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ORIGINAL ARTICLE

Which information derived from the Coma Recovery Scale-Revised provides the most reliable prediction of clinical diagnosis and recovery of consciousness? A comparative study using machine learning techniques

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ABSTRACT

BACKGROUND: The Coma Recovery Scale-Revised (CRS-R) is the most recommended clinical tool to examine the neurobehavioral condition of individuals with disorders of consciousness (DOCs). Different studies have investigated the prognostic value of the information provided by the conventional administration of the scale, while other measures derived from the scale have been proposed to improve the prognosis of DOCs. However, the heterogeneity of the data used in the different studies prevents a reliable comparison of the identified predictors and measures.

AIM: This study investigates which information derived from the CRS-R provides the most reliable prediction of both the clinical diagnosis and recovery of consciousness at the discharge of a long-term neurorehabilitation program.

DESIGN: Retrospective observational multisite study.

SETTING: The enrollment was performed in three neurorehabilitation facilities of the same hospital network.

POPULATION: A total of 171 individuals with DOCs admitted to an inpatient neurorehabilitation program for a minimum of 3 months were enrolled.

METHODS: Machine learning classifiers were trained to predict the clinical diagnosis and recovery of consciousness at discharge using clinical confounders and different metrics extracted from the CRS-R scale.

RESULTS: Results showed that the neurobehavioral state at discharge was predicted with acceptable and comparable predictive value with all the indices and measures derived from the CRS-R, but for the clinical diagnosis and the Consciousness Domain Index, and the recovery of consciousness was predicted with higher accuracy and similarly by all the investigated measures, with the exception of initial clinical diagnosis.

CONCLUSIONS: Interestingly, the total score in the CRS-R and, especially, the total score in its subscales provided the best overall results, in contrast to the clinical diagnosis, which could indicate that a comprehensive measure of the clinical diagnosis rather than the condition of the individuals could provide a more reliable prediction of the neurobehavioral progress of individuals with prolonged DOC.

CLINICAL REHABILITATION IMPACT: The results of this work have important implications in clinical practice, offering a more accurate prognosis of patients and thus giving the possibility to personalize and optimize the rehabilitation plan of patients with DoC using low-cost and easily collectable information.

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KEY WORDS: Consciousness disorders; Persistent vegetative state; Brain concussion; Prognosis; Machine learning.

Severe acquired brain injury, that causes coma for over 24 hours in the acute phase, can lead to a complex clinical condition commonly referred to as a disorder of consciousness (DOC).[1] Based on the presence and nature of the behavioral responses to multisensory stimuli,[2] individuals with DOC are diagnosed as either in an unresponsive wakefulness syndrome (UWS)/vegetative state (VS) if they are wake but only show unconscious reflexes, or in a minimally conscious state (MCS) if they show minimal but reproducible intentional responses. The MCS group has been subcategorized in individuals in an MCS+ or in an MCS- according to the presence or absence of higher-level behaviors, respectively.[3] Finally, individuals who show functional communication or functional use of objects are considered as emerging from the MCS.

Diagnosis of DOCs poses a clinical challenge, as it requires the accurate recognition of behavioral signs that can be weak or inconsistent.[4] Indeed, the concept of consciousness is multifaceted and complex and arises from the presence of both arousal, *i.e.* vigilance and wakefulness, and awareness, *i.e.* perception of the environment and self.[5] The Coma Recovery Scale-Revised (CRS-R) is the most recommended clinical tool worldwide for assessing the neurobehavioral condition of individuals with DOC and features multiple cross-cultural adaptations.[6] The CRS-R investigates the presence of 23 neurobehavioral responses, grouped in 6 different subscales, which evaluate auditory, visual, motor, oromotor, communication, and arousal functions. For each subscale, the responses are hierarchically ordered and are evaluated from higher responses (cognitively-mediated responses) to lower responses (reflexes).[7, 8] The diagnostic utility of the scale was first analyzed in 2004,[9] but it was not until the work by Seel *et al.* in 2010[10] that its interrater reliability, internal consistency, and prognostic or diagnostic validity supported its use for diagnosis among other behavioral tools. Additionally, the scale has demonstrated strong construct validity, with confirmed evidence of monotonicity, mutual independence, and invariant item ordering.[11] In this regard, the hierarchy of the CRS-R has also shown a lack of invariance across relevant group factors including age, sex, etiology, enrollment facility, time since injury, and time between assessments.[12] Concerning its diagnostic reliability, to avoid possible diagnostic errors related to clinical and vigilance fluctuations,[13] it is recommended that the diagnosis of DOCs is based on the clinical findings from five consecutive assessments[14] and combined with imaging or electrophysiological-derived measures.[15] Interestingly, some authors have proposed alternative indices and measures derived from the CRS-R, such as the CRS-R Modified Score[16] and the CRS-R Index,[17] to increase the diagnostic accuracy of the original version.

The total score in the CRS-R has been also identified as an important predictor of recovery of responsiveness in traumatic and non-traumatic individuals with DOC.[18-22] Measures derived from the CRS-R have been also proposed to improve prognosis of DOCs. Arnaldi *et al.* introduced the CRS+, a weighted score based on the CRS-R to investigate the prognostic value of sleep patterns in the recovery of consciousness.[23] More recently, Magliacano and Liuzzi proposed the Consciousness Domain Index, an unsupervised machine learning clustering technique based on information from the CRS-R sub-scales to improve the prediction of recovery of consciousness.[24]

However, although the information provided by the CRS-R might be essential to predict the clinical progress of individuals with DOCs and many attempts exist to find alternative measures that improve the predictive value of the original instrument, the heterogeneity of the data used in the different studies prevent a reliable comparison of the identified predictors and measures. In this context, our study aimed to evaluate which information derived from the CRS-R provides the most reliable prediction of both the clinical diagnosis and recovery of consciousness at discharge of a long-term neurorehabilitation program.

Materials and methods

Participants

Demographic and clinical data of individuals with DOC who had attended an inpatient neurorehabilitation program between February 2004 and December 2021 in three facilities of the same hospital network were retrospectively extracted from their medical records. Individuals who, at admission to the neurorehabilitation program, were older than 16 years and were diagnosed as with UWS/VS or in MCS due to either a vascular, anoxic or traumatic origin were included in the study. Individuals who did not attended the program for at least three months were excluded from the analysis

The study was approved by the Polytechnic University of Valencia (P1625072022) and was registered at clinicaltrials.gov (NCT05819177). Written informed consent to participate in the study was obtained from the legal representative of all patients.

Procedure

The baseline neurobehavioral condition of all the participants was determined in the first two weeks from admission based on the results of five examinations using the Spanish adaptation of the CRS-R.[25] Henceforth, the condition of the participants was assessed weekly until emergence from MCS, discharge or decease. All the examinations were conducted by an experienced neuropsychologist trained in the use of the CRS-R at the same time of the day. During their participation in the neurorehabilitation program, participants were medically monitored to avoid clinical complications, reduce agitation, and relieve pain, and were administered daily sessions of customized physical therapy and multimodal sensory stimulation according to their individual needs.

At study entry, data collection included: age, sex, side of the lesion (distinguished among none, right, left, bilateral or diffuse), time post-injury, etiology, total score in the Disability Rating Scale, and occurrence of epilepsy (considering either early or late epileptic seizures), and information derived from the CRS-R, comprising the total score in the scale, the score in each subscale, and the clinical diagnosis (either UWS or MCS). The clinical diagnosis at discharge (either UWS, MCS, or emerged from MCS) was also collected.

Statistical analysis

Shapiro-Wilk Tests were performed to investigate if the collected data were normally distributed. Descriptive analyses were conducted to determine the mean and standard deviation, or the median and interquartile range when appropriate, of the numerical variables. Categorical variables were described using proportions and percentages. Descriptive analyses were performed using SPSS Statistics v. 28.0 (IBM Corp, Armonk, NY, USA).

Indices and measures derived from the CRS-R, including the CRS-R total score, the total scores in the subscales of the CRS-R, the clinical diagnosis, the CRS-R Modified Score,[16] the CRS-R Index,[17] the CRS+[23] and the Consciousness Domain Index,[24] were estimated from the collected data as described in the corresponding manuscripts (Supplementary Digital Material 1: Supplementary Figure 1, 2, Supplementary Table I, II). It is worth to be noted that both CRS-R Modified Score and CRS-R Index calculated in this paper were approximations obtained from the scores on the subscales, instead of evaluating the neurobehavioral signs as required for their derivation.

Then, machine learning classifiers were implemented using seven different data sets, and were optimized and tested to predict either the clinical diagnosis, namely UWS, MCS or emerged from MCS; or the recovery of consciousness specifically understood as having emerged from MCS, both at discharge. Each data set included the collected predictors of consciousness described above, which were considered as confounders, and one of the seven types of information derived from the CRS-R, namely, the total score in the CRS-R, the total score in each subscale of the CRS-R, the clinical diagnosis, the CRS+, the CRS-R Modified Score, the CRS-R Index, and the Consciousness Domain Index. For each data set and outcome (clinical diagnosis or the recovery of consciousness), four different machine learning classifiers were implemented, for a total of 56 classifiers. The machine learning algorithms considered were Logistic Regression (LogReg), Support Vector Machine (SVM), Random Forest (RF), and k-Nearest Neighbors (KNN). The classifiers were developed in Python, using the Scikit-learn library.[26] The hyper-parameters of the classifiers were optimized within the inner loop of a 5x12 fold nested cross-validation. The models trained to predict the clinical diagnosis at discharge were optimized using the accuracy metric. In contrast, the models trained to predict the recovery of consciousness were optimized using the balanced accuracy metric, given that the data sets were unbalanced (as the number of individuals who emerged was considerably fewer than those who did not). The outer 12-fold cross-validation loop was used to test each classifier. In each loop of the 12-fold cross-validation, the missing data were imputed using a nearest neighbors algorithm optimized on the training set. The KNN-based imputer from the Scikit-learn library was used.[26]

The performance of the classifiers was determined by the accuracy and the F1-score. These parameters were estimated for each algorithm, as well as for the cumulative solutions, computed using the mode of the predictions (majority) and the sum of the posterior probabilities (weighted) of each algorithm. Additionally, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were calculated for a comparison and evaluation of the models. These values were presented using median and interquartile range [IQR] on the external folds. Additionally, fold-wise values of each model were compared using the Friedman test and considering a P value<0.05 as statistically significant.

Results

Participants

A total of 171 individuals were enrolled in this study. Participants were predominantly males (75.4%) and had a median age and interquartile range of 37[23] years, a time post-onset of 102.0 [80.0] days, and presented a comparable proportion of traumatic and non-traumatic etiologies. At admission, 82 participants had a UWS, and 89 participants were in an MCS. After a median stay and interquartile range of 365 [428] days, 83 participants transitioned from one state to another, 57 of whom recovered full consciousness. The demographic and clinical characteristics of the participants at admission and discharge are described in Table I.

Table I.—*Demographic and clinical characteristics of the participants.*

Characteristics	N.	Value
Sex	171	
Women		42 (24.6%)
Men		129 (75.4%)
Etiology	171	
Traumatic		86 (50.3%)
Vascular		44 (25.7%)
Anoxic		41 (24.0%)
Lateralization	128	
None		9 (5.3%)
Right		18 (10.5%)
Left		31 (18.1%)
Bilateral		35 (20.5%)
Diffuse		35 (20.5%)
Epilepsy		
Occurrence of epileptic seizures	100	68 (39.8%)
Occurrence of early epilepsy	82	31 (18.1%)
Occurrence of late epilepsy	91	51 (29.8%)
Age at admission	171	37.0 [26.0]
Time post-onset at admission	171	102.0 [80.0]
Disability rating scale at admission	168	24.0 [3.0]
CRS-R at admission		
Total score	171	8.0 [5.0]
Auditive subscale	171	1.0 [1.0]
Visual subscale	171	1.0 [3.0]
Motor subscale	171	2.0 [1.0]
Communication subscale	171	0.0 [0.0]
Oromotor subscale	171	1.0 [0.0]
Arousal subscale	171	2.0 [0.0]
Measures derived from the CRS-R at admission		
CRS-R Modified Score	171	13.2 [27.1]
CRS-R Index	171	13.2 [27.1]
CRS+	171	9.0 [6.0]
Consciousness Domain Index	171	
CDI0		96 (56.1%)
CDI1		75 (43.9%)
Clinical diagnosis		
Admission	171	
UWS		82 (48.0%)
MCS-		65 (38.0%)
MCS+		24 (14.0%)
Discharge	171	
UWS		45 (26.3%)
MCS		69 (40.4%)
E-MCS		57 (33.3%)
Participants who transitioned between states [a]	171	83 (48.5%)
Participants who recovered consciousness [b]	171	57 (33.3%)
Length of stay	171	365 [428]

Results are expressed in median and interquartile range, and in number of participants and percentage of participants from the total, as appropriate.
CDI: Consciousness Domain Index; CRS-R: Coma Recovery Scale-Revised; E-MCS: Emergence from Minimally Consciousness State; MCS: Minimally Consciousness State; UWS: Unresponsive Wakefulness Syndrome.
[a] Patients transitioning between admission and discharge from UWS to MCS or E-MCS, and from MCS to E-MCS; [b] participants entering with clinical diagnosis of either UWS or MCS and discharging in E-MCS state.

Prediction of clinical diagnosis and recovery of consciousness

The results of the best-performing classifiers are displayed, in terms of accuracy and F1-score, in Supplementary Digital Material 2 (Supplementary Table III). The confusion matrixes are also provided in Figure 1. A more detailed description of the performance of all the implemented and evaluated classifiers is provided in Supplementary Digital Material 1.

All the indices and measures derived from the CRS-R, excluding the clinical diagnosis and the Consciousness Domain Index, which showed worse results, had an acceptable and comparable predictive value to identify the clinical diagnosis at discharge (Supplementary Table III). From all the investigated measures, the scores in the subscales of the CRS-R and the CRS-R Index provided the best results. The AIC and BIC values partly confirmed the trend encountered on the performance metrics, showing the lowest median values, *i.e.* highest model fit, on the models using the scores on the CRS-R subscales, CRS-R Modified Score, and Consciousness Domain Index. Fold-wise AIC and BIC comparisons resulted in statistically significant lower AIC and BIC values on the models with CRS-R subscales and CRS-R Modified Score with respect to the models using the CRS-R total score (AIC P values: 0.023 and 0.003; BIC P values: 0.012 and 0.001), CRS+ (AIC P values: 0.033 and 0.004; BIC P values: 0.033 and 0.003), clinical diagnosis (AIC P values: <0.001 both; BIC P<0.001 both), and CRS-R Index (AIC P values: 0.007 and 0.001; BIC P values: 0.007 and <0.001). Additionally, statistically lower AIC and BIC values were observed on the model using Consciousness Domain Index with respect to the one using clinical diagnosis (AIC P=0.002; BIC P=0.001).

The recovery of full consciousness was predicted with higher accuracy and similarly by all the investigated measures, except for the initial clinical diagnosis. Both the total score in the CRS-R and the scores in the subscales of the CRS-R had the high predictive value to foresee

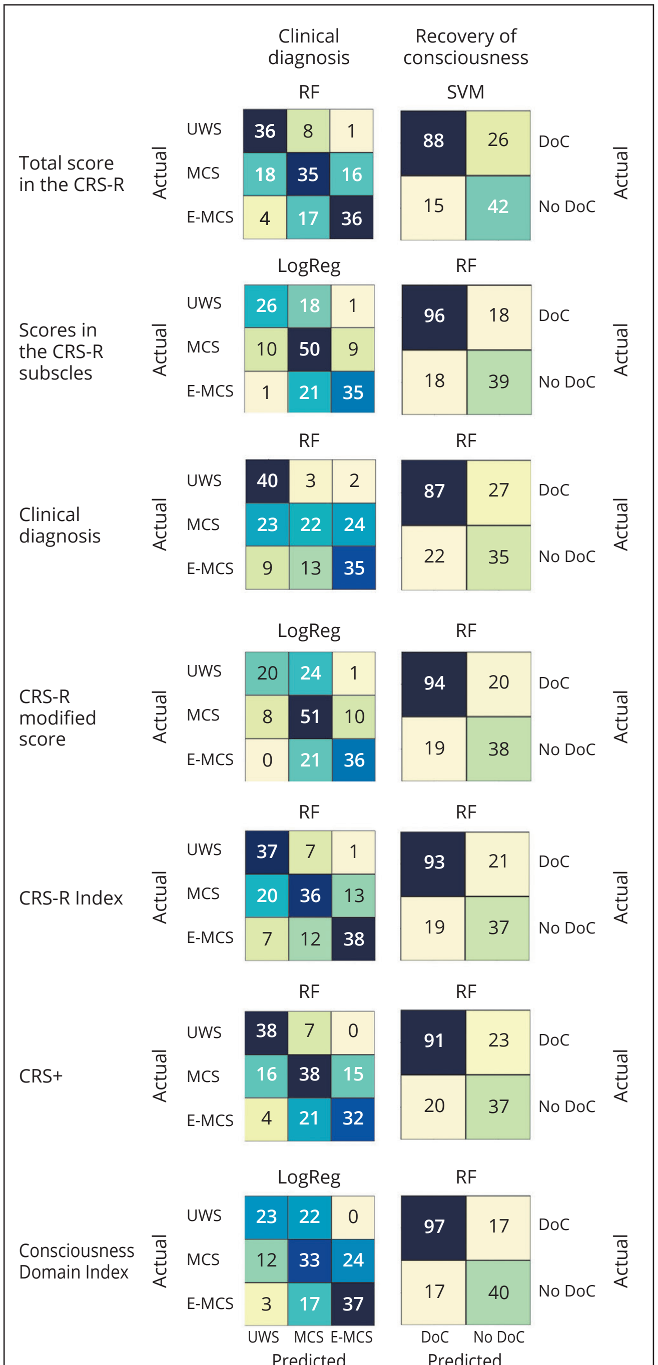

Figure 1.—Confusion matrices of the best performing algorithms for each classifier and prediction.

recovery of consciousness. Specifically, the scores in the subscales of the CRS-R, together with the Consciousness Domain Index, obtained the best results in terms of accuracy and F1-score. The AIC and BIC values confirmed a highest model fit of the models with the outcome of emergence with respect to the clinical diagnosis at discharge. The similarity among the models with the different measures was also confirmed, presenting a reduced variability of AIC and BIC median values with respect to those on the clinical diagnosis outcome. Indeed, a statistically significant difference among the fold-wise AIC values of each model resulted only between the total CRS-R score and the clinical diagnosis (P=0.038). Concerning fold-wise BIC values, statistically significant differences were encountered between the model using CRS-R total score and the models using the clinical diagnosis (P=0.003) and CRS-R Index (P=0.028).

Regardless of the information used to train the classifiers, the clinical diagnosis at discharge was better predicted by the classifiers based on RF and LogReg, whereas recovery of consciousness was better predicted by those based on RF and SVM.

Discussion

This work investigated which information derived from the CRS-R provides the most reliable prediction of both the clinical diagnosis and the recovery of consciousness at discharge of individuals admitted to a long-term neurorehabilitation program as having a DOC following a traumatic or non-traumatic brain injury. Different machine learning classifiers were implemented including predictors of consciousness and a specific type of information derived from the CRS-R. Results showed that the clinical diagnosis at discharge was predicted with acceptable and comparable predictive value with all the indices and measures derived from the CRS-R, but for the clinical diagnosis and the Consciousness Domain Index. The recovery of consciousness was predicted with higher accuracy and similarly by all the investigated measures, except for the initial clinical diagnosis.

Both the total score in the CRS-R and the clinical diagnosis are the most widely used measures derived from the scale found in the literature.[27-29] These two measures provide different yet complementary information, however, none of them is sufficient alone. While the total score on the scale provides a comprehensive but unspecific examination of the neurobehavioral condition of the individuals, the clinical diagnosis only indicates the presence of specific neurobehavioral responses.[17] Importantly, the clinical diagnosis of individuals with DOCs cannot be determined by comparing the total score in the CRS-R with certain cut-off values, as in other bedside instruments such as the Post-Acute Level of Consciousness scale[30] or the Disability Rating Scale.[31] Indeed, by analysing the total scores of the CRS-R scale associated with the different clinical diagnosis, it is possible to appreciate overlapping. As an example, the total score values between 7 and 9 points could belong to either UWS or MCS diagnosis classifications.[16] Consequently, the relationship between the total score and the clinical diagnosis is not straightforward. As a result, the same score in the CRS-R can be associated with different clinical diagnosis. Additionally, when interpreting the total score in the CRS-R, it is important to consider that the scale examines the neurobehavioral responses from higher to lower until finding the highest response that is consistently present in each domain. Thus, when a response is found, the lower responses are not investigated but presumed to be present, founded on the basis that they follow an inevitable hierarchical distribution.[7, 8]

The classifiers based on the clinical diagnosis, together with the Consciousness Domain Index, had the lowest accuracy at predicting the clinical diagnosis of the individuals at discharge, which could indicate that a more comprehensive view of the clinical diagnosis of the participants could be needed for an improved prediction.[32] The comparable performance of the Consciousness Domain Index to the clinical diagnosis (equally poor but in the classification of individuals with MCS-) could be explained by the fact that, the index is obtained by a given number of distance-based centroids that was optimized to improve the prediction of emergence from MCS,[24] thus the characteristics of patients in MCS- could be encoded within the Index as more closely related to UWS than MCS+. Coherent with this, the performance of the Consciousness Domain Index was dramatically higher when attempting to predict the emergence from MCS. Another interesting difference could be noticed on the AIC and BIC value of the models using the two measures. In fact, whilst the model using the clinical diagnosis presented on both outcomes higher AIC and BIC values, demonstrating a reduced model fit, the model using Consciousness Domain Index had a different behavior. In fact, on the outcome of clinical diagnosis at discharge, the model using Consciousness Domain Index, scores on the CRS-R subscales, and CRS-R Modified Score presented the lowest AIC and BIC values. Whilst in the case of the latter two, the AIC and BIC values could be explained by higher performances, the results on the model with Consciousness Domain Index could be explained by a reduced complexity of the model given by the measure itself.

Both the CRS-R Modified Score[16] and the CRS-R Index[17] were designed with the aim to amend the assumption underneath the scale administration that the neurobehavioral responses follow a hierarchical distribution. The hypotheses of both instruments rely on the fact that assuming a fixed hierarchy of responses could lead to less accurate assessments, as reflexes and cognitively-mediated functions might have different neural substrates.[33, 34] Hence, the hierarchical structure assumed by the conventional administration of the CRS-R could not be fully supported by neurological and physiological evidence. According to this, in some domains, such as the motor domain, the number of responses, rather than a score based on the highest response present, could lead to a more accurate description of the clinical diagnosis. Nevertheless, it should be noted that this approach requires to evaluate all the responses and, consequently, implies longer administration times. Interestingly, the classifiers based on the CRS-R Modified Score and the CRS-R Index were among the best to predict the clinical diagnosis at discharge and among the average to predict recovery of consciousness. The performances in the latter prediction could be explained by the fact that both instruments can diagnose individuals with UWS and MCS while having severe limitations at identifying emergence from the MCS.[17] Additionally, given that the medical records of the participants included the results of the conventional administration of the CRS-R, the number of neurobehavioral responses was not available and this information could not be used to estimate the CRS-R Modified Score and the CRS-R Index. The conventional scoring of the CRS-R was used instead and, consequently, the results of our study should be interpreted accordingly. Further analyses should be conducted to determine the full potential of these instruments for prognostic applications.

The classifier based on the CRS+, which provides a global score by weighting the total score in the CRS-R depending on the clinical diagnosis of the individual under examination,[23] had a comparable performance to that based on the total score in the subscales of the CRS-R, which proved to be the best. The classifiers based on both measures showed good accuracy at predicting both the clinical diagnosis and the recovery of consciousness.

To conclude, it should be highlighted that the total score in the CRS-R and, specifically, the total score in its subscales at admission provided the best overall results, proving to be between the most reliable information to predict both the clinical diagnosis and emergence from MCS at discharge, which contrasted the more limited predictive value of the clinical diagnosis at admission. Additionally, both measures could reach a good model fit, having lower AIC and BIC values. This is particularly highlighted for the models using the scores on the CRS-R subscales, where the higher number of features in the models could have potentially negatively impact on the final AIC and BIC values. These results seem to indicate that a comprehensive measure of the neurobehavioral condition rather than the clinical diagnosis of the individuals could be a better predictor of the neurobehavioral progress of individuals with prolonged DOC. Importantly, although the predictive value of these measures could probably enhanced with neurophysiological examinations,[15, 35, 36] it should be noted that they can be easily collected at the bedside without technical instruments such as neuroimaging or neurophysiological exams, which highlights the potential of the CRS-R.

Limitations of the study

The characteristics and limitations of the study should be taken into account when interpreting the results. First, the included sample of participants is representative of subjects with prolonged DOC and, consequently, the reliability of the predictors found in our study could not be representative of those for acute brain injuries. Second, the number of participants included in the study might be considered limited and especially unbalanced for the investigation of predictors of emergence. Finally, as previously mentioned, the number of neurobehavioral responses was not available in the medical records used in the retrospective analyses and the estimation of the CRS-R Modified Score and the CRS-R Index was done using the conventional scoring of the CRS-R. It is also important to highlight that each model was designed with the same confounding variables, which are identified in the guidelines of the American Academy of Neurology[36] as being the predictors with the most evidence for the recovery of consciousness.

Conclusions

The clinical diagnosis at discharge was predicted with acceptable and comparable predictive value with all the indices and measures derived from the CRS-R, but for the clinical diagnosis and the Consciousness Domain Index. The recovery of full consciousness was predicted with higher accuracy and similarly by all the investigated measures, with the exception of the initial clinical diagnosis. The total score in the CRS-R and, especially, the total score in its subscales provided the best overall results, in contrast to the clinical diagnosis, which could indicate that a comprehensive measure of the clinical diagnosis rather than the condition of the individuals could provide a more reliable prediction of the neurobehavioral progress of individuals with prolonged DOC.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Supplementary data
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