ORIGINAL ARTICLE

External validation of the Glasgow Coma Scale-Pupils in patients with severe head injury

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Objectives. To compare the ability of the Glasgow Coma Scale (GCS) score, the GCS Pupils (GCS-P) score, and the Pupil Reactivity Score (PRS) to predict mortality in patients with severe head injury.

Methods. Retrospective analysis of all patients with severe head injury and initial GCS scores of 8 or lower on initial evaluation for whom records included pupil dilation information and clinical course after admission to intensive care units of participating hospitals. We assessed the ability of each of the 3 scores (GCS, GCS-P, and PRS) to predict mortality using discrimination analysis. Discrimination was estimated by calculating the areas under the receiver operating characteristic curves (AUC) and 95% CIs.

Results. A total of 1551 patients with severe head injury and pupil dilation records were studied. The mean age was 50 years, 1190 (76.7%) were males, and 592 (38.2%) died. No pupil dilation was observed in 905 patients (58.3%), 362 (23.3%) had unilateral mydriasis, and 284 (18.3%) had bilateral mydriasis. The GCS-P score was significantly better at predicting mortality, with an AUC of 0.77 (95% CI, 0.74-0.79), versus 0.69 (95% CI, 0.67-0.72) for the GCS, and 0.75 (95% CI, 0.72-0.77) for the PRS. As the GCS-P score decreased, mortality increased.

Conclusion. The GCS-P was more useful than the GCS for predicting death after severe head injury.

Keywords: Head injury. Wounds and injuries, severe. Intensive care unit. Mortality. Predictive scales.

Validación externa de la Escala de Coma de Glasgow con valoración pupilar en pacientes con traumatismo craneoencefálico grave

Objetivos. Analizar la capacidad para predecir la mortalidad hospitalaria de la Escala de Coma de Glasgow con valoración pupilar (GCS-P) comparado con la Escala de Coma de Glasgow (GCS) y con la escala de reactividad pupilar (PRS) en pacientes con traumatismo craneoencefálico (TCE) grave.

Métodos. Análisis retrospectivo de cohortes de todos los pacientes con TCE, puntuación en la GCS ≤ 8 en la atención inicial, datos de exploración pupilar inicial y del desenlace hospitalario ingresados en las unidades de cuidados intensivos participantes. Se determinó la capacidad predictiva de mortalidad de la GCS, PRS y la GCS-P mediante un análisis de discriminación. La discriminación se analizó empleando curvas operativas del receptor (COR), el área bajo la curva (ABC) y su intervalo de confianza del 95% (IC 95%).

Resultados. Se analizaron 1.551 pacientes con TCE grave y datos sobre exploración pupilar. La edad media fue de 50 años, 1.190 (76,7%) eran hombres, y hubo 592 (38,2%) defunciones. Hubo 905 (58,3%) pacientes sin alteraciones pupilares, 362 (23,3%) con midriasis unilateral y 284 (18,3%) pacientes con midriasis bilateral. El análisis del ABC-COR para predecir la mortalidad hospitalaria mostró de forma significativa una mejor capacidad predictiva del GCS-P con ABC = 0,77 (IC 95% 0,74-0,79) respecto al GCS con ABC = 0,69 (IC 95% 0,67-0,72). La reactividad pupilar mostró un ABC = 0,75 (IC 95% 0,72-0,77). Se observó un incremento de mortalidad con la disminución del GCS-P.

Conclusiones. La escala GCS-P presentó mejor rendimiento que la GCS para predecir mortalidad en el TCE grave.

Palabras clave: Traumatismo craneoencefálico. Trauma grave. Unidad de cuidados intensivos. Predicción mortalidad. Escalas.

Introduction

The Glasgow Coma Scale (GCS) and pupillary response scale (PRS) scores are known prognostic factors after traumatic brain injury (TBI).[1,2] Among the different components of the GCS, the motor component has the greatest prognostic value.[2] Pupil size and reactivity may indicate a neurological emergency, usually caused by uncal herniation secondary to mass effect or ischemia.[2,3]

In an attempt to improve the predictive ability of mortality and neurological outcome in patients with TBI, the GCS score and pupillary assessment (size and reactivity) have been combined in the recently devel-

oped GCS-Pupils score (GCS-P).[4,5] This scale is easy to use in initial patient care and provides a numerical value between 1 and 15 that correlates with neurological outcome[4,5] and thus can be used in decision making and to provide prognostic information to family members. However, this scale, created from the IMPACT (International Mission on Prognosis and Analysis of Clinical Trials in TBI)[6] and CRASH (Corticosteroid Randomisation after Significant Head injury) databases,[7] has not been externally validated or evaluated in Spain.

The aim of this study was to analyze the mortality predictive ability of P-CSG compared to the traditionally used GCS and pupillary reactivity in patients with severe TBI.

Method

RETRAUCI is an observational, prospective, multicenter registry that includes 52 Spanish intensive care units (ICUs) and has the endorsement of the Neurointensivism and Trauma Working Group of the Spanish Society of Intensive, Critical and Coronary Units Medicine (SEMICYUC). The registry included all trauma patients consecutively admitted to the participating ICUs from March 2015 to December 2019 and has the approval of the Ethics Committee of the coordinating center (Hospital Universitario 12 de Octubre, Madrid CI-12/209).

In this study, a retrospective analysis of the RETRAUCI registry was performed. All patients with severe TBI, defined as those with a GCS score ≤ 8 at initial care and with available data on the initial pupillary examination, were included. Of note, GCS assessment was performed at the initial evaluation prior to receiving sedation, muscle relaxants or orotracheal intubation. The outcome at hospital discharge was collected in a dichotomized manner (survival vs. death).

The variables were recorded in an electronic database (retrauci.org), which includes demographic data, type, intentionality and mechanism of the trauma, consumption of toxic substances, prehospital and emergency care, need for intubation or prehospital alternative airway, initial constants, calculation of severity indices and scales, resource consumption, complications and outcome variables, including ICU mortality and hospital mortality.[8] As this was a study of patients with severe TBI, cranial radiological lesions were collected on computed tomography (CT) according to Marshall's classification, which analyzes the existence of evacuable lesions > 25 cc, midline deviation and basal cisternal patency.[9]

The GCS-P score is calculated with the following formula: GCS-P = GCS - PRS. PRS assesses pupillary reactivity and assigns 2 points in bilateral mydriasis, one point in unilateral mydriasis and zero points with normal pupils.[4,5] This yields a value between 1 and 15 that correlates with neurological prognosis. This study included only patients with severe TBI, so the values obtained will be between 1 and 8. For its calculation, the values obtained in the first medical attention were used.

Quantitative variables are shown as mean and standard deviation (SD) or median and interquartile range as appropriate, and qualitative variables as number (percentage). The predictive ability of GCS, pupillary reactivity, and GCS-P to predict mortality was determined by analyzing the discrimination of the models using the area under the curve (AUC) of the rectptor operating characteristic (ROC) and its 95% confidence interval (95% CI). Comparison of the ROC curves with each other were performed using the test described by DeLong et al.10 Sensitivity analysis was performed by excluding patients who received any type of limitation of life-sustaining treatments (LST) during their ICU stay. A value of $P < .05$ was considered statistically significant. Statistical analysis was performed with STATA 15 (StataCorp. 2017).

Results

Of the 9790 trauma patients admitted to the participating ICUs, 1551 patients (15.8%) with severe TBI were included, with data on pupillary examination and hospital outcome. The mean age was 50 years, there were 1190 men (76.7%), and 448 accidental falls were the main mechanism of injury (28.8%). The distribution of CT findings according to Marshall's classification was: 142 (9.2%) diffuse lesion type I, 562 (36.2%) diffuse lesion type II, 165 (10.6%) diffuse lesion type III, 79 (5.1%) diffuse lesion type IV, 331 (21.3%) evacuated mass lesion and 272 (17.5%) non-evacuated mass lesion. There were 905 patients (58.3%) with no pupillary alterations, 362 (23.3%) with unilateral mydriasis and 284 (18.3%) with bilateral mydriasis. During admission, 592 patients (38.2%) died. The remaining characteristics of the patients included in the study and the analysis according to in-hospital mortality are shown in Table 1.

The ability of the three proposed scales to predict hospital mortality was different ($P < .01$). GCS-P showed a predictive ability for hospital mortality with AUC = 0.77 (95% CI 0.74-0.79), GCS showed an AUC = 0.69 (95% CI 0.67-0.72), and pupillary reactivity an ABC = 0.75 (95% CI 0.72-0.77) (Figure 1). GCS-P was superior to GCS ($P < .0001$), PRS was superior to GCS ($P = .0004$) and there was no difference between GCS-P and PRS ($P = .063$). An increase in mortality was observed with decreasing GCS-P (Figure 2). Sensitivity, specificity and likelihood ratios parameters for each GCS-P point are shown in Table 2. The group of patients with GCS of 3 points was analyzed and had an overall mortality of 57.1%, GCS-P distinguished 3 populations with GCS-P 1, 2 and 3 that presented a mortality of 91.1%, 58.5% and 35.6% respectively. The distribution of in-hospital mortality according to GCS and GCS-P score is shown in Table 3.

In 311 (20.3%) of the cases, LST measurements were taken during ICU admission, so a sensitivity analysis was performed by re-evaluating the models, and

Table 1. Characteristics of the patients included in the study and univariate analysis according to in-hospital mortality

	Overall N = 1551 n (%)	Missing values	Survivors N = 959 n (61,8%)	Deceased N = 592 n (38,2%)	*P* value
Age (years) [mean (SD)]	50 (20.34)	21	45 (18.63)	58 (20.37)	< **.001**
Men	1190 (76.7)	0	748 (74.7)	442 (78)	.131
GCS (points) [median (IQR)]	4 (3-7)	0	6 (3-7)	3 (3-5)	< **.001**
GCS-P (points) [median (IQR)]	4 (2-6)	0	5 (3-7)	2 (1-4)	< **.001**
ISS (points) [mean (SD)]	26.89 (13.71)	0	24.04 (12.45)	31.52 (14.39)	< **.001**
NISS (points) [mean (SD)]	36.10 (18.16)	0	31.25 (16)	43.96 (18.72)	< **.001**
Alcohol intoxication	325 (23.8)	185	253 (29.4)	72 (14.2)	< **.001**
Antithrombotic treatment	273 (17.8)	19	108 (11.4)	165 (28.2)	< **.001**
Mechanism		0			< **.001**
Fall	448 (28.9)		218 (22.7)	230 (38.8)	
Car	242 (15.6)		175 (18.2)	67 (11.3)	
Precipitation	237 (15.3)		148 (15.4)	89 (15.0)	
Motorcycle	206 (13.3)		155 (16.2)	51 (8.6)	
Hit by car	161 (10.4)		93 (9.7)	68 (11.5)	
Others	257 (16.6)		170 (17.7)	87 (14.7)	
Blunt trauma	1513 (97.5)	0	942 (98.2)	571 (96.4)	**.028**
Prehospital airway isolation	1004 (65.07)	8	616 (64.5)	388 (66.0)	.057
Mechanical ventilation	1429 (92.3)	0	885 (92.3)	544 (91.9)	.781
Intracranial pressure motorization	748 (49.7)	47	544 (57.9)	204 (36.2)	**.001**
Limitation of life support treatment	311 (20.3)	23	23 (2.4)	288 (50.1)	**.001**
Pupillary reactivity		0			< **.001**
No alterations	905 (58.3)		716 (74.7)	189 (31.9)	
Unilateral mydriasis	362 (23.3)		205 (21.4)	157 (26.5)	
Bilateral mydriasis	284 (18.3)		38 (4.0)	246 (41.5)	

SD: standard deviation; GCS: Glasgow Coma Scale; GCS-P: Glasgow Coma Scale and Pupils; ISS: Injury Severity Score; NISS: New Injury Severity Score; IQR: interquartile range.
Bold p values denote statistical significance ($P < .05$).

their predictive ability increased in all cases; GCS-P had an AUC = 0.81 (95% CI 0.78- 0.84), GCS had an AUC = 0.72 (95% CI 0.69-0.75) and pupillary reactivity had an AUC = 0.79 (95% CI 0.75-0.82) (Figure 3). In this same population, GCS-P was superior to GCS ($P < .0001$), PRS was superior to GCS ($P = .0004$) and there was no difference between GCS-P and PRS ($P = .0878$).

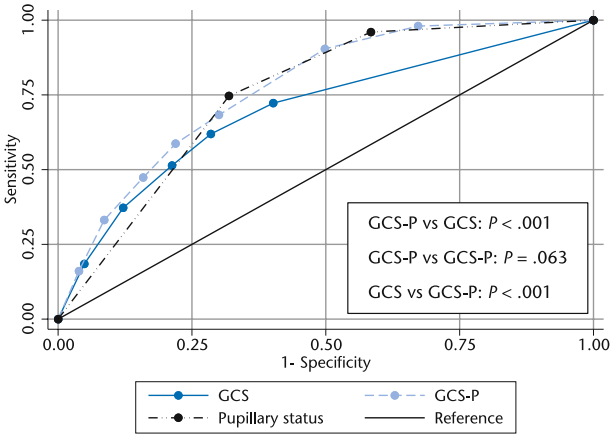

Figure 1. ROC operator receptive characteristic curves, area under the curve and comparison between the 3 scales using the DeLong test.
GCS: Glasgow Coma Scale; GCS-P: Glasgow Coma Scale and Pupils.

Discussion

The main finding of the present study was that the GCS-P scale performs better than the GCS alone in predicting in-hospital mortality in severe TBI. However, the GCS-P was not superior to the PRS in predicting hospital mortality ($P = .063$).

The prediction of neurological outcome in patients with TBI constitutes one of the great challenges in the management of these patients. The development of scales that combine clinical, radiological and laboratory findings has improved the prognostic ability of the models, both in patients with severe traumatic disease and in TBI.[11,12]

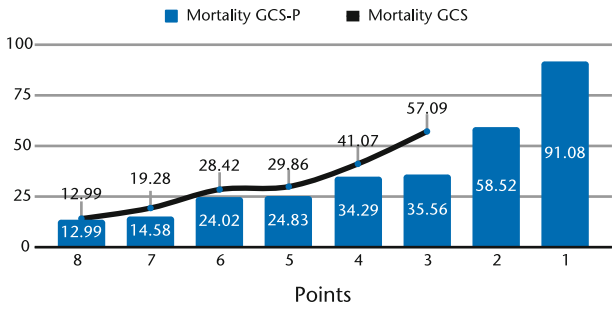

Figure 2. Percentage of hospital mortality in relation to the values on the GCS-P and GCS scales.
GCS: Glasgow Coma Scale; GCS-P: Glasgow Coma Scale and Pupils.

Table 2. Sensitivity, specificity, and likelihood ratios for each item of the Glasgow Coma Scale and Pupils (GCS-P)

GCS-P	Sensitivity	Specificity	PL+	NL-	Overall performance
1	100%	0	1	0	76%
2	98%	42	1.7	0.1	85%
3	90%	60	2.2	0.4	83%
4	68%	76	2.8	0.5	70%
5	59%	82	3.2	0.6	64%
6	47%	87	3.7	0.7	56%
7	33%	93	4.5	0.9	47%
8	16%	97	5	1	35%

PL+: positive likelihood ratio; NL-: negative likelihood ratio.

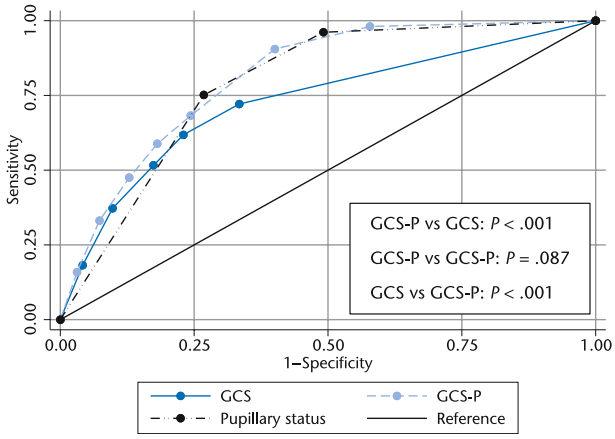

Figure 3. Receiver operating characteristic curves, area under the curve and comparison between the 3 scales using the DeLong test for the 3 scales studied after excluding patients with life-sustaining treatment limitation measures.
GCS: Glasgow Coma Scale; GCS-P: Glasgow Coma Scale and Pupils.

However, most of these scales are not available in the initial care of patients with TBI, where simple, easy-to-use scales that provide a good estimate of vital prognosis and functional recovery are needed. In this context, the GCS-P emerges, which combines in a simple way the 2 most studied variables as a prognostic factor after TBI.[4,5] This scale was developed from the IMPACT[6] and CRASH databases,[7] and obtains a simple score that allows us to increase the predictive capacity of the 2 most used variables in the clinical setting, even in the prehospital setting. It should be noted that the IMPACT and CRASH databases show differences between them and are also different from the population of TBI patients admitted to the Spanish ICU, which usually contains older patients with accidental falls as the main mechanism of injury.[15] The IMPACT database included 81% of patients with severe TBI and a mean age of 33 years, whereas the CRASH database included patients with GCS < 15, but 22% did not have a cranial CT scan and 23% had a normal CT scan. The mean age was 37 years.[4,6,7] This population is very different from that of the present study, where the mean age was 50 years and only those patients with GCS ≤ 8 were included. Another difference with respect to the CRASH and IMPACT databases lies in the timing of the GCS assessment: the CRASH database used the GCS closest to randomization, while the IMPACT database used different points in its studies.4 The present study used the coded GCS at first medical care. For all these reasons, we consider it necessary to validate the GCS-P in Spain.

The new scale has improved the predictive capacity of the GCS individually and, moreover, we have specifically demonstrated its special interest in the population with TBI and GCS of 3 in the initial collection, which always poses a healthcare challenge.[16] In our study, this population had an overall in-hospital mortality of 57.1%, but the P-CSG made it possible to distinguish 3 populations with highly differentiated mortality ranging from 35.6% to 91.1%.

In addition and given the need to consider LST decisions in prognostic models in severe trauma,[17] we have replicated the model excluding the population that during admission received LST in any form, achieving an improvement in predictive capacity, which we believe reinforces its reproducibility. This population also includes those patients with catastrophic brain injury and without the possibility of treatment, who are currently admitted as potential organ donors to the ICU after a family interview and acceptance of admission conditional on evolution to encephalic death or donation in controlled asystole as part of donation-oriented intensive care.[18,19] This is a growing population in the ICU due to the epidemiological trend towards a higher percentage of elderly trauma patients with severe TBI secondary to accidental falls.[15]

The present study has several strengths. The main one is that it is a large sample of patients with severe TBI at prehospital evaluation collected in a multicenter trauma registry. Trauma registries are useful in the im-

Table 3. Distribution of in-hospital mortality according to GCS and GCS-P scores

GCS	Total patients	GCS-P 1	GCS-P 2	GCS-P 3	GCS-P 4	GCS-P 5	GCS-P 6	GCS-P 7	GCS-P 8
	Mortality/ Total (%)	Mortality/ Total (%)	Mortality/ Total (%)	Mortality/ Total (%)	Mortality/ Total (%)	Mortality/ Total (%)	Mortality/ Total (%)	Mortality/ Total (%)	Mortality/ Total (%)
8	29/206 (14,1)						2/5 (40)	4/24 (16,7)	23/177 (13,0)
7	43/223 (19,3)					5/11 (45,4)	14/44 (31,8)	24/168 (14,3)	
6	54/190 (28,4)				11/13 (84,6)	16/47 (34,0)	27/130 (20,8)		
5	43/144 (29,9)			9/12 (75)	19/45 (42,2)	15/87 (17,2)			
4	69/168 (41,1)		25/30 (83,3)	26/56 (46,4)	18/82 (21,9)				
3	354/620 (57,1)	194/213 (91,1)	78/146 (53,4)	82/261 (31,4)					
Total GCS	592/1.551 (38,2)	194/213 (91,1)	103/176 (58,5)	117/329 (35,6)	48/140 (34,3)	36/145 (24,8)	43/179 (24,0)	28/192 (14,6)	23/177 (13,0)

GCS: Glasgow Coma Scale; GCS-P: Glasgow Coma and Pupillary Scale.

provement of the care process and in the quality control of the care provided.[20] Among its limitations, it should be mentioned that a detailed analysis of neurological outcome from a functional perspective has not been systematically performed, but rather an analysis in terms of in-hospital mortality. Unfortunately, the characteristics of the registry and the large sample analyzed do not allow this aspect to be evaluated at the present time. A second limitation is that pupillary reactivity has been assessed according to clinical examination by healthcare personnel. However, the increasing use of automated pupillometry could reclassify the group of reactive pupils[21] and thus modify the values obtained with the GCS-P. In addition, we used assessment in the prehospital setting instead of the GCS after initial resuscitation, as described in a previous study.[16] We believe that in the Spanish model of prehospital care, analysis in the trauma setting may have greater prognostic value and avoids interference from sedatives, although it may entail potential confusion in patients in shock or intoxicated. Finally, P-CSG was not superior to PRS in predicting in-hospital mortality.

In conclusion, the current study showed that the GCS-pupillary scale performs better than the GCS in the prediction of mortality in severe TBI. It is a simple scale that can be implemented in the prehospital setting or in emergency departments, so we support its use in clinical practice in the initial evaluation of patients with severe TBI because of its potential usefulness in decision making and in informing family members.

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