Score on Coma Recovery Scale-Revised at admission predicts outcome at discharge in intensive rehabilitation after severe brain injury

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ABSTRACT

Objective: To assess the prognostic utility of the Coma Recovery Scale-Revised (CRS-R) in rehabilitation of patients surviving from severe brain injury.

Methods: In this prospective cohort study, all patients consecutively admitted to an Italian Intensive Rehabilitation Unit, with a diagnosis of unresponsive wakefulness syndrome (UWS) or minimally conscious state (MCS) due to acquired brain injury, underwent clinical evaluations using the Italian version of the CRS-R. At discharge, patients transitioning from UWS to MCS or emergence from MCS (E-MCS) and from MCS to E-MCS were classified as improved responsiveness (IR). Score on the Glasgow Outcome Scale (GOS) at discharge was recorded.

Results: In total, 137 (66 UWS, 71 MCS) subjects were enrolled. After a mean hospital stay of 5.3 ± 2.9 months, 81 (59.1%) patients achieved an IR. In the multivariable analysis, IR was associated with higher CRS-R score at admission (p = 0.002) and younger age at injury (p = 0.010). Moreover, higher GOS scores at discharge were related to younger age at injury (p = 0.018), shorter time post-onset (p = 0.003) and higher CRS-R score at admission (p < 0.001).

Conclusions: Higher CRS-R scores at admission in intensive rehabilitation unit can help differentiate patients with better outcome at discharge, providing information for rehabilitation planning and communication with patients and their caregivers.

Introduction

The prediction of later outcome in patients with disorders of consciousness due to severe brain injury admitted to acute rehabilitation is still an unresolved issue. Over the last few decades, advances in intensive care technology and neurosurgical procedures led to a significant increase in the number of survivors from severe brain injury, who eventually access inpatient rehabilitation units. After the coma phase, patients can transition to an unresponsive wakefulness syndrome (UWS), a minimally conscious state (MCS) or emerge from the MCS (E-MCS) and recover a full consciousness. The evolution of disorders of consciousness has a great individual variability, depending on the aetiology of injury and other demographic, clinical and instrumental factors (1–9).

In the setting of inpatient rehabilitation unit, physicians face two main issues that are strictly intermingled: the accurate classification of consciousness level and the prediction of outcome. Estimates of consciousness misdiagnosis in this population consistently range from 30% to 45% (10–12). The errors derive from potential examiner, patient and environmental biases. Recently, the American Congress of Rehabilitation Medicine (13) reviewed the available assessment tools for patients with disorders of consciousness. Among the 13 scales evaluated, the authors recommended with minor reservations for the use in clinical practice only the Coma Recovery Scale-Revised (CRS-R) (14–16).

Regarding outcome prediction, although there is accumulating evidence on prognostic factors in the acute phase (17), there is limited information on the predictors of later outcome in patients with low levels of consciousness admitted to acute rehabilitation. In particular, there are a few small sample surveys providing preliminary indications on the role of CRS-R (18–20). With this background, the objective of the present study was to assess the prognostic utility of CRS-R performed at admission in intensive rehabilitation in low-awareness-state patients surviving from severe brain injury.

Materials and methods

Participants and procedures

All patients consecutively admitted to the Intensive Rehabilitation Unit at the IRCCS Don Gnocchi Foundation (Florence, Italy) from August 2012 to December 2016 were screened. Inclusion criteria were diagnosis of UWS or MCS due to acquired brain injury (2,21) and age older than 18 years.

Within 48 h from admission, all the patients underwent clinical evaluations using the Italian version of the CRS-R (22,23). Ratings were conducted by trained and experienced examiners (neurolo-
gists and speech therapists). Clinical assessment was performed in the absence of environmental interferences and of medical conditions that could have impacted patient alertness. The great majority of patients were assessed in their bed, with the chest raised up to increase arousal and avoid sleepiness. According to the CRF-R manual, at the beginning of each examination, spontaneous movements were observed for at least 1 min and the arousal protocol was applied if the patient was drowsy. The total CRF-R score was recorded.

During the hospital stay, all patients underwent an individualized multidisciplinary rehabilitation treatment (1–2 h daily, six days a week). Rehabilitation and pharmacologic approaches were homogeneously planned over the study period according to patient needs.

At discharge, the patient level of consciousness was classified on the basis of clinical assessment (UWS, MCS, or E-MCS) (21). Patients transitioning from UWS to MCS or E-MCS and from MCS to E-MCS were classified as patients with improved responsiveness (IR). We also included in the IR group patients who recovered responsiveness and then died because of new aetiologic events. Moreover, the outcome of brain injury was assessed through the Glasgow Outcome Scale (GOS) at discharge (24,25).

The study was approved by the local ethics committee, and written consent was obtained from the legal guardians of all patients.

**Statistical analysis**

The main outcome measures were the behavioural classification and score on the GOS at final discharge.

Baseline characteristics were reported as frequency (percentage) and mean ± standard deviation (SD) and compared with Pearson’s χ², Student’s t and Mann–Whitney U tests when appropriate.

Possible predictors of outcome measures at discharge were measured using stepwise multivariable logistic and linear regression models. Model assumptions and goodness of fit were assessed through the Hosmer and Lemeshow test (for logistic regression) and through checking for multicollinearity, and the graphical test of standardized residual plots (for linear regression). Regarding behavioural classification (IR vs. not-IR), the multivariable logistic regression model included the following covariates: age at brain injury, sex, aetiology, time post-onset and CRS-R at admission. Regarding the GOS score at discharge, the multivariable linear regression model included the following covariates: age at brain injury, sex, aetiology, time post-onset and CRS-R at admission.

All analyses were performed using SPSS 23.0 software running on Windows (SPSS, Chicago, IL, USA).

**Results**

During the study period, a total of 215 patients were admitted to the Intensive Rehabilitation Unit at the IRCCS Don Gnocchi Foundation (Florence, Italy). Among those, 74 were classified as having full consciousness at admission, whereas four patients had incomplete data collection. The remaining 137 (66 UWS, 71 MCS) fulfilled the inclusion criteria and were included in the analysis (Table 1). In comparison with minimally conscious subjects, patients diagnosed as UWS survived more frequently from anoxic injury (39.4% vs. 12.7%, p = 0.001; Table 1).

After a mean hospital stay of 5.3 ± 2.9 months, 81 (59.1%) patients achieved an IR. On the whole, 59 (43.4%) subjects emerged from the MCS (11 out of 66 UWS and 48 out of 70 MCS). Moreover, among the 66 subjects with UWS at admission, 21 transitioned to an MCS. Level of consciousness did not improve in the remaining 34 patients with UWS and 22 patients with MCS. Differences between patients with and without IR are reported in Table 2. IR was related with younger age at brain injury (56.7 ± 14.9 vs. 63.1 ± 14.9 years, p = 0.015), shorter median time post-onset (1.4 vs. 1.9 months, p = 0.002), higher median CRS-R score at admission (10.0 vs. 6.5, p = 0.001) and longer median hospital stay (5.3 vs. 4.1 months, p = 0.023). In the multivariable analysis, IR at discharge was confirmed to be associated with higher CRS-R score at admission (OR 1.12; 95%CI 1.04–1.21; p = 0.002) and younger age at brain injury (OR = 0.96; 95%CI 0.94–0.99; p = 0.010) (Table 3). The Hosmer and Lemeshow test was not significant (p = 0.978), confirming the goodness of fit for the regression model. Nagelkerke R-squared for the final model was 0.19.
At discharge, the majority of patients (69, 50.4%) were classified as severely impaired on the GOS, whereas independence (GOS scores 4–5) was obtained in 20 cases (14.6%). Thirty-four (29.2%) died during the hospital stay. In the multivariable analysis, higher GOS scores were related to younger age at brain injury (β = −0.01; 95% CI: −0.19/−2.40; p = 0.018), shorter time post-onset (β = −0.09; 95% CI: −0.24/−2.97; p = 0.003) and higher CRS-R score at admission (β = 0.050; 95% CI: 0.32/–4.03; p < 0.001) (Table 3). Multicollinearity and graphical testing of standardized residual plots confirmed the model assumptions. The R-squared value for the final model was 0.20.

### Discussion

In this prospective cohort study, the CRS-R assessment of low-awareness-state patients entering the intensive rehabilitation phase allowed the accurate classification of consciousness level and contributed to the prediction of later outcome. In particular, higher CRS-R scores at admission to inpatient rehabilitation were associated with IR and lower disability levels at discharge.

As for consciousness classification, CRS-R is based on the diagnostic criteria for disorders of consciousness by the Aspen Workgroup (26) and is recommended by the Brain Injury-Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine since its use reduced the 30–45% consciousness misdiagnosis reported in previous assessments (12,13). On the other hand, the prognostic value of CRS-R still needs to be clarified (13). A few studies showed a relationship between CRS-R score at inclusion and patient outcomes, stronger than that observed with scales of functional level (such as the Disability Rating Scale) (18,19).

The present prospective study is, to our knowledge, the largest study assessing the role of CRS-R as a prognostic tool in survivors from severe brain injury entering the inpatient rehabilitation phase. Higher score on the CRS-R at admission was related to a higher probability of recovering responsiveness or consciousness and to higher scores on the GOS at discharge. This relationship was independent of age, sex, aetiology and time post-onset.

These findings have important implications for prognosis definition in inpatient rehabilitation after severe brain injury. Assessment through the CRS-R should be performed early after a severe brain injury, even in the post-acute phase in the Intensive Care Unit and could be included in the panel of demographic, clinical, neuroradiological and electrophysiological parameters applied in the selection of patients who can benefit from inpatient rehabilitation. Moreover, our results can assist physicians in the communication process with patients and caregivers. Indeed, families have identified information about prognosis as one of their most important needs after a severe brain injury (27–29), a need often gone unmet (30).

Another important predictor of outcome was younger age at brain injury. This finding is in line with previous publications in which younger age was consistently associated with a better outcome in terms of recovery of responsiveness or consciousness (2,4,7,8,18).

Aetiology, another acknowledged prognostic factor, had a significant relationship with behavioural classification only at admission in our rehabilitation unit. Indeed, the majority of patients with post-anoxic injury were in unresponsive wakefulness status at study entry. This relationship disappeared at the end of the follow-up and in all the multivariable analyses. This could be due, at least in part, to the higher relevance of aetiology in short-term prognosis. In a previous study, aetiology significantly predicted outcome on the Disability Rating Scale at six weeks after enrolment, whereas it lost its significance at 13 weeks (7). Moreover, in other studies assessing recovery from UWS in the long term, the rate of improvement was not related to aetiology (8,31).

Chronicity has been consistently recognized as a predictor of recovery in UWS (2,4,7,18). In terms of IR, in our study its effect was evident only in the univariate analysis, since patients who recovered responsiveness or consciousness had a shorter time post-onset at admission. However, this effect disappeared in the multivariable analysis, suggesting that the predictive role of CRS-R scores at entry was stronger. On the other hand, in terms of disability level at discharge, shorter time post-onset was confirmed as an independent predictor of better outcome.

In interpreting the study findings, some possible issues should be taken into account. The analysis was based on the total score on the CRS-R, and the relevance of each subscale was not assessed. In previous studies (32,33), recovery of responsiveness was associated with higher scores and improvement on the visual subscale. It is possible that in our sample, the prognostic role of the total CRS-R was mainly driven by the performance on the visual subset. However, this does not change the value of CRS-R assessment in the early phase of intensive rehabilitation in terms of outcome prediction. Moreover, the time of observation was relatively short, and possible delayed recovery might have been missed. Finally, we did not take into account neuroradiological and electrophysiological parameters (such as somatosensory-evoked potentials and electroencephalographic patterns) (34,35) and clinical complications (such as infections, hydrocephalus) that might have influenced the outcome independent of the level of consciousness. Indeed, the variance explained by our models is relatively low (20%), and other factors have to be taken into account. Regarding this, an analysis on the predictive role of CRS-R score change during the earliest phase of inpatient rehabilitation is under way in our sample.

Despite these limitations, our findings indicate the usefulness of assessment on the CRS-R in subjects with severe brain injury entering inpatient rehabilitation. Patients with higher CRS-R scores have a higher probability of benefiting from rehabilitation and encountering a better outcome at discharge, providing information for rehabilitation planning and communication with patients and their caregivers. Further studies...
are needed to confirm its relevance in the long term and on thorough disability measures.

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References

