Misdiagnosis rate of the prolonged disorders of consciousness on a clinical consensus compared with a repeated Coma-Recovery Scale-Revised assessment

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Abstract

Background: Previous studies have shown that a single Coma-Recovery Scale-Revision (CRS-R) assessment can identify high misdiagnosis rate for a clinical consensus. The aim of this study was to investigate the misdiagnosis rate of clinical consensus compared to repeated behavior scale assessments in patients with prolonged disorders of consciousness (DOC). Methods: Patients with prolonged DOC during hospitalization were screened by clinicians, and the clinicians formed a clinical consensus diagnosis. Trained professionals also used the CRS-R to evaluate the consciousness levels of the enrolled patients for repeated times (≥5 times) within a week. After the repeated evaluation results, the enrolled patients with prolonged DOC were divided into unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS), and emergence from MCS (EMCS). Furthermore, the relationship between the results of the CRS-R and the clinical consensus were analyzed. Results: In this study, 137 patients with a clinical consensus of prolonged DOC were enrolled. After the single CRS-R behavior evaluation, it was found that the misdiagnosis rate of clinical MCS was 24.7%, while the repeated CRS-R evaluation results showed that the misdiagnosis rate of clinical MCS was 38.2%. A total of 16.7% of EMCS cases were misdiagnosed as MCS, and 1.1% of EMCS cases were misdiagnosed as UWS. Conclusions: The current clinical consensus of the misdiagnosis rate is still relatively high. Therefore, clinicians should be aware of the importance of the bedside CRS-R behavior assessment and should apply the CRS-R tool to daily procedures.

Background

The most severe injuries result in prolonged (i.e., lasting at least 28 days) disorders of consciousness (DOC), including unresponsive wakefulness syndrome (UWS) [1-3] and minimally conscious state (MCS) [4, 5]. Currently, the boundary between UWS and MCS patients has been well-defined [3-5]. The main difference between UWS and MCS is whether there is definite evidence that patients have a certain ability to be aware of themselves and the outside world, which is the key problem in the diagnosis of patients with prolonged DOC. Clinical evaluations of the level of consciousness in patients with prolonged DOC were conducted mainly through bedside spontaneous and stimulating behavioral responses [6-8]. The level of arousal is reflected by the patient's assessment of the open eye, whereas awareness is mainly assessed based on the patient's perception of himself or herself and the external environment, i.e., the patient's non-reflexive behavior under stimulation or the evaluator's accidental discovery of the patient's non-reflexive behavior. UWS patients have clear characteristics of awakening without awareness [9]. There are spontaneous or stimulus-induced open eye reactions, sleep-wake cycles, and spontaneous reflexes (such as grunts and yawns), but there is a complete lack of awareness of oneself or the environment [8, 10]. That is, there is no clear evidence of awareness or directed response to external stimuli; however, the presence of repetitive non-reflexive behavioral responses suggests a transition to the MCS state. MCS can generally show some behavioral response characteristics related to consciousness [4, 11]. There is weak and fluctuating but definite behavioral evidence of a distinct sense of self or of the environment, such as the ability to track things and the ability to understand verbal information and to follow instructions. At the same time, MCS can be further divided into MCS plus (MCS+) and MCS minus (MCS-) subtypes according to the complexity of the behavioral response (such as the presence of language comprehension) [5]. Once patients can communicate functionally or can use functional items, they are diagnosed with emergence from MCS (EMCS) [12, 13].

Due to the difficulty of performing bedside consciousness assessments of patients with prolonged DOC, the misdiagnosis rate is very high [14]. Different diagnosis results are crucial for clinical treatment and nursing and even affect the decision of life termination [7, 15, 16]. For example, the treatment effect of amantadine was similar for UWS patients and those in MCS patients from result of previous study [17], however, the treatment of transcranial direct current stimulation may be more effective in MCS than UWS patients [18]. In addition, Boly et al. found that the perception of pain is preserved in MCS patients, which indicated that these patients may need analgesic treatment [19]. The development and use of the Coma Recovery Scale–Revised (CRS-R) greatly reduce the clinical misdiagnosis rate of prolonged DOC [20]. The scale measures the patient's auditory, visual, motor, oromotor, communication, and arousal to assess the patient's level of consciousness and is now the most reliable diagnosis of patients with prolonged DOC and the most sensitive tool, and it has been as gold standard of a consciousness diagnostic globally [21]. Previous studies have shown that a single CRS-R assessment can identify a misdiagnosis rate of 40% for a clinical consensus, which is 40% of the clinical consensus when UWS patients are actually MCS patients [22]. In addition, recent studies have shown similar results with a clinical consensus of a 35.3% misdiagnosis rate [23]. To date, several versions of the CRS-R scale have been developed and validated [24-28]; however, due to the influence of patients' awakening or consciousness fluctuations, movement defects, aphasia, and other problems [29-31], a single standard CRS-R behavior evaluation still leads to a certain percentage of a misdiagnosis rate. Therefore, a repeated behavior scale evaluation [32] and personalized item selections [33, 34] of the neurobehavioral assessment instrument are recommended to be applied to the consciousness evaluations of clinical patients, which have the potential to improve the reliability/validity of a diagnosis.

In recent years, the concept of prolonged DOC has been well spread clinically [10, 35]; however, the CRS-R is still not often used in clinical practice but is mostly used by clinical psychologists or specialized researchers. Therefore, in this study, the difference between clinicians' diagnoses of patients' consciousness and the diagnosis of a single CRS-R assessment was compared, and the misdiagnosis rate of the clinical consensus compared with the assessment results of a repeated CRS-R was analyzed.

Patients And Methods

Patients

Patients with prolonged brain injuries admitted by the neurology department and the neurological rehabilitation department were primarily enrolled. The inclusion criteria were as follows: (1) at least 18 years old, (2) ≥28 days after onset, and (3) no neuromuscular blockers or sedatives were used within 72 hours of enrollment. The exclusion criteria were: (1) coma, (2) there are functional disorders caused by progressive mental diseases, (3) persistent seizures, and (4) unstable vital signs.

This study protocol was approved by the Ethics Committee of Hangzhou Normal University. Written informed consent was obtained from the guardians/next of kin of the patients who participated in this study.

Data collection

Patients with prolonged DOC during hospitalization were screened by clinicians, and the clinicians in charge determined the patients' consciousness according to their behaviors during hospitalization (including the Glasgow Coma Scale assessment and other physical examinations) and their own clinical experience to form a clinical consensus diagnosis; that is, the patients included those with UWS with no consciousness or MCS with minimal consciousness. Subsequently, experienced professionals (psychologist) used the CRS-R to evaluate the neurological behavior of the enrolled patients for multiple times (≥5 times) over the following week, the diagnosis results of each patient were recorded, and the special behaviors of the patients were recorded. Among the repeated evaluation results, the highest score and diagnosis were selected as the final bedside behavior diagnosis. All the patients with prolonged DOC were divided into UWS, MCS-, MCS +, and EMCS.

Statistical analysis

An evaluation of the descriptive statistics was performed for all demographic information. Number, percentage, median, and range were produced for categorical variables, and means and standard deviations (SD) were calculated for age, time since onset, and the score on the CRS-R scale.

The Chi-square test was used to analyze the effects of gender, etiology, age groups and injury time on the misdiagnosis rate. The Mann–Whitney U test (Wilcoxon rank-sum test) was used to analyze the difference between the score of the first diagnosis and the score of the final diagnosis. Statistical significance was set at $p < 0.05$.

Results

A total of 137 patients with DOC selected by their clinicians was included in the study from July 2017 and October 2019. Baseline patient characteristics (numbers, percentage, median, and range or mean ± SD) are provided for all included research individuals (Table 1). There were 40 female patients (29.2%) and 97 male patients (70.8%). Sixty-nine patients were traumatic brain injury (TBI, caused by a violent blow or jolt to the head or body) (50.4%), and 68 patients were non-traumatic brain injury (NTBI, caused by vascular, anoxic, metabolic, infective and autoimmune) (49.6%). The mean age was 51.88 ± 13.93 (ranged from 19 to 84). The mean time since onset was 5.58 ± 4.32 (ranged from 1 to 22), and 44 patients were permanent DOC (32.1%).

The mean score of the single CRS-R assessment was 7.93 ± 4.3 (range from 2 to 24), and the mean score of the final CRS-R assessment was 8.87 ± 4.32 (range from 2 to 24), which was higher than the single assessment score ($U = 7827.5$, $p = 0.02$).

Fig. 1 shows the diagnostic process and results for all patients with prolonged DOC. Of the 137 patients with acquired brain injury enrolled, 48 were diagnosed by clinical consensus as MCS and 89 as UWS. After a single CRS-R evaluation, 62 were MCS, eight were EMCS, and 67 were UWS. After repeated CRS-R evaluations, 73 were MCS, nine EMCS, and 55 UWS.

It was also found that after a single CRS-R evaluation, seven of the 48 MCS patients were diagnosed as EMCS (7/48 = 14.6%), 40 as MCS (40/48 = 83.3%), and one as UWS (1/48 = 2.1%) (Table 2). After repeated CRS-R evaluations, one of the 40 MCS was diagnosed as EMCS (1/40 = 2.5%) and 39 as MCS (39/40 = 97.5%, but two of them were diagnosed from MCS- to MCS+). The diagnosis of one UWS was still UWS; seven EMCS were still diagnosed as EMCS. Among the 89 UWS patients, the diagnosis of 22 patients was improved to MCS (22/89=24.7%) after a single CRS-R evaluation. One was improved to EMCS (1/89 = 1.1%), and 66 maintained the original UWS diagnosis (66/89 = 74.2%). After repeated CRS-R evaluations, 12 of the 66 UWS patients were diagnosed as MCS (12/66 = 18.2%), while 54 were diagnosed as UWS (54/66 = 81.8%). While 22 MCS were still diagnosed as MCS (22/22 = 100%, but one diagnosis was improved from MCS- to MCS+), one EMCS was still diagnosed as EMCS.

Overall, 24.7% of MCS patients were misdiagnosed as UWS based on the clinical consensus after single evaluations (22/89). The probability of EMCS being misdiagnosed as MCS was 16.7% (7/48 = 14.6%). After repeated evaluations, 38.2% of MCS patients were misdiagnosed as UWS based on the clinical consensus (34/89). The probability of EMCS being misdiagnosed as MCS was 16.7% (8/48 = 16.7%) (Table 2). Table 2 shows the clinical consensus of the misdiagnosis rate for different demographic variables, including frequency and misdiagnosis rate. It was found that there was no significant difference in the misdiagnosis rate among different genders, etiologies, different age groups and time since onset.

Fig. 2 shows the number of patients with CRS-R subscale scores representing signs of consciousness when diagnosed with MCS or EMCS at a single assessment and a final assessment. After a single CRS-R assessment, among 22 patients diagnosed with MCS, two patients observed a sign of consciousness on the auditory subscale (9.1%), 16 patients on the visual subscale (72.7%), 12 patients on the motor subscale (54.5%), zero patients on the oromotor/verbal subscale (0%), and one patient on the communication subscale (4.5%). After repeated CRS-R assessments of 34 patients with a diagnosis of MCS, four patients showed signs of consciousness on the auditory subscale (11.8%), 26 on the visual subscale (76.5%), 16 on the motor subscale (47.1%), zero on the oromotor/verbal subscale (0%), one on the communication subscale (2.9%). Of the seven patients diagnosed with EMCS after a single assessment, four (57.1%) scored on the motor subscale, and seven (100%) scored on the communication subscale. After repeated evaluations, five (55.6%) of the nine patients diagnosed with EMCS scored on the motor subscale, and eight (88.9%) scored on the communication subscale.

Discussion

The main objective of this study was to investigate the misdiagnosis rate of clinical consensus compared to repeated behavior scale assessments. After the single CRS-R behavior evaluation, it was found that the misdiagnosis rate of clinical MCS was 24.7%, while the repeated CRS-R evaluation results showed that the misdiagnosis rate of clinical MCS was 38.2%. A total of 16.7% of EMCS patients was misdiagnosed as MCS, and 1.1% of EMCS patients was misdiagnosed as UWS.

For the evaluation of the consciousness level of patients with prolonged DOC, a large number of previous studies has compared the diagnostic results of the standard CRS-R scale with other scales, and it has been found that the CRS-R scale has a high sensitivity in detecting the consciousness of patients with MCS or EMCS [36, 37]. When the CRS-R scale is used, it can be found that many patients with a clinical consensus diagnosis of unconscious actually remain minimally conscious. Schnakers et al. found that 41% of patients with a clinical consensus diagnosis of UWS was actually found to be MCS patients after an evaluation using the standard CRS-R behavior scale, whereas the clinical consensus is that 10% of patients with MCS are actually higher conscious EMCS (fully conscious) [22]. A recent study on repeated CRS-R behavior assessments showed that the clinical consensus still had a 33% misdiagnosis rate when diagnosing MCS patients [23]. This also supports the results of the current study. It was found that repeated behavioral assessments could identify patients with MCS with a high misdiagnosis rate of 38.2%. Moreover, the misdiagnosis rate of EMCS with full consciousness was 16.7%. When the evaluation results of the single CRS-R scale were compared with the clinical consensus, it was found that 24.7% of patients were misdiagnosed with MCS by clinical consensus, which was significantly lower than the previous studies on the misdiagnosis rate at 41%; however, the 14.6% misdiagnosis rate of EMCS was similar to the 10% misdiagnosis rate in a previous study [22]. During this decade, with the continuous progress in the field of prolonged DOC, clinicians have a deeper understanding of this concept. This may be the reason for the significant difference in the misdiagnosis rate over the past 10 years. In addition, the difference between single assessment and repeated assessment emphasizes that the fluctuations of patients' responsiveness have an effect on the neuro-behavioral assessment, and also emphasizes the importance of repeated assessment in the clinical diagnosis.

When whether the patient’s demographic factors would lead to clinical misdiagnosis was analyzed, it was found that the difference in gender, etiology, age groups and post-injury time was not the reason for the clinical consensus misdiagnosis. Therefore, it is highly likely that the clinical worker is highly dependent on the patients’ bedside behaviors in the patients’ daily management and may not be using systematic and standardized behavioral assessment tools to diagnose awareness. In addition, it was found that the Glasgow Coma Scale (GCS) was widely used for almost all patients admitted to the hospital, and a previous study also showed that the scale was not appropriate for assessing a patient’s level of consciousness [24]. Different from the GCS scale, the CRS-R scale has very clear MCS diagnostic criteria, and the evaluation consciousness from various angles can be used to diagnose the consciousness level of patients more sensitively, which greatly reduces the misdiagnosis of patients with prolonged DOC.

Therefore, the use of standardized CRS-R assessment tools is particularly important for the detection of clinical patients' level of consciousness and patient management.

During the implementation of the standardized CRS-R scale, a large number of studies has found that the standard CRS-R scale still has some misdiagnosis rates. Cheng and Gosseries et al. found that the name of the patient is more suitable for the detection of auditory localization than other sound stimuli [38]. Vanhaudenhuys et al. also found that the best way to check visual pursuit in MCS patients is to use a moving mirror rather than a moving object or person [39, 40]. Therefore, the application of personally related visual and auditory stimulation can better reduce the misdiagnosis rate of patients compared with natural stimulation [34]. In addition, when the CRS-R was used to evaluate the use of functional objects for MCS patients, the use of personalized objects seemed to elicit better responses from patients, thereby identifying misdiagnosed EMCS [33]. For this study, repeated CRS-R behavior assessments were employed, during which family members or caregivers were asked about patients' items of interest. To better elicit the patients' responses according to the patients' preferences, a variety of different stimuli were selected according to the patients' performance during the evaluation process, namely natural stimuli and personally related stimuli. It was found that when patients were diagnosed with MCS based on the first behavior evaluation, most of them showed signs of consciousness on the visual subscale (72.7%) and the motor subscale (54.5%), and few showed signs of consciousness on the auditory subscale (9.1%) and the communication scale (4.5%). After repeated evaluations, 10 patients showed signs of consciousness for visual subscale, four patients with motor subscale signs of consciousness, and two patients with auditory subscale signs of consciousness. This is most likely due to fluctuations in the patients' levels of arousal or consciousness and due to the use of the patients' own associated stimuli.

It was also found that for the vast majority of patients diagnosed with MCS, the items showing signs of consciousness were mainly related to the visual subscale (visual pursuit and visual fixation), the motor subscale (automatic motor response and localization to noxious stimulation), and the auditory subscale (reproducible movement to command). The results were confirmed by a previous study [41], but the difference is that the most sensitive item in this study was the visual subscale, while the most sensitive item in the previous study was the reproducible movement to command items on the auditory subscale.

Based on the results, it was found that the clinical consensus had a higher rate of misdiagnosis, especially compared to repeated CRS-R scales. This also highlights the importance of the CRS-R scale in the assessment of patient consciousness. Therefore, it is suggested that for patient daily management, clinicians should at least evaluate visual pursuit and visual fixation for the visual subscale, automatic motor response and localization to noxious stimulation for the motor subscale, and reproducible movement to command for the auditory subscale when assessing patients' levels of consciousness. This can greatly reduce the misdiagnosis rate of patients, although for patients with prolonged DOC, the bedside neurobehavioral assessment has some limitations, and neuroimaging is considered an important method for the diagnosis of consciousness [23]; however, a behavioral assessment is still the most direct and portable method and should be promoted in clinical practice.

The limitation of this study was that no neuroimaging methods were used to evaluate the enrolled patients with prolonged DOC. Because the CRS-R scale still has some false negatives, behavioral assessments combined with neuroimaging should be used to truly understand the misdiagnosis rate of a clinical consensus in the future. Besides, we did not analyze the difference in regards to complications in patients with prolonged DOC during hospitalization which may play a role for the results, and we can analyze this factor in the future studies.

Conclusions

Although a large number of studies has emphasized the importance of diagnosis, this study showed that the current clinical consensus of the misdiagnosis rate is still relatively high. This misdiagnosis rate greatly affects the clinical management of patients with prolonged DOC. Therefore, it is emphasized that clinicians should be aware of the importance of the bedside CRS-R behavior assessment and should apply the CRS-R scale to their daily procedures. Choosing stimuli that are relevant to the patient and evaluating them on a standard scale can better identify the patient's covert consciousness. In addition, for a rapid evaluation of patients, visual pursuit and visual fixation for the visual subscale, automatic motor response and localization to noxious stimulation for the motor subscale, and reproducible movement to command for the auditory subscale are recommended.

Abbreviations

DOC: Disorders of Consciousness; UWS: Unresponsive Wakefulness Syndrome; MCS: Minimally Conscious State; MCS+: Minimally Conscious State Plus; MCS-: Minimally Conscious State Minus; EMCS: Emergence from Minimally Conscious State; CRS-R: Coma Recovery Scale-Revised; TBI: Traumatic Brain Injury; NTBI: Non-Traumatic Brain Injury

Declarations

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Authors' contributions

JW, ZH, ZS and XH collected data and managed the patients; JW performed data analyses; JW, HD and SL designed the study; JW wrote the paper. HD revised the manuscript for important intellectual content. All authors discussed the results and commented on the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study protocol was approved by the Ethics Committee of Hangzhou Normal University. Written informed consent was obtained from the guardians/next of kin of the patients who participated in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Demographic characteristics and clinical data of patients with DOC (n = 137)

Characteristics/Variables	n	%	Mean ± SD	Median (range)
Sex				
Male	97	70.8		
Female	40	29.2		
Etiology				
TBI	69	50.4		
NTBI	68	49.6		
Age (years)	137		51.88 ± 13.93	52 (19-84)
18-44	37		34.41 ± 6.9	35 (19-44)
45-59	57		51.3 ± 4.44	51 (45-59)
≥60	43		67.7 ± 5.95	66 (60-84)
Time post-onset (m)				
Whole sample	137		5.58 ± 4.32	4 (1-22)
Non-permanent	93	67.9	3.92 ± 2.45	3 (1-11.5)
Permanent	44	32.1	9.1 ± 5.23	7 (4-22)
CRS-R scores				
Single assessment	137		7.93 ± 4.3	7 (2-24)
Repeated assessment	137		8.87 ± 4.32	8 (2-24)

SD = standard deviation; ***DOC*** = disorders of consciousness; ***TBI*** = traumatic brain injury; ***NTBI*** = non-traumatic brain injury; ***CRS-R*** = Coma Recovery Scale-Revised; ***n*** = numbers; ***m*** = months.

Permanent = three months after postinjury (non-traumatic), 12 months after postinjury (traumatic)

Table 2 Numbers of misdiagnosis in relation to demographic profiles of patients with prolonged DOC in different diagnosis settings (n = 137)

	Clinical consensus		Single assessment		Repeated assessment	
	UWS, n	MCS, n	MCS, n (%) [a]	EMCS, n (%) [b]	MCS, n (%) [a]	EMCS, n (%) [b]
Sex						
Male	65	32	18 (27.7)	4 (12.5)	28 (43.1)	4 (12.5)
Female	24	16	4 (16.7)	3(18.8)	6 (25)	4 (25)
p value, c2			> 0.05, 1.45	> 0.05, 0.33	> 0.05, 2.83	> 0.05, 1.20
Etiology						
TBI	44	25	11 (25)	4 (16)	17 (38.6)	5 (20)
NTBI	45	23	11 (24.4)	3 (13.0)	17 (37.8)	3 (13.0)
p value, c2			> 0.05, 0.004	> 0.05, 0.08	> 0.05, 0.56	> 0.05, 0.41
Age (years)						
18-44	27	10	6 (22.2)	1 (10)	11 (41)	1 (10)
45-59	37	20	12 (32.4)	4 (20)	16 (43.2)	5 (25)
≥60	25	18	4 (16)	2 (11.1)	7 (28)	2 (11.1)
p value			> 0.05	> 0.05	> 0.05	> 0.05
Time post-onset						
Permanent	27	17	6 (22.2)	1 (5.9)	9 (33.3)	1 (5.9)
Non-permanent	62	31	16 (25.8)	6 (19.4)	25 (40.3)	7 (22.6)
p value, c2			> 0.05, 0.13	> 0.05, 1.6	> 0.05, 0.39	> 0.05, 2.20
Total	48	89	22	7	34	8

[a] = Numbers of MCS patients were misdiagnosed as UWS; [b] = Numbers of EMCS patients were misdiagnosed as MCS.

DOC = disorders of consciousness; ***UWS*** = unresponsive wakefulness syndrome; ***MCS*** = minimally conscious state; ***EMCS*** = emergence from minimally conscious state; ***c2*** = Chi-square; ***n*** = numbers

Figures

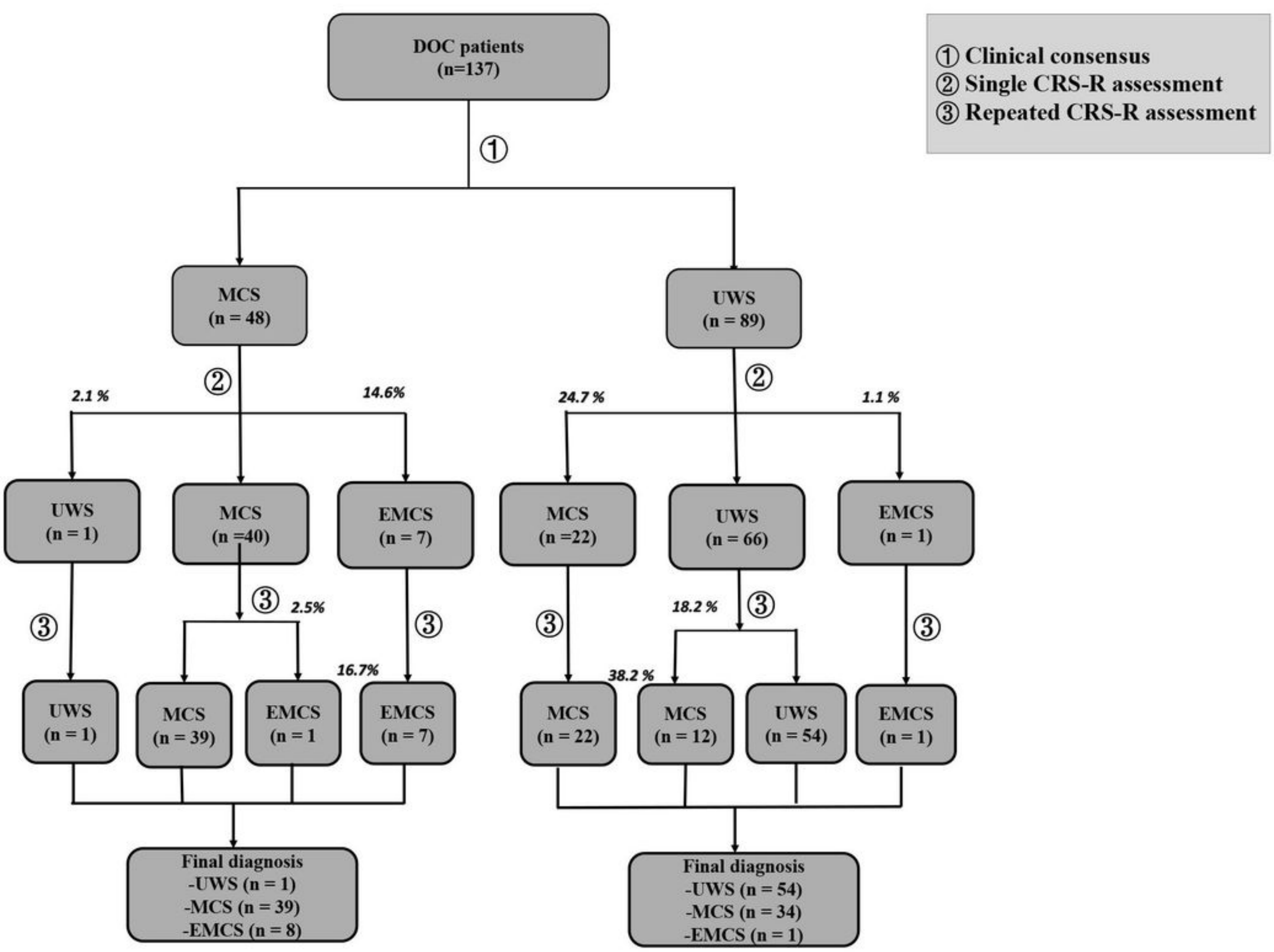

Figure 1

Flowchart of diagnosis by clinical consensus, single assessment, and repeated assessment. Of the 137 patients with acquired brain injury enrolled, 48 were diagnosed by clinical consensus as MCS and 89 as UWS. After a single CRS-R evaluation, 62 were MCS, eight were EMCS, and 67 were UWS. After repeated CRS-R evaluations, 73 were MCS, nine EMCS, and 55 UWS. DOC disorders of consciousness, UWS unresponsive wakefulness syndrome, MCS minimally conscious state, EMCS emergence from minimally conscious state, n numbers

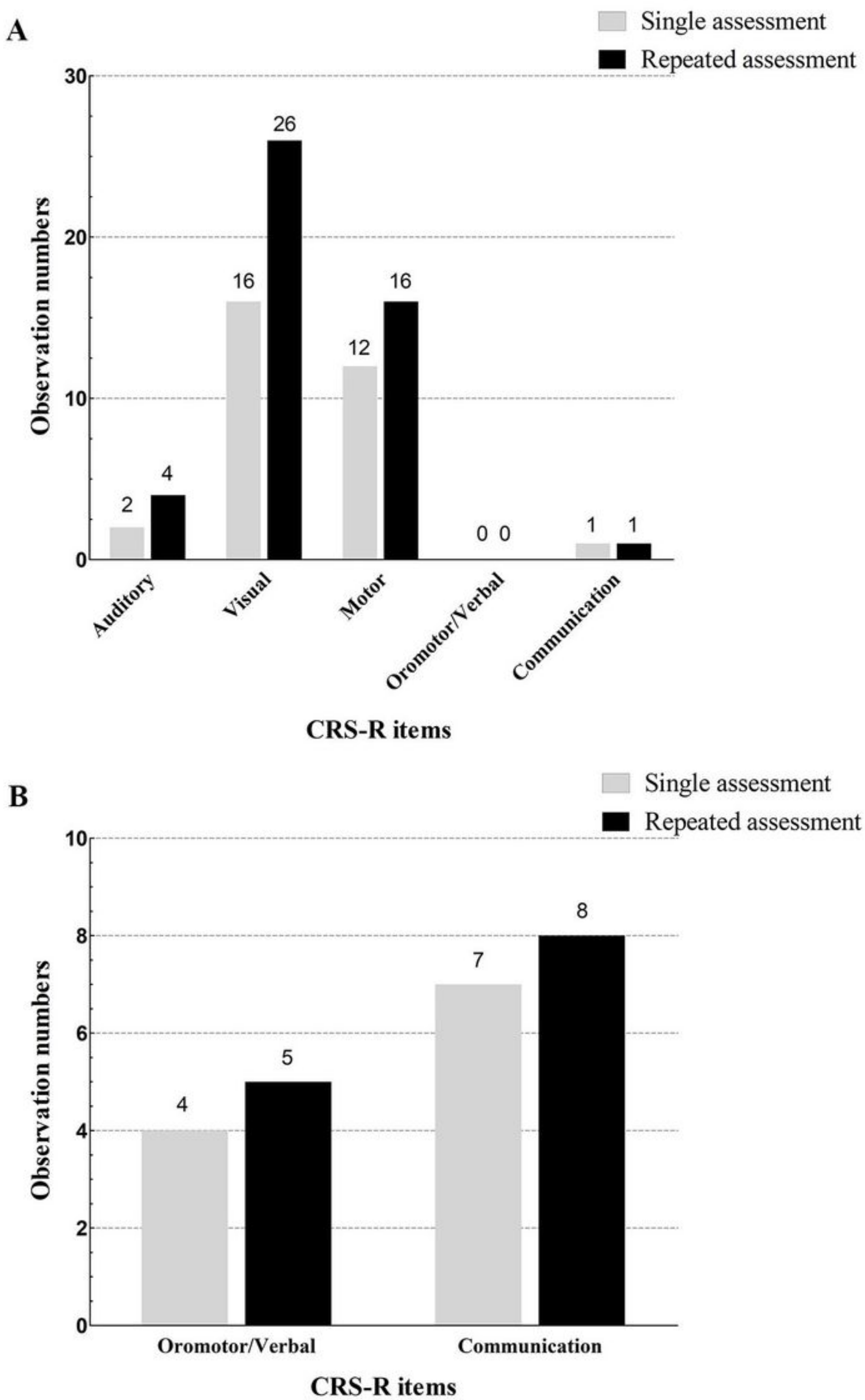

Figure 2

The number of CRS-R items that show signs of consciousness of MCS or EMCS after a single assessment and repeated assessments. [A]. In these terms, Auditory = 3-4 OR Visual = 2-5 OR Motor = 3-5 OR Oromotor/Verbal = 3 OR Communication = 1, indicating that the patient has signs of consciousness and is diagnosed as MCS. Of the patients with a clinical consensus diagnosis of UWS, 22 were diagnosed with MCS after a single CRS-R assessment. After repeated CRS-R assessments, 34 patients were diagnosed with MCS. [B]. In these terms, Motor ≥ 6 OR Communication ≥ 2, indicating that the patient has signs of full consciousness and is diagnosed as EMCS. Of the patients with a clinical consensus diagnosis of MCS and UWS, eight were diagnosed with EMCS after a single CRS-R assessment. After repeated CRS-R assessments, nine patients were diagnosed with EMCS. CRS-R Coma Recovery Scale-Revised, MCS minimally conscious state, EMCS emergence from minimally conscious state