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ANNALS of Clinical and Translational Neurology
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RESEARCH ARTICLE

Minimally conscious state plus versus minus: Likelihood of emergence and long-term functional independence

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Received: 31 July 2023; Revised: 7 December 2023; Accepted: 1 January 2024

***Annals of Clinical and Translational Neurology* 2024; 11(3): 719–728**

doi: 10.1002/acn3.51993

Abstract

Objective: Severe brain injuries can result in disorders of consciousness, such as the Minimally Conscious State (MCS), where individuals display intermittent yet discernible signs of conscious awareness. The varied levels of responsiveness and awareness observed in this state have spurred the progressive delineation of two subgroups within MCS, termed "plus" (MCS+) and "minus" (MCS-). However, the clinical validity of these classifications remains uncertain. This study aimed to investigate and compare the likelihood of emergence from MCS, as well as the functional independence after emergence, in individuals categorized as in MCS+ and MCS-. **Methods**: Demographic and behavioral data of 80 participants, admitted as either in MCS+ (n = 30) or MCS- (n = 50) to a long-term neurorehabilitation unit, were retrospectively analyzed. The neurobehavioral condition of each participant was evaluated weekly until discharge, demise, or emergence from MCS. The functional independence of those participants who emerged from MCS was assessed 6 months after emergence. **Results**: While only about half of the individuals classified as in MCS- (n = 24) emerged from the MCS, all those admitted as in MCS+ did, and in a shorter postinjury period. Despite these differences, all individuals who emerged from the MCS demonstrated similar high disability and low functional independence 6 months after emergence, regardless of their state at admission. **Interpretation**: Individuals classified as MCS+ exhibited a higher likelihood of emergence and a shorter time to emergence compared to those in MCS-. However, the level of functional independence 6 months after emergence was found to be unrelated to the initial state at admission.

Introduction

Severe brain injuries can profoundly impair awareness, wakefulness, and responsiveness, potentially leading to a spectrum of Disorders of Consciousness (DOC). This spectrum encompasses two prominent clinical states: the Unresponsive Wakefulness State (UWS) and the Minimally Conscious State (MCS). The UWS, formerly known as the vegetative state,[1] is characterized by preserved wakefulness but lacks any detectable signs of self-awareness or purposeful interaction with the environment.[2] In this state, individuals may exhibit sleep–wake cycles, spontaneously open their eyes, and demonstrate rudimentary reflexive behaviors. However, they lack consistent, reproducible responses to external stimuli and show no signs of conscious awareness. Conversely, the MCS represents a distinct category within the spectrum of DOC, lying between UWS and full consciousness. Individuals in MCS display inconsistent but discernible behavioral evidence of conscious awareness.[3] Unlike those in UWS, individuals in MCS demonstrate intermittent or inconsistent purposeful responses to external stimuli, such as following simple commands, reaching for objects, or vocalizing purposefully. Therefore, the MCS is a highly heterogeneous state that includes subjects with markedly different neurobehavioral conditions. As a

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result, individuals may display varying levels of responsiveness and awareness, ranging from minimal signs of consciousness to more robust and consistent responses. These differences have prompted the definition of an "MCS plus" (MCS+) state for subjects with high-level behavioral interactions and an "MCS minus" (MCS-) state for those displaying low-level intentional behavior.

Different authors have made progressive and remarkable attempts to define the MCS+ and MCS- states with specific criteria. Initially, Bruno et al. characterized the MCS+ by the presence of command following, intelligible verbalization or gestural or verbal yes/no responses.[4] Conversely, the authors identified the MCS- by the presence of nonreflex movements such as orientation of noxious stimuli, pursuit eye movements that occur in direct response to moving or salient stimuli, and movements or affective behaviors that occur appropriately in relation to relevant environmental stimuli.[4] Importantly, this preliminary categorization has been supported by neuroimaging findings.[5,6] In a later communication, Schnakers et al. identified object recognition, reproducible response to command, and intelligible verbalization, but not intentional communication, as indicators of MCS+.[7] The authors also considered spontaneous eye opening, object manipulation, localization and fixation, localization of pain, and unreliable communication as indicators of MCS-, in contrast. More recently, Thibaut et al. proposed the first operational criteria to identify the MCS+ and MCS- using the *Coma Recovery Scale-Revised* (CRS-R), the most commonly used and widely recommended instrument to assess the neurobehavioral condition of individuals with DOCs,[8,9] with the aim of standardizing the clinical definition of these states and ensuring consistent communication between clinicians.[10] In a corrected version of their manuscript,[11] the authors determined that the ability to follow commands, representative of the MCS+, could be indicated by response to command (score of 3 or 4 on the auditory subscale of the CRS-R; i.e., A3 or A4), object recognition (score of 5 on the visual function subscale; i.e., V5), intelligible verbalization (score of 3 on the verbal subscale; i.e., O3), and/or intentional communication (score of 1 on the communication subscale; i.e., C1) (Fig. 1). In the absence of these signs, the presence of object localization in space, visual pursuit or fixation (scores of 4 to 2 on the visual function subscale; i.e., V4 to V2, respectively), or automatic motor behaviors, object manipulation, localizing noxious stimuli (scores of 5 to 3 on the motor function subscale; i.e., M5 to M3, respectively) are considered as indicators of MCS- (Fig. 1). Interestingly, the authors also found that the level of disability of groups of individuals who showed any combination of signs of command-following was comparable and less severe than that exhibited by participants in an MCS- at discharge at 3 to 4 months postinjury.

Although the scholarly discussion in recent years has succeeded in defining unambiguous criteria to identify MCS+ and MCS-,[4,7,10] and preliminary empirical investigation has shown short-term differences in the level of disability of individuals in these states,[10] the clinical validity of the MCS+ and MCS-, it is the extent to which these states represent different clinical entities, remains unknown.

We hypothesized that individuals in MCS+ would show better clinical progress, evidenced by higher likelihood of emergence from MCS, and a better functional condition after emerging from MCS, indicated by greater independence and lower disability, compared to individuals in an MCS-. Consequently, the aim of this study was to investigate and compare the likelihood of emergence from MCS and the functional independence after emergence of individuals in MCS+ and MCS-.

Methods

Participants

Demographic and behavioral data were retrospectively extracted from a database containing clinical data of individuals with DOC admitted to an inpatient neurorehabilitation program from January 2004 to December 2022. Participation criteria included: (a) diagnosis of MCS+ or MCS- after a severe brain injury of any etiology upon admission to the neurorehabilitation program; (b) age $\geq$ 18 years; (c) time since injury to admission $\geq$28 days, which characterizes a prolonged DOC, and <6 months; and (d) a follow-up period of no less than 12 months from the onset to detect cases of late recovery of consciousness, and no less than 6 months from emergence to enable investigation of long-term functional independence.

The study was approved by Comité Ético de Investigación Clínica del Hospital Clínic Universitari de València (2019002) and was performed in accordance with the Declaration of Helsinki and its later amendments. The study was registered at ClinicalTrials.gov (NCT05954650). Written informed consent to participate in the study was obtained from the legal representative of all participants.

Procedure

The neurobehavioral and clinical condition of all the participants was assessed upon admission using the Spanish adaptation of the CRS-R.[12,13] Five separate assessments were performed during the first week after admission, in

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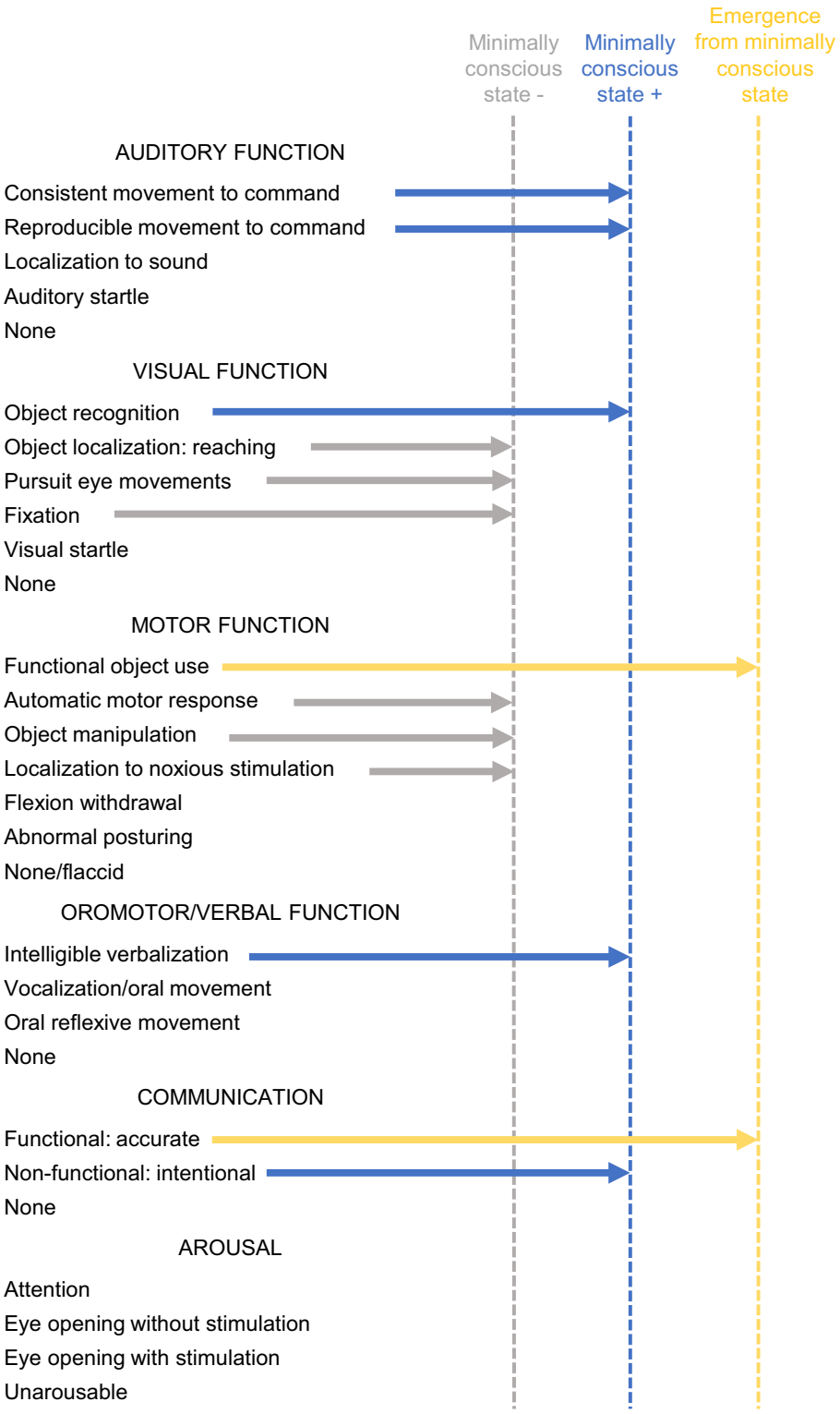


Figure 1. Items of the Coma Recovery Scale-Revised that indicate a diagnosis of minimally conscious state "minus," minimally conscious state "plus" and emergence from the minimally conscious state. The figure highlights the behavioral signs examined by the Coma Recovery Scale-Revised that indicate a diagnosis of minimally conscious state "minus," minimally conscious state "plus" and emergence from the minimally conscious state.

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accordance with the recommendations.[14] Diagnosis of MCS+ and MCS- was made according to the criteria established by Thibaut and colleagues.[10,11]

All participants received daily therapeutic interventions tailored to their specific needs, featuring physical therapy and multimodal stimulation. Medical oversight emphasized proactive prevention and treatment of potential complications due to physical condition and sustained immobility. This included passive range-of-motion exercises, postural care, daily sitting routines, and other related practices. Agitation was managed with the administration of beta-blockers such as propranolol and atenolol, or neuroleptics like quetiapine and olanzapine. Pain was mitigated using analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs. In addition, a combination of pharmacological interventions (e.g., amantadine and zolpidem) and techniques like multisensory stimulation (interactive projections, aroma therapy, musical selections, tactile stimulation, and others) and noninvasive brain stimulation (transcranial direct current stimulation[15] or transcutaneous auricular vagus nerve stimulation[16]) were employed to foster the resurgence of consciousness.

The neurobehavioral condition of each participant was systematically evaluated on a weekly basis using the CRS-R. These assessments continued until discharge, demise, or emergence from MCS. Evaluations were carried out during the morning hours, specifically from 10 a.m. to 12 p.m., by an adept neuropsychologist.

Participants who emerged from MCS continued with the established rehabilitation regimen, which included physical, occupational, cognitive, and speech therapy. These therapeutic interventions were appropriately adjusted to match their new clinical circumstances. The disability and functional independence subsequent to their emergence from MCS were assessed at the 6-month milestone with the *Disability Rating Scale*,[17] the *Barthel Index*,[18] and the *Functional Independence Measure*.[19]

Data analysis

The normality of the data was investigated using Shapiro–Wilk tests. Descriptive statistics (median and interquartile range [IQR]) were used to summarize demographic and clinical information.

Differences in demographic and clinical variables between groups of participants at different time periods were investigated using chi-square and Mann–Whitney U tests.

The interpretation of independence measures was conducted separately, as the three instruments assess distinct constructs. Scores obtained from the *Disability Rating Scale* were interpreted as indicators of various levels of disability, including no disability (score of 0), mild (1), partial (2–3), moderate (4–6), moderately severe (7–11), severe (12–16), extremely severe (17–21), vegetative state (22–24), and extreme vegetative state (25–29).[20] However, it should be considered that these scores have not undergone validation.[21] The scores in the *Barthel Index* were interpreted as indicators of dependence, such as total dependence (scores below 21), severe dependence (21–60), moderate dependence (61–90), and slight dependence (scores above 90).[18] The total score of the *Functional Independence Measure* was interpreted as a general measure of functional independence. Additionally, the stages of functional independence within activities of daily living, sphincter management, mobility, and executive function domains were estimated based on the scores, according to Stineman et al.[22] These stages encompassed total assistance (Stage 1), maximal assistance (Stage 2), moderate assistance (Stage 3), minimal assistance (Stage 4), supervision (Stage 5), modified independence (Stage 6), and complete independence (Stage 7). The results obtained from each instrument were analyzed separately due to the distinct constructs of the three scales.

All statistical analyses were performed using IBM SPSS Statistics version 22 (IBM, New York, NY). Statistical significance was set at $p < 0.05$ for all analyses.

Results

Participants

A total of 80 individuals in MCS after a brain injury, 19 women (23.8%) and 61 men (76.2%), with a median age of 40.2 [25.7–54.6] years, met the participation criteria and were consequently included in the analysis. The causes of brain injuries were traumatic in 46 cases (57.5%) and nontraumatic in the remaining 34 cases (42.5%), which included hemorrhagic stroke ($n = 19$), anoxia ($n = 9$), and other causes such as intoxication, infection, ischemic stroke, and tumor ($n = 6$). Participants were admitted to the neurorehabilitation unit a median of 89 [70.5–127] days postinjury, with a median score in the CRS-R of 11 [9–15] and a median score in the *Disability Rating Scale* of 23 [22–24].

Out of all participants, 30 (37.5%) were diagnosed as being in MCS+ and 50 (62.5%) as being in MCS-. Both groups of participants had comparable demographic and clinical characteristics but different neurobehavioral condition, as indicated by the CRS-R ($U = 20.5$, $p < 0.001$), and disability, as described by the *Disability Rating Scale* ($U = 311.0$, $p < 0.001$). Specifically, compared to participants in MCS-, participants in MCS+ had higher median scores in the CRS-R (16 [14.7–16.2] vs 9 [8–11]) and lower median scores in the *Disability Rating Scale* (22

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[21–23] vs 24 [23–24]). During the follow-up period, one participant admitted in MCS+ and three participants admitted in MCS- died.

Likelihood of emergence

Fifty-four participants from the total (67.5%) emerged from MCS after a median of 156 [108.5–216.2] days from the onset, either by demonstrating functional communication ($n = 17$), functional object use ($n = 16$), or both ($n = 21$).

However, the likelihood of emergence significantly differed between groups in the follow-up period. While all of the 30 participants in MCS+ emerged from the MCS, only 24 from the 50 participants in MCS- (48%) did so ($X^2 = 23.1$; $p < 0.001$) (Fig. 2). Additionally, time from the onset to emergence also differed between groups ($U = 207.5$, $p < 0.01$). Participants admitted in MCS+ emerged after a median of 141.5 [90.2–195.2] days from the onset. In contrast, participants admitted in MCS- emerged after a median of 200.5 [133.2–264.2] days. The 26 participants in MCS- who did not emerge from MCS either passed away ($n = 3$) or remained in this condition during the follow-up period ($n = 23$).

Participants who emerged after being admitted in MCS+ had higher scores in the CRS-R (16 [14.7–16.2] vs 10.5 [8.2–11.7]; $U = 12.0$, $p < 0.001$) and lower scores in the *Disability Rating Scale* (22 [21–23] vs 23.5 [23–24]; $U = 152.0$, $p < 0.001$) than those who emerged after being admitted in MCS-. No other differences in demographical or clinical variables were found between groups of participants.

Functional independence

One participant who was admitted in an MCS- passed away after emerging from the MCS. Data from the remaining 53 participants who emerged from the MCS were available for analysis.

Six months after emergence from MCS, participants who were admitted in MCS+ as well as those who were admitted in MCS- demonstrated comparable disability and functional independence, as indicated by their scores on the *Disability Rating Scale* ($U = 332.0$, $p = 0.814$), the *Barthel Index* ($U = 313.0$, $p = 0.561$), and the *Functional Independence Measure* ($U = 334.0$, $p = 0.843$).

Regarding disability, participants who were admitted in MCS+ had a median score in the *Disability Rating Scale* of 15.5 [8–19.2], similarly to participants in MCS-, who had a median score of 18 [7–18]. Both groups displayed a comparable distribution of levels of disability 6 months after emerging from MCS ($X^2 = 7.2$; $p = 0.303$), with most participants exhibiting moderate to extremely severe disability (Table 1).

In terms of functional independence, participants admitted in MCS+ had a median score in the *Barthel Index* of 13 [2.2–36.2], while those admitted in MCS- had a median score of 9 [0–51]. Both groups had a comparable distribution of participants across levels of functional independence based on their scores in this scale in the follow-up assessment after emergence ($X^2 = 2.23$;

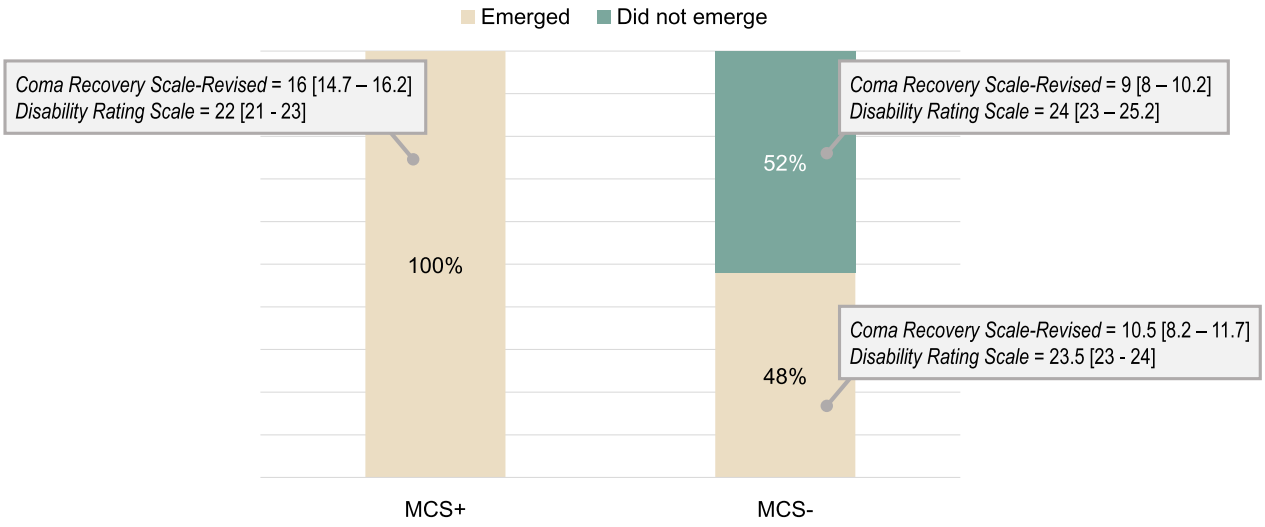


Figure 2. Likelihood of emergence from the minimally conscious state. The figure shows the percentage of participants who did and did not emerge from the minimally conscious state, together with their neurobehavioral condition and disability at admission. MCS: minimally conscious state.

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Table 1. Distribution of participants according to their level of disability and functional independence 6 months after emergence.

	Minimally conscious state plus				Minimally conscious state minus			
Disability rating scale								
No disability	–				–			
Mild disability	–				–			
Partial disability	1 (3.3%)				–			
Moderate disability	1 (3.3%)				3 (12.5%)			
Moderately severe disability	8 (26.7%)				4 (16.7%)			
Severe disability	6 (20%)				4 (16.7%)			
Extremely severe disability	11 (36.7%)				12 (50%)			
Vegetative state	3 (10%)				–			
Extreme vegetative state	–				–			
Barthel index								
Total dependence	19 (63.3%)				15 (62.5%)			
Severe dependence	6 (20%)				3 (12.5%)			
Moderate dependence	3 (10%)				2 (8.3%)			
Slight dependence	2 (6.7%)				3 (12.5%)			
Functional independence measure	*Activities of daily living*	*Sphincter management*	*Mobility*	*Executive function*	*Activities of daily living*	*Sphincter management*	*Mobility*	*Executive function*
Total assistance	23 (76.3%)	17 (56.7%)	21 (70%)	16 (53.3%)	15 (65.5%)	15 (65.2%)	17 (73.9%)	10 (43.5%)
Maximal assistance	3 (10%)	3 (10%)	1 (3.3%)	7 (23.3%)	3 (13%)	–	1 (4.3%)	8 (34.3%)
Moderate assistance	–	1 (3.3%)	1 (3.3%)	5 (16.7%)	–	–	1 (4.3%)	3 (13%)
Minimal assistance	1 (3.3%)	1 (3.3%)	2 (6.7%)	1 (3.3%)	4 (17.4%)	1 (4.3%)	1 (4.3%)	1 (4.3%)
Supervision	1 (3.3%)	1 (3.3%)	–	–	1 (4.3%)	1 (4.3%)	2 (8.7%)	1 (4.3%)
Modified Independence	1 (3.3%)	3 (10%)	4 (13.3%)	1 (3.3%)	–	2 (8.7%)	1 (4.3%)	–
Complete independence	1 (3.3%)	4 (13.3%)	1 (3.3%)	–	–	4 (17.4%)	–	–

Distribution of participants who emerged from the minimally conscious state according to their disability, as described by the *Disability Rating Scale*, and functional independence, as described by the *Barthel Index* and the *Functional Independence Measure*, 6 months after emergence.

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$p = 0.693$), with the majority of participants showing total dependence. Analogously, participants admitted in MCS+ had a median score in the *Functional Independence Measure* of 32 [21–61.5], while those admitted in MCS- had a median score of 27 [20–59]. In accordance with the *Barthel Index*, the analysis of the *Functional Independence Measure* showed that both groups had a comparable distribution of participants across stages of functional independence in activities of daily living ($X^2 = 4.64$; $p = 0.461$), sphincter management ($X^2 = 3.46$; $p = 0.749$), mobility ($X^2 = 2.54$; $p = 0.864$), and executive function ($X^2 = 3.08$; $p = 0.688$). Participants predominantly required total assistance in all four domains but were more likely to achieve complete independence in sphincter management (Table 1).

Discussion

This study investigated and compared the likelihood of emergence, disability and functional independence of individuals in MCS+ and MCS-. Our findings demonstrated that, in the follow-up period, individuals in MCS+ had a higher likelihood of emergence (all individuals in this state emerged, while only about half of the individuals in MCS- did) and shorter time from injury to emergence. However, all individuals who emerged exhibited comparably high disability and very poor functional independence at a 6-month follow-up, regardless of their state at admission.

The likelihood of emergence for individuals in MCS as a whole, as found in the follow-up period of our study, is consistent with the findings of previous research on the clinical progress of individuals in this state, which report highly variable odds, ranging from 33%[23] to 80%.[24] Although the demographic and clinical characteristics of the sample, such as age, time postinjury and the etiology of the injury, could explain the differences in the results, our findings suggest that a varying percentage of participants in MCS+ and MCS- in existing studies could also account for the discrepancies.[10,23–28] The likelihood of emergence in our study greatly surpasses the figures from the only existing examination of long-term behavioral recovery of individuals in MCS+ and MCS-, which reported the eventual emergence from MCS in only one of 15 individuals in MCS- and in two of seven individuals in MCS+.[29] The extended average length of time from injury to participation in this study, at 1018.6 days, could explain the limited likelihood of emergence in comparison with our study. However, there are contradictory reports on the prognostic value of time postinjury.[8] Though the other longitudinal study that has investigated the progression of individuals in MCS- and MCS+ included participants less than 2 months postinjury, potentially indicating a much higher likelihood of emergence, it only followed individuals until an average of 119 days postinjury, which did not allow for the detection of cases of late recovery of consciousness.[10]

While there is substantial evidence supporting the fact that UWS and MCS are undeniably different clinical entities,[26] our findings provide the first evidence that MCS+ and MCS- are also distinct clinical entities, at least in terms of neurobehavioral condition. The clearly distinguishable and superior progression of the neurobehavioral condition of individuals in MCS+ compared to individuals in MCS- in our study could be explained by the presence of a greater neurobiological support in the former group. Previous studies have shown that, compared to individuals in MCS+, individuals in MCS- evidence a reduced metabolism in the Broca's and Wernicke's regions, left premotor, left caudate, and post- and precentral cortices,[30] decreased fractional anisotropy in the white matter tracts connecting the thalamus and precuneus and posterior cingulate,[31] less connectivity between the thalamus and bilateral premotor cortices, as well as left temporal cortex,[5] and less connectivity in the left frontoparietal network, specifically between the left dorso-lateral prefrontal cortex and left temporo-occipital fusiform cortex,[6] which may involve differences in the language-related executive control network between groups of individuals.

The number of studies that investigate long-term disability and functional independence after emergence from MCS is scant, likely due to the short hospital and rehabilitation stays, and the lack of records of individuals after discharge. However, all of them have shown severe disabilities and very poor functional independence upon emergence[32,33] that persist months and even years after[23] and support the findings of our study in the *Disability Rating Scale*,[25] the *Barthel Index*,[34] and the *Functional Independence Measure*.[25] The less-than-optimal clinical condition of individuals who emerged from MCS in our study, as measured by the clinical instruments referenced, could also be partially attributed to the 6-month interval between emergence and the follow-up assessment, which might be inadequate to fully capture potential improvements in cognitive and motor functions these individuals could achieve. While longer follow-up periods may reveal some improvement in disability and functional independence,[25,34] the severity of deficits should be highlighted and taken into account in the quest for resources, environmental adaptation, and adjustments of expectations.

The absence of differences in the level of disability and functional independence between individuals admitted in MCS+ and in MCS- contradicts our initial hypothesis and presents a unique clinical finding. The assessment

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protocol of the study might have contributed to this outcome. The sensitivity of the clinical instruments used could have been insufficient to detect differences between the groups. It should be taken into account that all participants, regardless of their group, had severe disabilities and the majority of participants obtained similar scores on the clinical instruments, resulting in their predominant distribution within the lower or higher parts of the possible score range. Moreover, the follow-up period might not have been long enough to detect distinct clinical trajectories between groups. As previously mentioned, effects that occurred beyond the 6-month period post-emergence went undetected in our study. However, the comparable clinical progress of both groups might suggest that the recovery of consciousness and the recovery of functional independence are distinct processes. While being in either MCS+ or MCS- upon admission could be relevant for the likelihood of emergence, the clinical state at admission could not be relevant for functional recovery. The functional condition upon emergence could have a greater influence on future disability and functional independence. Consistent with this, the duration of post-traumatic amnesia[35,36] or the baseline score in the *Galveston Orientation and Amnesia Test*[37,38] after a head trauma has been found to have more predictive value than the duration of coma.[39]

The results of our study should be interpreted taking into account the following limitations. Firstly, although the number of participants was significantly higher than in previous studies, it may prevent unequivocal extrapolation of the findings. Secondly, all participants received adjusted physical therapy and multimodal stimulation within an inpatient neurorehabilitation program, which may not accurately reflect the circumstances of individuals from different countries or with varying conditions. Finally, as previously mentioned, the follow-up period may have overlooked clinical changes, such as improvements in the level of disability and functional independence, or a different time course of recovery in both groups, that could have occurred beyond that period. Future studies should examine larger samples from different centers and for a longer time to facilitate generalization and extension of results. Despite these limitations, this study provides preliminary evidence that the MCS+ and MCS- are clearly different states in terms of neurobehavioral progress, but not as much in long-term disability and functional independence.

Acknowledgments

The authors wish to thank the staff and patients of IRENEA for their support during the study.

Author Contributions

Roberto Llorens and Enrique Noé were responsible for the conceptualization of the study. Camilla Ippoliti, María Dolores Navarro, Carolina Colomer, and Joan Ferri participated in the data acquisition. Roberto Llorens, Enrique Noé, Anny Maza, and Sandra Goizueta contributed to the data curation and analysis. Roberto Llorens was responsible of funding acquisition. Roberto Llorens and Camilla Ippoliti participated in drafting the manuscript. All authors reviewed and edited the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Funding Information

This study was supported by Conselleria d'Innovació, Universitats, Ciència i Societat Digital of Generalitat Valenciana (CIDEXG/2022/15).

Data Availability Statement

Data are available for research purposes upon request to the corresponding author.

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