oman	Prospective observational	Mortality at 3 months	AUC ROC = 0.697 ($p = 0.001$)	AUC ROC = 0.655 ($p = 0.009$)
			Good outcome at 3 months	AUC ROC = 0.708 ($p = 0.001$)	AUC ROC = 0.683 ($p = 0.003$)
Iyer 2009 Validity of the FOUR Score Coma Scale in the Medical ICU	USA	Prospective observational	Poor neurologic outcome (modified Rankin Scale score of 3–6) at 3 months	AUC ROC = 0.75 OR = 0.88 95% CI 0.72–1.06	AUC ROC = 0.76 OR = 0.91 95% CI 0.71–1.19
			In-hospital mortality	OR = 0.70 95% CI 0.58–0.85	OR = 0.64 95% CI 0.35–1.14
Said 2016 Usefulness of full outline of unresponsiveness score to predict extubation failure in intubated critically ill patients: A pilot study	Bahrain	Prospective observational	Successful extubation at 14 days after intubation	AUC ROC = 0.867 95% CI 0.790–0.944	AUC ROC = 0.832 95% CI 0.741–0.923 ($p = 0.014$)
*Topcuoglu 2009 Prognostic value of magentic resonance imaging in post-resuscitation encephalopathy	Turkey	Prospective observational	Poor prognostic classification (Glasgow–Pittsburg Cerebral Performance score of 4–5) at day 3	Motor score sensitivity = 68.7% 95% CI 41.4–88.9 Total score AUC ROC = 0.859 95% CI 0.645–0.0.967	Motor score sensitivity = 87.5% 95% CI 61.6–92.6 Total score AUC ROC = 0.953 95% CI = 0.769–0.992
Weiss 2015 Daily FOUR score assessment provides accurate prognosis of long-term outcome in out-of-hospital-cardiac arrest	France	Prospective observational	Poor outcome (Glasgow–Pittsburgh Cerebral Performance score of 4–5) at 6 months	Change in FOUR from day 1–3 AUC ROC = 0.87 95% CI 0.74–0.95	Change in GCS from day 1–3 AUC ROC = 0.75 95% CI.56–0.86
			6-month mortality	Change in FOUR from day 1–3 AUC ROC = 0.84 95% CI 0.69–0.92	Change in GCS from day 1–3 AUC ROC = 0.75 95% CI 0.58–0.86.

Table 3 (continued)

Citation	Country	Design	Outcome studied	FOUR result	GCS result
Wijdicks 2015 Comparison of the Full Outline of UnResponsiveness Score and the Glasgow Coma Scale in predicting mortality in critically ill patients	USA	Prospective observational	ICU mortality	AUC ROC = 0.742 95% CI 0.694–0.790	AUC ROC = 0.715 95% CI 0.663–0.768 ($p = 0.001$)
			In-hospital mortality	AUC ROC = 0.702 95% CI 0.661–0.744	AUC ROC = 0.684 95% CI 0.641–0.723 ($p = 0.078$)

*Failed to show equal or superior prognostic value when compared to GCS

AUC area under the curve, *CI* confidence interval, *FOUR* full outline of unresponsiveness, *GCS* Glasgow Coma Scale, *GLS* glasgow liege scale, *GOS* glasgow outcome scale, *IBD* imminentbrain death, *ICU* intensive care unit, *k* weighted kappa score, *NPV* negative predictive value, *OR* odds ratio, *PPV* positive predictive value, *ROC* receiver operating characteristic curve

only. In patients with receptive aphasia, application of both the FOUR score and GCS may be difficult secondary to inability of the patient to process motor commands; however, the FOUR score subcategories of eye, motor, brainstem and respiratory function can be quantified in a greater number of patients than GCS including those that are intubated or with expressive language impairment only.

In comparison to the GCS, the FOUR score may also be helpful in further subcategorizing patients with severe neurological impairment based on their brainstem function and respiratory pattern, which the GCS is unable to do. This has the potential to better stratify patients with severe neurological injury and provide clinicians with further information regarding overall prognosis. These advantages, combined with its good inter-rater reliability, give the FOUR score the potential to replace conventional scoring systems and allow for precise and consistent neurological assessments among health care providers.

Limitations

Despite the promising results surrounding the application of the FOUR score across these varied patient populations, there are some limitations which deserve highlighting.

First, a main limitation of this review is the heterogeneity of the studies included. Given the assortment of study designs, objectives and patient populations, a meaningful meta-analysis of results was impossible to conduct. Thus, we are left with a purely descriptive analysis of the available literature. With that said, the body of literature which includes almost 10,000 patients provides evidence in support of its use for clinical grading in a variety of situations.

Second, the FOUR score itself is limited by the fact that it requires a more detailed neurological examination and the experience to confidently conduct such an examination. The saving grace of more simplistic systems, such as GCS, is they can be readily employed by various medical and paramedical professionals with fairly consistent reliability. This flexibility of GCS in the face of varied training and backgrounds of the assessor is a major benefit of the system. The FOUR score requires a slightly higher background knowledge of the nervous system, which may limit its application in other settings, such as the pre-hospital environment.

Third, the majority of the literature identified within this review focuses on general medical/ICU or traumatic brain injury patients. Thus, the conclusion regarding the association of the FOUR score with outcome or its performance compared to GCS in other populations, such as subarachnoid hemorrhage or intracerebral hemorrhage, is quite limited at this time. Further work is required in

Table 4 Studies on traumatic brain injury patients examining the prognostic value of the FOUR score versus GCS

Citation	Country	Design	Outcome studied	FOUR result	GCS result
Gorgi 2014 A comparison of the diagnostic power of the Full Outline of Unresponsiveness scale and the Glasgow Coma Scale in the discharge outcome prediction of patients with traumatic brain injury admitted to the intensive care unit	Iran	Prospective observational	In-hospital mortality	AUC ROC = 0.92 95% CI 0.81–0.97	AUC ROC = 0.96 95% CI 0.87–0.99 ($p < 0.05$)
			Poor neurologic outcome (Glasgow Outcome Scale 1–3) at discharge from hospital	FOUR AUC ROC = 0.95 95% CI 0.86–0.99	GCS AUC ROC = 0.90 95% CI 0.79–0.96 ($p < 0.05$)
Jalali 2014 A Comparison of the Glasgow Coma Scale Score with Full Outline of Unresponsiveness scale to predict patients' traumatic brain injury outcomes in intensive care units	Iran	Prospective observational	Mortality at 2 weeks or hospital discharge	Sensitivity = 68.4% Specificity = 77.3% PPV = 63.4% NPV = 81.0%	Sensitivity = 68.4% Specificity = 63.6% PPV = 52.0% NPV = 77.8%
Kasprowicz 2016 A comparison of the Full Outline of UnResponsiveness (FOUR) score and Glasgow Coma Score (GCS) in predictive modeling in traumatic brain injury	Poland	Prospective observational	In-ICU mortality	FOUR score combined with age, CT Rotterdam score, systolic blood pressure and being placed on a ventilator within day one AUC ROC = 0.906 ± 0.024	GCS with the same set of predictors plus pupil reactivity AUC ROC = 0.913 ± 0.022 ($p < 0.05$)
			3 month unfavorable outcome	FOUR score combined with CT Rotterdam score and age AUC ROC = 0.852 ± 0.037	GCS with the same predictors AUC ROC = 0.866 ± 0.034 ($p < 0.05$)
McNett 2014 The FOUR Score and GCS as Predictors of Outcome After Traumatic Brain Injury	USA	Prospective observational	Functional independence at rehabilitation discharge	FOUR at 24 h: AUC ROC = 0.625 95% CI 0.425–0.826 FOUR at 72 h: AUC ROC = 0.640 95% CI 0.439–0.841	GCS at 24 h: AUC ROC = 0.602 95% CI 0.392–0.812 GCS at 72 h: AUC ROC = 0.688 95% CI 0.496–0.879
			Cognitive status measured by Weschler Memory Scale scores 3 months post-injury	FOUR at 24 h: AUC ROC = 0.703 95% CI 0.469–0.938 FOUR at 72 h: AUC ROC = 0.837 95% CI 0.683–0.991	GCS at 24 h: AUC ROC = 0.731 95% CI 0.478–0.983 GCS at 72 h: AUC ROC = 0.674 95% CI 0.434–0.913
			In-hospital mortality	FOUR at 24 h: AUC ROC = 0.913 95% CI 0.822–1.00 FOUR at 72 h: AUC ROC = 0.837 95% CI 0.683–0.991	GCS at 24 h: AUC ROC = 0.935 95% CI 0.876–0.995 GCS at 72 h: AUC ROC = 0.884 95% CI 0.798–0.969
McNett 2015 A Comparative Study of Glasgow Coma Scale and Full Outline of Unresponsiveness scores for predicting long-term outcome after brain injury	USA	Prospective observational	Glasgow Outcome Scale score at 6 months	AUC ROC = 0.846 95% CI 0.734–0.959	AUC ROC = 0.902 95% CI 0.813–0.991
			Glasgow Outcome Scale score 12 months.	AUC ROC = 0.879 95% CI 0.771–0.986	AUC ROC = 0.931 95% CI 0.852–1.000

Table 4 (continued)

Citation	Country	Design	Outcome studied	FOUR result	GCS result
Nyam 2017 FOUR Score predicts early outcome in patients after traumatic brain injury	Taiwan	Prospective observational	Mortality on discharge from ICU	AUC ROC = 74.47%	AUC ROC = 73%
Okasha 2014 The FOUR Score predicts mortality, endotracheal intubation and ICU length of stay after traumatic brain injury	Egypt	Prospective observational	In-hospital mortality	AUC ROC = 0.850	AUC ROC = 0.796 ($p = 0.025$)
			Unfavorable outcome (Glasgow outcome scale extended 1–4) at 1 month	AUC ROC = 0.813	AUC ROC = 0.779 ($p = 0.136$)
			Endotracheal intubation in the emergency department	AUC ROC = 0.961	ROC = 0.982 ($p = 0.06$)
			ICU length of stay	Coefficient of determination $r2 = 0.40$	Coefficient of determination $r2 = 0.41$
Sadaka 2012 The FOUR Score Predicts Outcome in Patients After Traumatic Brain Injury	USA	Prospective observational	In-hospital mortality	FAUC ROC = 0.93	AUC ROC = 0.89
			Poor neurologic outcome (Glasgow outcome scale 1–3) at 3–6 months	AUC ROC = 0.85	AUC ROC = 0.83
			Poor neurologic outcome (modified Rankin scale 3–6) at 3–6 months	AUC ROC = 0.80	AUC ROC = 0.78
Saika 2015 Prognostic value of FOUR and GCS scores in determining mortality in patients with traumatic brain injury	India	Prospective observational	2 week mortality	At a cutoff score of 7, AUC ROC = 0.97 ($p < 0.0001$) OR = 0.348 95% CI 0.22–0.56 ($p < 0.001$)	At a cutoff score of 6, AUC ROC = 0.95 ($p < 0.0001$) OR = 0.336 95% CI 0.215–0.525 ($p < 0.001$)
Sepahvand 2016 Glasgow Coma Scale Versus Full Outline of Unresponsiveness Scale for prediction of outcomes in patients with traumatic brain injury in the intensive care unit	Iran	Prospective observational	In-hospital mortality	AUC ROC = 0.961	AUC ROC = 0.928

AUC area under the curve, *CI* confidence interval, *FOUR* full outline of unresponsiveness, *GCS* Glasgow Coma Scale, *ICU* intensive care unit, *k* weighted kappa score, *NPV* negative predictive value, *OR* odds ratio, *PPV* positive predictive value, *ROC* receiver operating characteristic curve

Table 5 Studies on other neurology and neurosurgical patients examining the prognostic value of the FOUR score versus GCS

Citation	Country	Design	Outcome studied	FOUR result	GCS result
General neurology and neurosurgery					
Chen 2013 Validation of a new neurological score (FOUR score) in the assessment of neurosurgical patients with severely impaired consciousness	Germany	Prospective	Mortality at 30 days	AUC ROC = 0.768 ($p = 0.0001$)	AUC ROC = 0.699 ($p = 0.001$)
			Poor outcome (Glasgow Outcome Scale 2–3) at 30 days	AUC ROC = 0.683 ($p = 0.018$)	AUC ROC was 0.682 ($p = 0.019$)
			Favorable outcome (Glasgow Outcome Scale 4–5) at 30 days	AUC ROC = 0.748 ($p = 0.001$)	AUC ROC = 0.704 ($p = 0.002$)
Gorgi 2015 Which score should be used in intubated patients' Glasgow Coma Scale or full outline of unresponsiveness?	Iran	Prospective observational	Early mortality (up to 14 days after admission)	AUC ROC = 0.90 95% CI 0.88–0.90	AUC ROC = 0.80 95% CI 0.78–0.84
			Late mortality (14 days or later after admission)	AUC ROC = 0.86 95% CI 0.84–0.90	AUC ROC = 0.89 95% CI 0.78–0.88
Khanal 2016 Comparison of outcome prediction by the Glasgow Coma Scale and the Full Outline of UnResponsiveness score in the neurological and neurosurgical patients in the Intensive Care Unit	Nepal	Prospective observational	In-hospital mortality	AUC ROC = 0.82 95% CI 0.73–0.91 ($p < 0.001$) OR = 0.70 95% CI 0.60–0.82 ($p < 0.001$)	AUC ROC = 0.79 95% CI 0.74–0.91 ($p < 0.001$) OR = 0.66 95% CI 0.55–0.79 ($p < 0.001$)
Temiz 2016 A Comparison Between the Effectiveness of Full Outline of Unresponsiveness and Glasgow Coma Score at Neurosurgical intensive care unit Patients	Turkey	Prospective observational	Correlation of FOUR and GCS to Karnofsky performance score (KPS) as a measure of functionality	KPS correlation with FOUR At admission: 0.718 At discharge from ICU: 0.734	KPS correlation with GCS At admission: 0.771 At discharge from ICU: 0.709
			Correlation of FOUR and GCS to Acute Physiology and Chronic Health Evaluation II score (APACHE II) as a measure of mortality	APACHE II correlation with FOUR: 0.851	APACHE II correlation with GCS: 0.853
Wijdicks 2005 Validation of a New Coma Scale: The FOUR Score	USA	Prospective observational	In-hospital mortality	AUC ROC = 0.81 OR = 0.79 95% CI 0.68–0.93	AUC ROC = 0.81 OR = 0.72 95% CI 0.66–2.72
			Poor outcome (modified Rankin Score 3–6) at 3 months	AUC ROC = 0.86 95% CI 0.75–0.98	GCS AUC ROC = 0.89 95% CI 0.76–1.03
Wijdicks 2011 FOUR Score and Glasgow Coma Scale in Predicting Outcome of Comatose Patients: A Pooled Analysis	USA	Retrospective study	Poor outcome (modified Rankin Scale 3–6) at 3 months	AUC ROC = 0.88	AUC ROC = 0.87
			Mortality	Those with FOUR ≤ 1 were more likely to die than those with a FOUR ≥ 2 (84% vs 44%, $p = 0.0039$)	–

Table 5 (continued)

Citation	Country	Design	Outcome studied	FOUR result	GCS result
Ischemic stroke					
Kocak 2012 A useful new coma scale in acute stroke patients; FOUR score	Turkey	Prospective observational	Mortality	FOUR on day 3: AUC ROC = 0.675 95% CI 0.565–0.786 FOUR on day 10: AUC ROC = 0.981 95% CI 0.947–1.015	GCS on day 3: AUC ROC = 0.624 95% CI 0.510–0.738 GCS on day 10: AUC ROC = 0.982 95% CI 0.951–1.013
Mansour 2015 Acute ischemic stroke prognostication, comparison between Glasgow Coma Score, NIHS Scale and Full Outline of UnResponsiveness Score in intensive care unit	Egypt	Prospective observational	In-hospital mortality	FOUR at 24 h: AUC ROC = 0.796 FOUR at 72 h: AUC ROC = 0.977	GCS at 24 h: AUC ROC = 0.779 GCS at 72 h: AUC ROC = 0.975
			Poor outcome (modified Rankin scale 3–6) at 3 months	FOUR at 24 h: AUC ROC = 0.893	GCS at 24 h: AUC ROC = 0.868
Spontaneous intraventricular hemorrhage					
Giray 2009 Spontaneous Primary Intraventricular Hemorrhage in Adults: Clinical Data, Etiology and Outcome	Turkey	Retrospective chart review	In-hospital mortality	FOUR score ≤ 10: OR = 4.22 95% CI 1.17–21.47 ($p = 0.037$)	GCS ≤ 8: OR = 4.72 95% CI 1.127–18.67 ($p = 0.034$)
Subarachnoid hemorrhage					
Zeiler 2017 Predicting Outcome in Subarachnoid Hemorrhage (SAH) Utilizing the Full Outline of UnResponsiveness (FOUR) Score	Canada	Prospective observational	1-month mortality	AUC ROC = 0.762 ($p = 0.009$)	AUC ROC = 0.753 ($p = 0.012$)
			6-month mortality	AUC ROC = 0.823 ($p = 0.004$)	AUC ROC = 0.820 ($p = 0.005$)
			1-month Glasgow Outcome Scale (dichotomized; good = 4–5, poor = 3 or less)	AUC ROC = 0.810 ($p < 0.001$)	AUC ROC = 0.796 ($p < 0.001$)
			6-month Glasgow Outcome Scale (dichotomized; good = 4–5, poor = 3 or less)	AUC ROC = 0.832 ($p = 0.001$)	AUC ROC = 0.832 ($p < 0.001$)

AUC area under the curve, *CI* confidence interval, *FOUR* full outline of unresponsiveness, *GCS* Glasgow Coma Scale, *k* weighted kappa score, *NPV* negative predictive value, *OR* odds ratio, *PPV* positive predictive value, *ROC* receiver operating characteristic curve

these sub-populations of patients to determine the role of the FOUR score. Studies directly comparing the utility of the FOUR score versus GCS in intubated versus non-intubated patients, and those with brain stem lesions versus those without, are also lacking within these populations. While the advantages of using the FOUR score over GCS in intubated patients is logical, and as previously described relates primarily to its ability to bypass a verbal assessment, this has not been specifically demonstrated in the literature and deserves focused attention in future studies.

Lastly, as with many outcome prediction studies, the presence of observer bias is possible. Only 12 of the 49 studies were transparent about the presence of blinding in their study protocol. Many authors failed to mention whether they blinded their raters and outcome observers, making the presence of observer bias unclear. The numbers of patients in whom life-sustaining therapies were withdrawn in their clinical course is also poorly described in the literature, potentially introducing an element of selection bias as well.

Conclusions

The existing literature favors the FOUR score as a useful outcome predictor in many patients with depressed level of consciousness. It has been studied in a wide variety of critically ill patients, both with and without neurologic pathology in predicting mortality and functional outcomes. It displays good inter-rater reliability among physicians and nurses.

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Author Contribution
AA contributed to the conception and design of this work, the acquisition and interpretation of data, the initial drafting of the manuscript and the critical revision of intellectual content. MH contributed to the interpretation of data and the critical revision of intellectual content. FAZ contributed to the conception and design of this work, the interpretation of data and the critical revision of intellectual content. All authors were involved in the final approval of the manuscript to be published.

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Compliance with ethical standards

Conflict of interest
The authors declare that they have no conflict of interest.

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