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ORIGINAL RESEARCH

Improvement on the Coma Recovery Scale—Revised During the First Four Weeks of Hospital Stay Predicts Outcome at Discharge in Intensive Rehabilitation After Severe Brain Injury

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Abstract

Objectives: To evaluate the prognostic utility of serial assessment on the Coma Recovery Scale—Revised (CRS-R) during the first 4 weeks of intensive rehabilitation in patients surviving a severe brain injury.

Design: Prospective cohort study.

Setting: An intensive rehabilitation unit.

Participants: Patients (N=110) consecutively admitted to the intensive rehabilitation unit. Inclusion criteria were (1) a diagnosis of unresponsive wakefulness syndrome (UWS) or minimally conscious state (MCS) caused by an acquired brain injury, and (2) aged >18 years.

Interventions: All patients underwent clinical evaluations using the Italian version of the CRS-R during the first month of hospital stay.

Main Outcome Measures: Behavioral classification on the CRS-R and the score on the Glasgow Outcome Scale (GOS) at final discharge. Patients transitioning from UWS to MCS or emergence from MCS (E-MCS), and from MCS to E-MCS were classified as patients with improved responsiveness (IR).

Results: After a mean ± SD hospital stay of 5.3±2.7 months, 59 of 110 patients (53.6%) achieved IR. In the multivariable analysis, a higher CRS-R score change at week 4 (odds ratio =1.99; 95% confidence interval [CI], 1.49−2.66; $P<.001$) was the only significant predictor of IR at discharge. Fifty-three patients (48.2%) were classified as severely impaired at discharge (GOS=3). In the multivariable analysis, higher GOS scores were related to a higher CRS-R score at admission (B=.051; 95% CI, .027−.074; $P<.001$), a higher CRS-R score change at week 4 (B=.087; 95% CI, .064−.110; $P<.001$), and an absence of severe infections (B=−.477; 95% CI, −.778 to −.176; $P=.002$).

Conclusions: An improvement on the total CRS-R score and on different subscales across the first 4 weeks of inpatient rehabilitation discriminates patients who will have a better outcome at discharge, providing information for rehabilitation planning and for communication with patients and their caregivers.

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Over the last decades, the number of survivors from severe brain injury has increased considerably because of continuous advances in intensive care technology and neurosurgical procedures. After the acute phase, these patients generally are transferred to an inpatient rehabilitation unit, where the physicians face 2 main issues: the need to (1) accurately classify the patient's level of consciousness, and (2) reliably predict the rehabilitation outcome.

The clinical evaluation of patients with disorders of consciousness is hindered by different potential examiner, patient and environmental biases. Indeed, the estimated rates of misdiagnosis of

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consciousness in this population consistently range from 30% to 45%.[1-3] Recently, the American Congress of Rehabilitation Medicine[4] reviewed 13 assessment tools for patients with disorders of consciousness, and only the Coma Recovery Scale-Revised (CRS-R) was recommended with minor reservations for use in clinical practice.[5-7] Moderate-major reservations were indicated for other scales such as the Sensory Modality Assessment Technique, the Western Neuro Sensory Stimulation Profile, the Sensory Stimulation Assessment Measure, the Wessex Head Injury Matrix, the Disorders of Consciousness Scale, and the Coma/Near-Coma Scale.[4] The CRS-R is a standardized measure of neurobehavioral function consisting of 23 hierarchically arranged items that comprise 6 subscales designed to assess arousal level, audition and language comprehension, expressive speech, visuoperceptual abilities, motor functions, and communication ability. The lowest item on each subscale represents reflexive behavior, while the highest item reflects cognitively mediated activity.[5-7]

As for the evolution of the disorders of consciousness, after the coma phase, patients can transition to an unresponsive wakefulness syndrome (UWS), a minimally conscious state (MCS), or emerge from the MCS and recover a full consciousness (emergence from MCS [E-MCS]). The prognosis of coma patients has great interindividual variability, depending on the etiology of injury and other demographic, clinical, and instrumental factors.[8-16] While there is accumulating evidence on prognostic factors in the acute phase,[17] the information on possible predictors of disease evolution applicable to acute rehabilitation is still scarce. With this background, we hypothesized that, in the setting of an intensive rehabilitation unit, early longitudinal assessment of patients through the CRS-R can provide prognostic information on rehabilitation outcome at discharge. Therefore, the objective of the present study was to evaluate the prognostic utility of CRS-R assessment during the first 4 weeks of the hospital stay, taking into account possible demographic and clinical confounders.

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 (1) a diagnosis of UWS or MCS caused by an acquired brain injury,[9,18,19] and (2) aged >18 years.

At admission and at discharge, the patients' level of consciousness was classified on the basis of clinical assessment as UWS, MCS, or E-MCS.[9,18,19]

Within 24 hours of admission, all the patients underwent clinical evaluations using the Italian version of the CRS-R.[20,21] The CRS-R was repeated at least 3 times a week or until E-MCS during the first month of the hospital stay. The evaluations were performed at different moments of the day (morning and afternoon). Ratings were conducted by trained and experienced examiners (neurologists and speech therapists). For each patient, the same examiner performed the assessments during the follow-up period. Clinical assessment was performed in the absence of environmental interferences and of medical conditions that could have affected patient alertness. Most patients were assessed in their bed, with the chest raised to increase comfort and arousal and avoid sleepiness. Less frequently, when possible, patients were assessed comfortably sitting in a wheelchair. In case of patient discomfort before and/or during testing, the examination was stopped and the score was not recorded. In accordance with the CRS-R manual, at the beginning of each examination, spontaneous movements were observed for at least 1 minute, and the arousal protocol was applied if the patient was drowsy. The total CRS-R score was recorded. In particular, the total scores on the CRS-R at admission and at week 4 were recorded.

During the study period, data on possible complications (eg, severe infections, hydrocephalus, neurosurgical interventions) were obtained.

Finally, the outcome of brain injury at discharge was assessed with the Glasgow Outcome Scale (GOS).[22,23]

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

List of abbreviations:

CI	confidence interval
CRS-R	Coma Recovery Scale−Revised
E-MCS	emergence from minimally conscious state
GOS	Glasgow Outcome Scale
IR	improved responsiveness
MCS	minimally conscious state
UWS	unresponsive wakefulness syndrome

Statistical analysis

The main outcome measures were the behavioral classification of level of consciousness and the score on the GOS at final discharge. In particular, 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 etiologic events.

Baseline characteristics were reported as frequency (percentage) and mean ± SD, and compared with Pearson's chi-square, Student's *t*, and Mann-Whitney *U* tests when appropriate.

When simultaneous assessments were available, the reliability of the CRS-R cumulative score was determined by calculating the kappa coefficient for interobserver agreement across ratings.

The CRS-R scores during the first month of hospital stay in patients with and without IR at discharge were compared using 2-factor group (IR vs not IR) × time (baseline, week 4, discharge) mixed analysis of variance, with repeated measures on the second factor. This allows evaluation of differences between the 2 groups (effect for group) and within each group over time (effect for time), and the interaction between group and time (effect for group × time).

Possible predictors of behavioral classification (IR vs not IR) and GOS score at discharge were assessed through stepwise multivariable logistic and linear regression models. The following covariates were entered: age at brain injury, sex, etiology, time postonset, CRS-R at admission, change of CRS-R at week 4, and occurrence of severe infections, hydrocephalus, and neurosurgical procedures.

All analyses were performed using the SPSS 24.0 software[a] running on Windows.[b]

Results

During the study period, a total of 215 patients were admitted to the intensive rehabilitation unit at the IRCCS Don Gnocchi

Table 1 Characteristics of study sample

Characteristics	Total Sample (N=110)	UWS (n=62)	MCS (n=48)	*P*
Age at brain injury (y)	58.7±16.2	59.6±15.0	57.4±17.6	.493
Sex				.977
Women	46 (41.8)	26 (41.9)	20 (41.7)	
Men	64 (58.2)	36 (58.1)	28 (58.3)	
Etiology				.009
Traumatic	34 (30.9)	18 (29.1)	16 (33.3)	
Anoxic	32 (29.1)	25 (40.3)	7 (14.6)	
Vascular/other	44 (40.0)	19 (30.6)	25 (52.1)	
Time postonset (mo)	2.1±2.1, 1.7	2.2±2.6, 1.7	1.9±1.4, 1.7	.565
CRS-R at admission	8.7±5.5, 7.0	4.5±1.8, 4.0	14.0±3.8, 14.0	<.001

NOTE. Values are mean ± SD; n (%); mean ± SD, median; or as otherwise indicated.

Foundation. Among those, 74 were classified as E-MCS, and 31 had incomplete data collection during the first 4 weeks of their hospital stay. Therefore, the remaining 110 patients (62 UWS, 48 MCS) were included in the analysis (table 1). Patients with UWS survived more frequently from anoxia and had lower CRS-R scores at admission. There were no differences in terms of age at brain injury, sex, and time postonset.

At admission, simultaneous assessments on the CRS-R were available in 60 subjects, conducted by a team of 6 raters. Two trained investigators simultaneously assessed each subject. The kappa coefficient for total scores yielded a rate of agreement of .827 across raters.

After a mean ± SD hospital stay of 5.3±2.7 months, 59 (53.6%) of the patients achieved an IR (table 2). In particular, among the 62 subjects with UWS at admission, 11 recovered to E-MCS and 20 transitioned to MCS, whereas 28 of 48 subjects with MCS at admission progressed to E-MCS. Patients with IR were younger (mean age ± SD, 55.2±16.2y vs 62.7±15.3y, *P*=.014), with a shorter median time postonset (1.2mo vs 1.9mo, *P*=.003) and a higher score on the CRS-R at admission (9.7±6.0 vs 7.5±4.8, *P*=.047). CRS-R scores increased significantly during the first 4 weeks of hospital stays in patients with IR, whereas they remained stable in patients without IR (CRS-R change at week: 4 7.4±5.8 vs 0.6±1.6, *P*<.001). The CRS-R scores in patients with IR and not IR are depicted in figure 1. IR at discharge was associated with overall higher scores on the CRS-R (effect for group: $F_{1,104}$=56.919, *P*<.001) and CRS-R improvement during the first month of the hospital stay (effect for group × time: $F_{1.887,196.296}$=66.857, *P*<.001).

In the multivariable analysis, a higher total CRS-R score change at week 4 (odds ratio =1.99; 95% confidence interval [CI], 1.49−2.66; *P*<.001) was the only significant predictor of IR at discharge (table 3). At week 4, IR was achieved by 53 patients. IR occurred on the visual subscale in 51 of 53 cases (96.2%), alone (15.1%) or in combination with other subscales (81.1%). All 10 of the 53 patients (18.9%) improving in 1 subscale alone at week 4 were classified as MCS at the end of the follow-up.

Classification on the GOS at discharge is depicted in table 4. Most patients were classified as severely impaired (48.2%). Independence (GOS scores 4−5) was obtained in 17 cases (15.4%). In the multivariable analysis, higher GOS scores were related to a higher CRS-R score at admission (B=.051; 95% CI, .027−.074; *P*<.001), a higher CRS-R score change at week 4 (B=.087; 95% CI, .064−.110; *P*<.001), and an absence of severe infections (B=−.477; 95% CI, −.778 to −.176; *P*=.002) (see table 3).

Table 2 Characteristics of patients with or without IR

Characteristics	IR (n=59)	Not IR (n=51)	*P*
Age at brain injury (y)	55.2±16.2	62.7±15.3	.014
Sex			.155
Women	21 (35.6)	25 (49.0)	
Men	38 (64.4)	26 (51.0)	
Etiology			.658
Traumatic	19 (32.2)	15 (29.4)	
Anoxic	15 (25.4)	17 (33.3)	
Vascular/other	25 (42.4)	19 (37.3)	
Time postonset (mo)	1.9±2.5, 1.2	2.4±1.6, 1.9	.003
CRS-R at admission	9.7±6.0, 7.0	7.5±4.8, 6.0	.047
CRS-R change at week 4	7.4±5.8, 6.0	0.6±1.6, 0.0	<.001
Severe infections	13 (22.0)	10 (19.6)	.751
Hydrocephalus	10 (16.9)	7 (13.7)	.735
Neurosurgical procedures	13 (22.0)	13 (25.5)	.497

NOTE. Values are mean ± SD; n (%); mean ± SD, median; or as otherwise indicated.

Discussion

The definition of diagnostic criteria for disorders of consciousness by the Aspen Workgroup[19] and the following development of standardized rating scales incorporating these criteria recently allowed a significant improvement in the clinical classification of the level of consciousness in patients surviving a severe brain injury. In particular, the Brain Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine recommended the use of the CRS-R, resulting in a reduction of the 30% to 45% rate of misdiagnosis of the consciousness level in previous assessments.[3,4] The excellent psychometric characteristics of the CRS-R[5] were confirmed in our study. In particular, we found an interobserver agreement of .827, in line with that reported in the Italian validation study.[24] Conversely, the prognostic value of CRS-R still needs to be clarified.[4] A few studies[25,26] 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). The information on the role of longitudinal assessment on the CRS-R is even more limited. In a dated article by Giacino et al,[27]

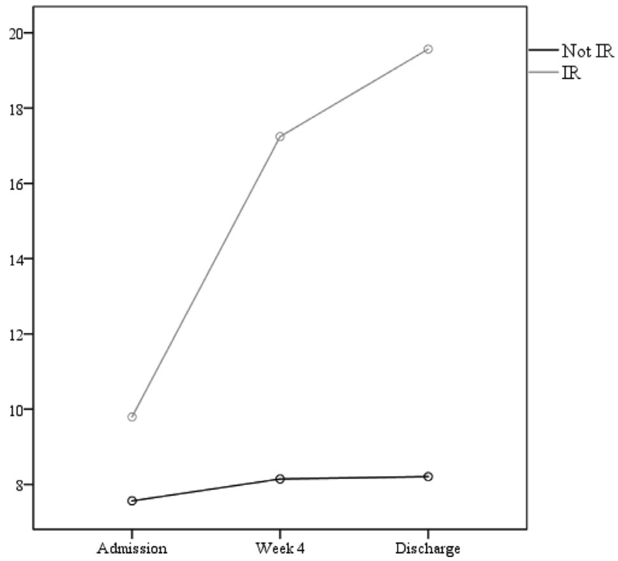

Fig 1 CRS-R score during the first 4 weeks of hospital stay and at discharge in patients with IR and not IR. Effect for group: $F_{1,104}=56.919$, $P<.001$; effect for group × time: $F_{1.887,196.296}=66.857$, $P<.001$.

with the use of the original version of the CRS, the score change during the first month of observation was a significant predictor of outcome. In the present prospective study, we confirmed the role of CRS-R score in providing prognostic information in survivors of severe brain injury entering the inpatient rehabilitation phase. Improvement on the CRS-R during the first 4 weeks of hospital stay was strongly associated with a better outcome at discharge, independent of age, sex, etiology, time postonset, and presence of main clinical complications. As reported in previous studies,[28,29] recovery of responsiveness was mainly associated with improvement on the visual subscale. However, our findings suggest the importance of the number of improving subscales, independent of their type. Indeed, no subject improving on 1 subscale alone at week 4 was classified as E-MCS at the end of the follow-up, whereas E-MCS was achieved by 81.4% of patients improving on 2 or more subscales. Therefore, serial assessment using the whole CRS-R can provide reliable information in terms of outcome prediction. Patients whose CRS-R scores increased in the early phases of inpatient rehabilitation achieved better outcomes in terms of both responsiveness and functional independence. Stability on the CRS-R after 4 weeks (arbitrarily defined as a change of ≤2 points, without behavioral improvement) was associated with IR at discharge in only 6 of 59 cases (10.2%). Among these subjects, 2 patients had a malfunctioning ventricular-peritoneal shunt, and 1 patient had hydrocephalus; they underwent neurosurgical revision or shunting with subsequent clinical improvement. Another patient had hepatic encephalopathy and recovered clinically after treatment of the metabolic complications. We did not find any evident explanations in the other 2 cases.

Table 3 Predictors of IR or higher GOS score at discharge

IR at Discharge	OR (95% CI)	*P*
CRS-R change at week 4	1.99 (1.49−2.66)	<.001
GOS Score at Discharge	**B (95% CI)**	***P***
CRS-R at admission	0.051 (0.027−0.074)	<.001
CRS-R change at week 4	0.087 (0.064−0.110)	<.001
Severe infections	−0.477 (−0.778 to −0.176)	.002

Abbreviation: OR, odds ratio.

Table 4 GOS score at discharge

GOS Score	Patients (N=110)
1	7 (6.4)
2	33 (30.)
3	53 (48.2)
4	16 (14.5)
5	1 (0.9)

NOTE. Values are n (%).

These findings have important implications for prognosis prediction in inpatient rehabilitation after severe brain injury. Our study suggests that a time frame of 4 weeks is an adequate window of observation and treatment to obtain reliable information on realistic goals of rehabilitation. Consistently, in a recent evaluation of 33 patients with UWS/MCS, longitudinal regression modeling of the CRS-R data discriminated outcome evolution starting from 19 days of observation.[30] On the one hand, 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,[31-33] a need that has often gone unmet.[34] On the basis of our findings, family and caregivers of patients with disorders of consciousness could be informed after a 1-month follow-up period about the evolution and further probability of clinical improvement. On the other hand, the observation of CRS-R change over the first 4 weeks of the hospital stay could be included as part of the clinical and instrumental assessment in order to plan the prosecution of rehabilitation program.

However, the 10% rate of recovery of responsiveness or consciousness in patients who remained stable after 4 weeks is not negligible, and continuous efforts are needed particularly when a better outcome would be expected, taking into account other prognostic factors such as etiology and severity/extension of brain damage. In these subjects, a comprehensive screening for possible complications such as hydrocephalus, infections, and other disturbances is advisable, although these variables were not retained in our multivariable models on IR. Of note, some patients with hydrocephalus had already received neurosurgical shunting at admission, whereas in other subjects the occurrence of hydrocephalus slowed or stopped the ongoing clinical improvement, avoiding the IR achievement only in 1 case. Moreover, severe infections were significantly related to worse functional outcome. The latter finding was mainly related to higher mortality after sepsis, leading to worse GOS scores despite recovery of responsiveness.

Age at brain injury and chronicity have been consistently recognized as predictors of recovery in UWS.[9,11,14,25] In our study, their effects were evident only in the univariate analysis, since patients who recovered responsiveness or consciousness had a younger age at brain injury and a shorter time postonset at admission. However, these effects disappeared in the multivariable analyses, suggesting that the predictive role of CRS-R score change during the first month of hospital stay was stronger. Of note, in a Spearman correlation analysis, a shorter time postonset

(Spearman $\rho = -.340$, $P < .001$) and, marginally, a younger age at brain injury (Spearman $\rho = -.167$, $P = .081$) were related to higher changes on the CRS-R after 4 weeks.

As for etiology, another acknowledged prognostic factor, it had a significant relationship with behavioral classification only at admission in our rehabilitation unit. Indeed, most patients with postanoxic injury were classified as UWS 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 etiology in short-term prognosis.[17,35] In a previous study,[14] etiology significantly predicted outcome on the Disability Rating Scale at 6 weeks after enrollment, whereas it lost its significance at 13 weeks. Moreover, in other studies assessing recovery from UWS in the long-term, the rate of improvement was not related to etiology.[15,36]

Study limitations

In interpreting the study findings some possible issues should be considered. For the functional evaluation we used the total GOS score, which might represent an oversimplification of the survival outcome.[23] Moreover, the time of observation was relatively short, and possible delayed recovery might have been missed. Finally, we did not take into account electrophysiological parameters (such as somatosensory-evoked potentials and electroencephalographic patterns),[37,38] and preinjury factors that might have influenced the outcome independently of the level of consciousness.

Conclusions

The accurate classification of consciousness level and the prediction of outcome are 2 important issues in the setting of intensive rehabilitation after severe brain injury. The CRS-R can represent a valuable option for both purposes. While its ability in classification of consciousness status has been well established, our findings indicate the usefulness of serial assessments on the CRS-R during the first 4 weeks of inpatient rehabilitation. An improvement across this time frame in terms of both total score and number of improving subscales discriminates patients who will have 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 longer follow-up periods and on more comprehensive disability measures.

Suppliers

a. SPSS 24.0 software; IBM Corp.
b. Windows; Microsoft Corp.

Keywords

Brain injury; Coma; Prognosis; Rehabilitation

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