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Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury

--Manuscript Draft--

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Abstract:	Objective : Characterize the temporal profile of recovery of communication after severe brain injury. Design: Retrospective cohort study. Setting: Inpatient rehabilitation hospital. Participants : Patients with severe acquired brain injury and no evidence of communication on the Coma Recovery Scale-Revised (CRS-R). Main Outcome Measures: Time from injury to recovery of intentional communication (IC, inconsistent yes/no responses) and functional communication (FC, consistent and accurate yes/no responses) on the CRS-R Communication subscale. Results: 175 patients (Median [IQR]: 48 [27 – 61] years old, 105 males, 28 [21 – 38] days post-injury, 100 traumatic etiology) were included in the primary observation period of the first eight weeks of inpatient rehabilitation. Fifty-four (31%) patients did not recover IC or FC. Thirty (17%) patients recovered IC only (Median [IQR] days from injury to IC= 40 [34 – 54]), 72 (41%) patients recovered IC followed by FC (days from injury to FC= 50 [42 – 61]) and 19 (11%) patients recovered FC without first recovering IC (43 [32 - 63]). The patients who recovered neither IC nor FC within eight weeks of admission were admitted to rehabilitation later than those who recovered IC and/or FC ($p<0.01$). Sixteen patients who did not recover communication within eight weeks of admission to rehabilitation subsequently recovered FC prior to discharge. Conclusions: In patients with severe brain injury receiving inpatient rehabilitation, discernible yes-no responses emerged approximately six weeks after injury and became reliable one week later. Approximately one in three patients did not demonstrate IC or FC within eight weeks of admission to rehabilitation, although 33% of these individuals recovered communication prior to discharge. In total, 61% of patients recovered FC prior to discharge from rehabilitation.

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Dear Editorial Staff,

We are pleased to submit a revised version of our manuscript entitled, "Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury" (ARCHIVES-PMR-D-19-01194). We are grateful for the constructive criticisms of the reviewers and have addressed their concerns as outlined below.

The work presented here is original, has not been published and is not under review elsewhere. All authors contributed to the work and the research was conducted consistent with ethical guidelines for the conduct of research. There are no conflicts of interest affecting any authors.

Thank you for considering this manuscript.

Sincerely,

Géraldine Martens
Corresponding Author

We thank the reviewers for their constructive comments on our manuscript. Below, are each reviewers' comments, followed by our response in italics. If changes were made to the manuscript, we indicate the page numbers and provide the new text in quotes.

Reviewers' comments:

Reviewer #1: * This compact written brief report highlights an important topic in the treatment of DOC patients and their families. As far as I know this has never been done, so the authors make a strong contribution to the knowledge about the recovery processes of DOC patients.

1. I suppose it was the intent to write in a compact way. It's a pity that this results in a lack of information about topics that could be of interest, for instance the content of the rehab treatments. Especially, it can be important to know whether communication is part of the treatments, and if so, from what moment on.

The reviewer is correct that this manuscript was submitted for the Brief Report section of APMR and was therefore written compactly. The focus of our study was to establish time-points regarding communication recovery in a sample of patients with severe brain injury who lost communication abilities. Providing evidence for how the rehabilitation interventions affect the time to communication recovery is beyond the

scope of the study. We agree however that the inpatient DoC Program could be described and therefore added information in the Methods - Participants section. It now reads (page 7):

"All participants were admitted to a specialized DoC rehabilitation program that is based on a core battery of standardized assessment and systematic, evidence-based treatment approaches. Rehabilitation sessions include serial assessment of level of consciousness and, in conscious patients, identifying volitional movements that can be used to develop a system of communication. For patients who demonstrate the ability to volitionally control movements or to verbally respond to questions, treatment sessions are focused on establishing reliable communication and expressing basic needs."

2. Also I would like to have more information about the significant differences between the groups (lines 112-113, and in table 1). These differences seem to be important for understanding the recovery process, but I couldn't find the explanation.

Following the reviewer's suggestion, we added information regarding these differences in the Results section (page 9-10) and elaborated on the findings in the Discussion section (page 10-11). It now reads:

"After controlling for multiple comparisons, we found that patients in Group 1 (-IC-FC) were younger than Group 2 (+IC-FC), had longer acute length of stay than Groups 3 (+IC+FC) and 4 (-IC+FC) and longer rehab length of stay than Group 3 (+IC+FC). In addition, patients who recovered IC but not FC within eight weeks (Group 2: +IC-FC) had longer rehab lengths of stay than patients who recovered IC and then FC within eight weeks (Group 3: +IC+FC)."

"We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication."

3. I'm confused about the %numbers in the abstract. Firstly, the total amount of numbers in the result section of the abstract makes it rather difficult to extract the main message. Secondly, in line 26 the authors state that about 50% of the patients can be expected to communicate reliably during the first two months post-injury. Why not mentioning here the total number at the end of the rehab period? What is the rationale to restrict to two months after injury, if there is a substantially amount of patients (16, as far as I can see = 9%) who do recover FC after 8 weeks, but before discharge?

We agree that the findings in the abstract should be clarified. The primary aim of this study was to address recovery of communication during the 8-week period of the DoC program. Extending the primary observation period beyond the 8-week prescribed program would lead to a sample with varying lengths of stay, and therefore varying opportunities to recover communication. Some, but not all patients continue to receive inpatient rehabilitation, including standardized assessments, beyond the 8-week period. Because discharge from the DoC program and from the inpatient rehabilitation facility is not based on a standard length of stay or a systematic recovery criterion, such as achieving a specific level of function, but rather on external factors like insurance coverage, the data beyond the 8-week period is not a true

reflection of the potential to recover communication. Thus, we elected to report primary on the 8-week DoC program period because we were able to ensure that assessment during this time was standardized, systematic, and complete.

We have modified the results of the abstract (page 3-4) to read:

"175 patients (Median [IQR]: 48 [27 – 61] years old, 105 males, 28 [21 – 38] days post-injury, 100 traumatic etiology) were included in the primary observation period of the first eight weeks of inpatient rehabilitation. Fifty-four (31%) patients did not recover IC or FC. Thirty (17%) patients recovered IC only (Median [IQR] days from injury to IC= 40 [34 – 54]), 72 (41%) patients recovered IC followed by FC (days from injury to FC= 50 [42 – 61]) and 19 (11%) patients recovered FC without first recovering IC (43 [32 - 63]). The patients who recovered neither IC nor FC within eight weeks of admission were admitted to rehabilitation later than those who recovered IC and/or FC (p<0.01). Sixteen patients who did not recover communication within eight weeks of admission to rehabilitation subsequently recovered FC prior to discharge."

In addition, we now provide further rationale for using the 8-week observation period for the primary outcome in the Methods section (page 6). It now reads:

"The eight-week cut-off corresponds to the period of the inpatient DoC program during which patients receive standardized assessments and care, even though some patients continue to receive inpatient rehabilitation afterwards. However, the data beyond this period does not accurately reflect the potential to recover communication because of the varying lengths of stay."

4. The weblink in line 80 is incorrect. It should be www.projectredcap.org.

Thank you for pointing out this error. We have corrected the weblink.

5. I would like to know more about the patients that were not included. Especially the group '43 followed for fewer than eight weeks without recovery of FC' (line 105) triggers my attention. What happened to these patients? Why did they leave the rehab program, assuming that there was no recovery?

We agree that to generalize our findings across settings and patients it is important to understand why patients were excluded. Unfortunately, we do not systematically collect data on reasons for patient discharge from the DoC Program or from inpatient rehabilitation. It is likely that some patients recovered quickly and were discharged home, while others showed no or minimal recovery and were discharged to nursing facilities. Alternatively, our healthcare system is driven, in part, by insurance approvals, so some patients who were recovering may have been discharged due to a lack of insurance benefits. It is also possible that a clinical team discontinued CRS-R administration prior to the 8-week observation period.
To ensure that our study sample was not affected by the exclusion of this group of patients, we checked for significant differences between the excluded patients (n=43) and our final sample (n=175) in terms of gender, age, days between injury and admission, etiology and length of rehab stay. We now specify in the Results section (page 9) that this group does not significantly differ from our study sample:

"The 43 excluded patients did not significantly differ from the final study sample in terms of gender (p=0.8), age (p=0.93), days between injury to admission to rehabilitation (p=0.18) or etiology (p=0.76)."

6. Again, the section in which the results are presented is difficult to read. Now, the order in which the groups are presented is the opposite from the order in the abstract, what is a little bit confusing. Furthermore, the authors name groups (1-4, lines 108-110), but do not use these group names in the text just below that lines (lines 114-117), while in the figure, the group names are presented. I suggest to use the group names (1-4) as a standard.

We now present the results in the same order as the abstract and consistently specify group numbers and names throughout the manuscript.

7. Also in the discussion, the 8 weeks restriction has been used to position the main outcome (here 52% instead of about 50%, not very consistent). I'm afraid that in quick reading this article, readers will conclude that that's the total amount of patients who will recover FC, what is untrue, as I earlier said. If the authors want to stick to the eight week period, than I would suggest to write: "More than half (52%) .....post-injury, and another 9% recovered FC before discharge from rehab".

We agree with the reviewer and have modified the mentioned text (page 11) to highlight the total number of patients who recovered communication prior to discharge.

"More than half (n=91; 52%) of the patients in our sample recovered FC within eight weeks of rehabilitation admission, and another 16 (9% of the total sample) recovered FC before discharge from rehabilitation."

Reviewer #2: I have reviewed the manuscript titled "Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury" and feel that overall, the authors present a clearly written and organized manuscript. I feel that the article would benefit from the addition of a few details and elaboration of concepts presented in the introduction and discussion sections of the paper. Detailed comments are provided below.

Introduction

1. In general, the introduction section is a bit broad and would benefit from references to back up the authors statements. For example, the first two sentences may be considered general knowledge, but citations for these statements would be recommended.

We agree with the reviewer and have expanded and added references to the introduction. The excerpt now reads (page 5):

"Patients who sustain severe brain injury may experience prolonged disturbance in consciousness during which they are unable to follow commands or communicate [1]. Recovery of reliable communication is a highly anticipated milestone for both families and clinicians in related diseases states such as locked-in syndrome and stroke [2,3]."

1. Laureys, S., Owen, A. M. & Schiff, N. D. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 3, 537–546 (2004).
2. Krishnan, S. et al. Needs of Stroke Survivors as Perceived by Their Caregivers: A Scoping Review. Am. J. Phys. Med. Rehabil. 96, 487–505 (2017).
3. Lugo, Z., Pellas, F., Blandin, V., Laureys, S. & Gosseries, O. Assessment of needs, psychological impact and quality of life in families of patients with locked-in syndrome. Brain Inj. 31, 1590–1596 (2017).

2. Line 45 - the authors mention alternative studies that investigated retrospective communication in patients with prolonged DoC. Although the authors briefly state the potential flaws of the previous studies, they do not provide information about the findings of those studies. Very brief documentation of the results would be beneficial in the introduction so that the authors could discuss how their findings align with these other studies when commenting on study conclusions.

We now provide a summary of the literature cited in the instruction, it now reads:

"Two early studies investigated communication in patients with prolonged DoC and showed that most patients eventually (i.e., between four months and several years after injury) recover this behavior [4,5]. However, both studies included few patients and relied either on retrospective medical chart review [5] or on unvalidated, non-standardized methods [4] of identifying communication. A prospective study of 32 patients in DoC admitted to rehabilitation approximately five months post-injury used the Coma Recovery Scale-Revised (CRS-R [6], a standardized and validated assessment of behaviors associated with impaired consciousness) to show that eight patients emerged from the minimally conscious state (MCS) within one year of admission to rehabilitation. However, emergence from MCS can be achieved by recovering either functional object use or functional communication, and the results for recovery of communication were not reported separately [7]. Another multi-site study of patients with traumatic DoC admitted to rehabilitation approximately seven weeks post-injury found that 30% (n=29) recovered functional communication on the CRS-R within the following six weeks [8]."

4. Najenson, T., Sazbon, L., Fiselzon, J., Becker, E. & Schechter, I. Recovery of communicative functions after prolonged traumatic coma. Scandinavian Journal of Rehabilitation Medicine 10, 15–21 (1978).
5. Andrews, K. Recovery of patients after four months or more in the persistent vegetative state. BMJ 306, 1597–600 (1993).
6. Giacino, J. T., Kalmar, K. & Whyte, J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 85, 2020–2029 (2004).
7. Noé, E. et al. Behavioral recovery in disorders of consciousness: A prospective study with the Spanish version of the coma recovery scale-revised. Arch. Phys. Med. Rehabil. 93, 428-433.e12 (2012).
8. Giacino, J. T. et al. Behavioral Recovery and Early Decision Making in Patients with Prolonged Disturbance in Consciousness after Traumatic Brain Injury. J. Neurotrauma neu.2019.6429 (2019). doi:10.1089/neu.2019.6429

We further address the need for studies focused on caregiver perspectives on communication after TBI in the discussion section (page 11-12). It now reads:

"Even though there is no literature to support that our approach to assessment and treatment promotes recovery of communication, it seems that earlier rehabilitation may improve functional outcome. Future studies employing comparative effectiveness methods are needed to determine whether rehabilitation promotes or accelerates recovery of communication after severe brain injury and the optimal time to initiate therapy. It will also be important to identify the aspects of communication that are most valuable for families and patients. This has been studied in other disease-states such as locked-in syndrome and stroke, but not in DoC."

Methods

3. I assume based on the study title that inclusion criteria related to severe ABI (line 60)? Please specify how this was determined.

Data were obtained from a database of patients enrolled in a DoC program. The DoC program includes only patients with acquired brain injury. We have clarified this in the methods (page 7) which now reads:

"Inclusion criteria were: 1) acquired severe brain injury determined by medical chart review for a traumatic or non-traumatic neurological event leading to DoC…"

Discussion

4. Line 138: The authors state that individuals with less severe injuries may have had significantly shorter rehabilitation stays; however, it is possible that some individuals recovered based on the rehabilitation therapies that they received. Please consider commenting on how cognitive or communicative therapy may have influenced outcomes for some individuals in the cohort.

Unfortunately, there are currently no published studies that show the efficacy of cognitive or communication interventions in patients with DoC. Although it is possible that rehabilitation therapies contribute to recovery of communication, our study design prevents us from making such a conclusion. We now address this issue in the discussion (page 11) that now reads:

"Although it is possible that rehabilitation interventions contributed to recovery of communication in our study sample, the current study did not include patients who did not receive inpatient rehabilitation, and therefore was not designed to empirically answer this question. Even though there is no literature to support that our approach to assessment and treatment promotes recovery of communication, it seems that earlier rehabilitation may improve functional outcome 14. Future studies employing comparative effectiveness methods are needed to determine whether rehabilitation promotes or accelerates recovery of communication after severe brain injury and the optimal time to initiate therapy."

5. Line 155: As I finished reading the manuscript I found myself wondering what the results tell a clinician. It may be beneficial for the authors to comment on the clinical implications of these findings relative to rehabilitation assessment or treatment efforts. In other words, because we know that the majority of people may recover communication at some point, do we wait to provide therapy? Do we initiate therapy sooner? Does a particular therapy contribute to these outcomes more than others? Although this report is meant to be a brief description of findings, I am concerned that the application of these results are lacking for the readers.

The reviewer makes several good points regarding the clinical relevance of these findings. However, we are unable to recommend a specific rehabilitation approach to promote communication or that therapy be started earlier (or later) because our study only included patients in inpatient rehabilitation receiving the standard of care, and did not compare recovery of communication in patients receiving alternate treatments. Without such a control group, we are unable to definitively report that the rehabilitation received by the patients in this study contributed to recovery of communication. The primary aim of this study was to describe the temporal profile of recovering communication so that clinicians and families had realistic expectations of when this behavior emerges, which is critical for early decision-making, promoting autonomy and facilitating meaningful interactions. One key clinical message related to our findings is that clinicians should not withhold early rehabilitation in patients who are not communicating. Indeed, these patients, who present with severe injury and are often given a devastating prognosis may eventually recover this important milestone. We now further highlight the clinical applications of our findings and the implications for future research in the Discussion section. It now reads (page 12-13):

"Patients who were admitted to rehabilitation without any sign of communication following severe brain injury, went on to recover communication in 61% of cases overall. Patients with devastating injuries suggestive of a poor prognosis may achieve this highly relevant recovery milestone long after leaving the acute care setting. This finding has important implications for clinicians; referral to rehabilitation therapy should not be deferred and should be strongly encouraged, even when the initial clinical picture seems hopeless."

6. As mentioned earlier, the authors may wish to consider briefly triangulating their study results with the findings of the two previous publications to demonstrate what new information is added to the literature.

We agree with the reviewers and now link several of our findings with previous ones of the literature (see Discussion section page 10-11). It now reads:

"We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication. More than half (n=91; 52%) of the patients in our sample recovered FC within eight weeks of rehabilitation admission, and another 16 (9% of the total sample) recovered FC before discharge from rehabilitation. This time interval falls within the broad range reported by previous studies which showed that recovery can continue many months to years after injury."

Reviewer #3: It was a pleasure to read your study, titled "Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury." The objective of this study was to document the time to recovery of communication in persons with a disorder of consciousness. The authors measured communication response using the CRS-R over a period of at least 8 weeks during inpatient rehabilitation and up to time of discharge in secondary analyses. They authors reported that most (52%) recovery functional communication with a median 49 days postinjury, and a minority of patients who did not achieve functional communication by 8 weeks post-rehabilitation admission eventually did so.

This study had several strengths:

* The topic is important to families of persons with DoC, rehabilitation professionals who treat DoC patients, and brain injury researchers. As well, the topic is likely of interest to readers of Archives of PM&R.
* Although there is a growing body of literature on diagnostic accuracy between vegetative and minimally conscious states, and emergence from MCS, there is scant literature systematically documenting the timing of recovery of functional communication specifically. Ability to reliably communicate has obvious clinical implications.
* This study employed a large sample size relative to the literature with DoC patient samples.
* Study procedures were clearly described and the flow was logical and easy to follow from section to section.

The study also has some weaknesses. The major issues were as follows:

1. The authors should better communicate the impact of their study findings. They report results, but provide little discussion on how their findings compare with the existing literature on the topic, nor do the authors expand on the implications for early decision making and rehabilitation planning which was hinted at in their introduction.

We agree with the reviewers and now link several of our findings with previous ones of the literature (see Discussion section page 10-11). It now reads:

"We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication. More than half (n=91; 52%) of the patients in our sample recovered FC within eight weeks of rehabilitation admission, and another 16 (9% of the total sample) recovered FC before discharge from rehabilitation. This time interval falls within the broad range reported by previous studies which showed that recovery can continue many months to years after injury."

We also now provide some clinical implications in the Conclusion (page 13). It now reads:

"Patients who were admitted to rehabilitation without any sign of communication following severe brain injury, went on to recover communication in 61% of cases overall. Patients with devastating injuries suggestive of a poor prognosis may achieve this highly relevant recovery milestone long after leaving the acute care setting. This finding has important implications for clinicians; referral to rehabilitation therapy should not be deferred and should be strongly encouraged, even when the initial clinical picture seems hopeless."

2. The authors mention there were other studies on this topic albeit with limitations. The authors are encouraged to summarize those findings (which may inform their discussion).

We agree with the reviewer and have summarized these findings in the introduction. It now reads (page 5):

"Two early studies investigated communication in patients with prolonged DoC and showed that most patients eventually (i.e., between four months and several years after injury) recover this behavior. However, both studies included few patients and relied either on retrospective medical chart review or on unvalidated, non-standardized methods of identifying communication."

3. It is unclear whether their study sample were indeed persons with DoC, which the title and introduction suggests. There is no mention of DoC in the study inclusion criteria "page 4). If they did indeed intend to include only persons with DoC, the authors should describe how this determination was made. Although they may have failed to demonstrate functional communication at admission,

they could have demonstrated functional object use, but this information was not presented in the study.

Data were obtained from a database of patients enrolled in a DoC program. The DoC program includes only patients with acquired brain injury. We have clarified this in the methods (page 7) which now reads:

"Inclusion criteria were: 1) acquired severe brain injury determined by medical chart review for a traumatic or non-traumatic neurological event leading to DoC…"

We agree that some patients may have recovered functional object use however for the purpose of the study (i.e., describe the temporal profile of recovering communication) we focused on the communication subscale.

4. The use of different arbitrary time-based cutoffs (8 weeks; by discharge) was not well justified. Also wonder if survival analysis might be a better way to examine this outcome.

We now provide further rationale for using the 8-week observation period for the primary outcome in the Methods section (page 6). It now reads:

"The eight-week cut-off corresponds to the period of the inpatient DoC program during which patients receive standardized assessments and care, even though some patients continue to receive inpatient rehabilitation afterwards. However, the data beyond this period does not accurately reflect the potential to recover communication because of the varying lengths of stay."

We followed the reviewer's suggestion to perform a survival analysis, which returned the survival curve presented below (data up to 1-year post injury). We consulted a biostatistician to help us interpret these results. The biostatistician did not think a survival analysis was a good fit for these data. As illustrated in the figure, the curve is shifted to the left, largely because the data extend out to one-year post-injury and a few subjects had a very protracted time to recovery, then levels off. In addition, the rate of censored data (i.e., patients for whom the time to recovery of functional communication is unknown) is fairly high- 45%. Interpreting the results will require extensive explanation and may be confusing to readers. An alternative to the survival curve would be to simply provide the percentage of patients who recovered functional communication overall, and at specific time points. To that end, we have revised the text at the end of the Results section (page 10) to read:

"Overall, 52% (n=91) of patients recovered FC within eight weeks of admission to inpatient rehabilitation (i.e., primary endpoint), or within approximately seven weeks of injury. When we combined all of the

available data, including recoveries that occurred before and after the close of the eight-week observation period, 61% (n=107) of patients recovered FC, and did so within approximately 15 weeks of injury."

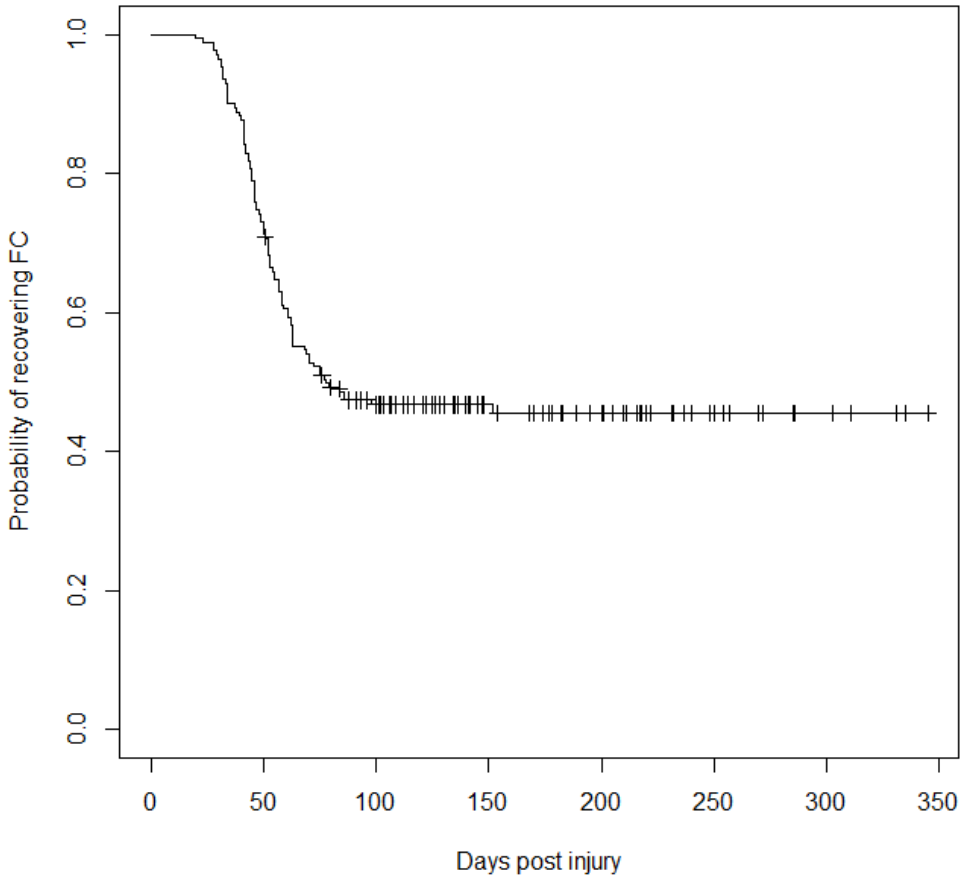

Figure 1: Survival curve (Kaplan-Meier method). Each event represents the recovery of FC. Censored data are indicated with vertical lines. FC=Functional Communication

5. The authors made several ad hoc group comparisons, and restate the results in the discussion, but provide no meaningful discussion about their findings.

Following the reviewer's suggestion, we elaborated on the findings in the Discussion sections. It now reads (page 10-11):

"We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger,

which contradicts with prior reports associating younger age with better outcome. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication."

Other minor points:

5. Clarify if the criteria "at least 16 years old" refers to time of injury, time of admission, time of study enrollment, or something else.

We have clarified at the criterion refers to age at admission to rehabilitation.

7. Table 1 is organized in an unusual manner. Typically, groups are represented in columns according to most style guides (AMA, APA, etc).

We have modified the table to present the groups in columns.

8. It is mentioned that the data were housed in an IRB-approved REDCap database, but it is not stated whether this study in particular was IRB-approved (or reviewed but determined to be exempt).

We have specified in the methods (page 6) that the study was approved as part of of the REDCap database. It now reads:

The study was approved by the local Institutional Review Board. Informed consent was not required because all data were retrospectively acquired from the medical record.

We thank the reviewers for their constructive comments on our manuscript. Below, are each reviewers' comments, followed by our response in italics. If changes were made to the manuscript, we indicate the page numbers and provide the new text in quotes.

Reviewers' comments:

Reviewer #1: * This compact written brief report highlights an important topic in the treatment of DOC patients and their families. As far as I know this has never been done, so the authors make a strong contribution to the knowledge about the recovery processes of DOC patients.

1. I suppose it was the intent to write in a compact way. It's a pity that this results in a lack of information about topics that could be of interest, for instance the content of the rehab treatments. Especially, it can be important to know whether communication is part of the treatments, and if so, from what moment on.

The reviewer is correct that this manuscript was submitted for the Brief Report section of APMR and was therefore written compactly. The focus of our study was to establish time-points regarding communication recovery in a sample of patients with severe brain injury who lost communication abilities. Providing evidence for how the rehabilitation interventions affect the time to communication recovery is beyond the scope of the study. We agree however that the inpatient DoC Program could be described and therefore added information in the Methods - Participants section. It now reads (page 7):

"All participants were admitted to a specialized DoC rehabilitation program that is based on a core battery of standardized assessment and systematic, evidence-based treatment approaches. Rehabilitation sessions include serial assessment of level of consciousness and, in conscious patients, identifying volitional movements that can be used to develop a system of communication. For patients who demonstrate the ability to volitionally control movements or to verbally respond to questions, treatment sessions are focused on establishing reliable communication and expressing basic needs."

2. Also I would like to have more information about the significant differences between the groups (lines 112-113, and in table 1). These differences seem to be important for understanding the recovery process, but I couldn't find the explanation.

Following the reviewer's suggestion, we added information regarding these differences in the Results section (page 9-10) and elaborated on the findings in the Discussion section (page 10-11). It now reads:

"After controlling for multiple comparisons, we found that patients in Group 1 (-IC-FC) were younger than Group 2 (+IC-FC), had longer acute length of stay than Groups 3 (+IC+FC) and 4 (-IC+FC) and longer rehab length of stay than Group 3 (+IC+FC). In addition, patients who recovered IC but not FC within eight weeks (Group 2: +IC-FC) had longer rehab lengths of stay than patients who recovered IC and then FC within eight weeks (Group 3: +IC+FC)."

"We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities.

Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication."

3. I'm confused about the %numbers in the abstract. Firstly, the total amount of numbers in the result section of the abstract makes it rather difficult to extract the main message. Secondly, in line 26 the authors state that about 50% of the patients can be expected to communicate reliably during the first two months post-injury. Why not mentioning here the total number at the end of the rehab period? What is the rationale to restrict to two months after injury, if there is a substantially amount of patients (16, as far as I can see = 9%) who do recover FC after 8 weeks, but before discharge?

We agree that the findings in the abstract should be clarified. The primary aim of this study was to address recovery of communication during the 8-week period of the DoC program. Extending the primary observation period beyond the 8-week prescribed program would lead to a sample with varying lengths of stay, and therefore varying opportunities to recover communication. Some, but not all patients continue to receive inpatient rehabilitation, including standardized assessments, beyond the 8-week period. Because discharge from the DoC program and from the inpatient rehabilitation facility is not based on a standard length of stay or a systematic recovery criterion, such as achieving a specific level of function, but rather on external factors like insurance coverage, the data beyond the 8-week period is not a true reflection of the potential to recover communication. Thus, we elected to report primary on the 8-week DoC program period because we were able to ensure that assessment during this time was standardized, systematic, and complete.

We have modified the results of the abstract (page 3-4) to read:

"175 patients (Median [IQR]: 48 [27 – 61] years old, 105 males, 28 [21 – 38] days post-injury, 100 traumatic etiology) were included in the primary observation period of the first eight weeks of inpatient rehabilitation. Fifty-four (31%) patients did not recover IC or FC. Thirty (17%) patients recovered IC only (Median [IQR] days from injury to IC= 40 [34 – 54]), 72 (41%) patients recovered IC followed by FC (days from injury to FC= 50 [42 – 61]) and 19 (11%) patients recovered FC without first recovering IC (43 [32 - 63]). The patients who recovered neither IC nor FC within eight weeks of admission were admitted to rehabilitation later than those who recovered IC and/or FC ($p<0.01$). Sixteen patients who did not recover communication within eight weeks of admission to rehabilitation subsequently recovered FC prior to discharge."

In addition, we now provide further rationale for using the 8-week observation period for the primary outcome in the Methods section (page 6). It now reads:

"The eight-week cut-off corresponds to the period of the inpatient DoC program during which patients receive standardized assessments and care, even though some patients continue to receive inpatient rehabilitation afterwards. However, the data beyond this period does not accurately reflect the potential to recover communication because of the varying lengths of stay."

4. The weblink in line 80 is incorrect. It should be www.projectredcap.org.

Thank you for pointing out this error. We have corrected the weblink.

5. I would like to know more about the patients that were not included. Especially the group '43 followed for fewer than eight weeks without recovery of FC' (line 105) triggers my attention. What happened to these patients? Why did they leave the rehab program, assuming that there was no recovery?

We agree that to generalize our findings across settings and patients it is important to understand why patients were excluded. Unfortunately, we do not systematically collect data on reasons for patient discharge from the DoC Program or from inpatient rehabilitation. It is likely that some patients recovered quickly and were discharged home, while others showed no or minimal recovery and were discharged to nursing facilities. Alternatively, our healthcare system is driven, in part, by insurance approvals, so some patients who were recovering may have been discharged due to a lack of insurance benefits. It is also possible that a clinical team discontinued CRS-R administration prior to the 8-week observation period.
To ensure that our study sample was not affected by the exclusion of this group of patients, we checked for significant differences between the excluded patients (n=43) and our final sample (n=175) in terms of gender, age, days between injury and admission, etiology and length of rehab stay. We now specify in the Results section (page 9) that this group does not significantly differ from our study sample:

"The 43 excluded patients did not significantly differ from the final study sample in terms of gender (p=0.8), age (p=0.93), days between injury to admission to rehabilitation (p=0.18) or etiology (p=0.76)."

6. Again, the section in which the results are presented is difficult to read. Now, the order in which the groups are presented is the opposite from the order in the abstract, what is a little bit confusing. Furthermore, the authors name groups (1-4, lines 108-110), but do not use these group names in the text just below that lines (lines 114-117), while in the figure, the group names are presented. I suggest to use the group names (1-4) as a standard.

We now present the results in the same order as the abstract and consistently specify group numbers and names throughout the manuscript.

7. Also in the discussion, the 8 weeks restriction has been used to position the main outcome (here 52% instead of about 50%, not very consistent). I'm afraid that in quick reading this article, readers will conclude that that's the total amount of patients who will recover FC, what is untrue, as I earlier said. If the authors want to stick to the eight week period, than I would suggest to write: "More than half (52%) .....post-injury, and another 9% recovered FC before discharge from rehab".

We agree with the reviewer and have modified the mentioned text (page 11) to highlight the total number of patients who recovered communication prior to discharge.

"More than half (n=91; 52%) of the patients in our sample recovered FC within eight weeks of rehabilitation admission, and another 16 (9% of the total sample) recovered FC before discharge from rehabilitation."

Reviewer #2: I have reviewed the manuscript titled "Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury" and feel that overall, the authors present a clearly written and organized manuscript. I feel that the article would benefit from the addition of a few details and elaboration of concepts presented in the introduction and discussion sections of the paper. Detailed comments are provided below.

Introduction

1. In general, the introduction section is a bit broad and would benefit from references to back up the authors statements. For example, the first two sentences may be considered general knowledge, but citations for these statements would be recommended.

We agree with the reviewer and have expanded and added references to the introduction. The excerpt now reads (page 5):

"Patients who sustain severe brain injury may experience prolonged disturbance in consciousness during which they are unable to follow commands or communicate [1]. Recovery of reliable communication is a highly anticipated milestone for both families and clinicians in related diseases states such as locked-in syndrome and stroke [2,3]."

1. Laureys, S., Owen, A. M. & Schiff, N. D. Brain function in coma, vegetative state, and related disorders. Lancet Neurol 3, 537–546 (2004).
2. Krishnan, S. et al. Needs of Stroke Survivors as Perceived by Their Caregivers: A Scoping Review. Am. J. Phys. Med. Rehabil. 96, 487–505 (2017).
3. Lugo, Z., Pellas, F., Blandin, V., Laureys, S. & Gosseries, O. Assessment of needs, psychological impact and quality of life in families of patients with locked-in syndrome. Brain Inj. 31, 1590–1596 (2017).

2. Line 45 - the authors mention alternative studies that investigated retrospective communication in patients with prolonged DoC. Although the authors briefly state the potential flaws of the previous studies, they do not provide information about the findings of those studies. Very brief documentation of the results would be beneficial in the introduction so that the authors could discuss how their findings align with these other studies when commenting on study conclusions.

We now provide a summary of the literature cited in the instruction, it now reads:

"Two early studies investigated communication in patients with prolonged DoC and showed that most patients eventually (i.e., between four months and several years after injury) recover this behavior [4,5]. However, both studies included few patients and relied either on retrospective medical chart review [5] or on unvalidated, non-standardized methods [4] of identifying communication. A prospective study of 32 patients in DoC admitted to rehabilitation approximately five months post-injury used the Coma Recovery Scale-Revised (CRS-R [6], a standardized and validated assessment of behaviors associated with impaired consciousness) to show that eight patients emerged from the minimally conscious state (MCS) within one year of admission to rehabilitation. However, emergence from MCS can be achieved by recovering either functional object use or functional communication, and the results for recovery of communication were not reported separately [7]. Another multi-site study of patients with traumatic DoC admitted to rehabilitation approximately seven weeks post-injury found that 30% (n=29) recovered functional communication on the CRS-R within the following six weeks [8]."

4. Najenson, T., Sazbon, L., Fiselzon, J., Becker, E. & Schechter, I. Recovery of communicative functions after prolonged traumatic coma. Scandinavian Journal of Rehabilitation Medicine 10, 15–21 (1978).
5. Andrews, K. Recovery of patients after four months or more in the persistent vegetative state. BMJ 306, 1597–600 (1993).
6. Giacino, J. T., Kalmar, K. & Whyte, J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil 85, 2020–2029 (2004).
7. Noé, E. et al. Behavioral recovery in disorders of consciousness: A prospective study with the Spanish version of the coma recovery scale-revised. Arch. Phys. Med. Rehabil. 93, 428-433.e12 (2012).

8. Giacino, J. T. et al. Behavioral Recovery and Early Decision Making in Patients with Prolonged Disturbance in Consciousness after Traumatic Brain Injury. J. Neurotrauma neu.2019.6429 (2019). doi:10.1089/neu.2019.6429

We further address the need for studies focused on caregiver perspectives on communication after TBI in the discussion section (page 11-12). It now reads:

"Even though there is no literature to support that our approach to assessment and treatment promotes recovery of communication, it seems that earlier rehabilitation may improve functional outcome. Future studies employing comparative effectiveness methods are needed to determine whether rehabilitation promotes or accelerates recovery of communication after severe brain injury and the optimal time to initiate therapy. It will also be important to identify the aspects of communication that are most valuable for families and patients. This has been studied in other disease-states such as locked-in syndrome and stroke, but not in DoC."

Methods

3. I assume based on the study title that inclusion criteria related to severe ABI (line 60)? Please specify how this was determined.

Data were obtained from a database of patients enrolled in a DoC program. The DoC program includes only patients with acquired brain injury. We have clarified this in the methods (page 7) which now reads:

"Inclusion criteria were: 1) acquired severe brain injury determined by medical chart review for a traumatic or non-traumatic neurological event leading to DoC…"

Discussion

4. Line 138: The authors state that individuals with less severe injuries may have had significantly shorter rehabilitation stays; however, it is possible that some individuals recovered based on the rehabilitation therapies that they received. Please consider commenting on how cognitive or communicative therapy may have influenced outcomes for some individuals in the cohort.

Unfortunately, there are currently no published studies that show the efficacy of cognitive or communication interventions in patients with DoC. Although it is possible that rehabilitation therapies contribute to recovery of communication, our study design prevents us from making such a conclusion. We now address this issue in the discussion (page 11) that now reads:

"Although it is possible that rehabilitation interventions contributed to recovery of communication in our study sample, the current study did not include patients who did not receive inpatient rehabilitation, and therefore was not designed to empirically answer this question. Even though there is no literature to support that our approach to assessment and treatment promotes recovery of communication, it seems that earlier rehabilitation may improve functional outcome 14. Future studies employing comparative effectiveness methods are needed to determine whether rehabilitation promotes or accelerates recovery of communication after severe brain injury and the optimal time to initiate therapy."

5. Line 155: As I finished reading the manuscript I found myself wondering what the results tell a clinician. It may be beneficial for the authors to comment on the clinical implications of these findings relative to rehabilitation assessment or treatment efforts. In other words, because we know that the majority of people may recover communication at some point, do we wait to provide therapy? Do we initiate therapy

sooner? Does a particular therapy contribute to these outcomes more than others? Although this report is meant to be a brief description of findings, I am concerned that the application of these results are lacking for the readers.

The reviewer makes several good points regarding the clinical relevance of these findings. However, we are unable to recommend a specific rehabilitation approach to promote communication or that therapy be started earlier (or later) because our study only included patients in inpatient rehabilitation receiving the standard of care, and did not compare recovery of communication in patients receiving alternate treatments. Without such a control group, we are unable to definitively report that the rehabilitation received by the patients in this study contributed to recovery of communication. The primary aim of this study was to describe the temporal profile of recovering communication so that clinicians and families had realistic expectations of when this behavior emerges, which is critical for early decision-making, promoting autonomy and facilitating meaningful interactions. One key clinical message related to our findings is that clinicians should not withhold early rehabilitation in patients who are not communicating. Indeed, these patients, who present with severe injury and are often given a devastating prognosis may eventually recover this important milestone. We now further highlight the clinical applications of our findings and the implications for future research in the Discussion section. It now reads (page 12-13):

"Patients who were admitted to rehabilitation without any sign of communication following severe brain injury, went on to recover communication in 61% of cases overall. Patients with devastating injuries suggestive of a poor prognosis may achieve this highly relevant recovery milestone long after leaving the acute care setting. This finding has important implications for clinicians; referral to rehabilitation therapy should not be deferred and should be strongly encouraged, even when the initial clinical picture seems hopeless."

6. As mentioned earlier, the authors may wish to consider briefly triangulating their study results with the findings of the two previous publications to demonstrate what new information is added to the literature.

We agree with the reviewers and now link several of our findings with previous ones of the literature (see Discussion section page 10-11). It now reads:

"We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication. More than half (n=91; 52%) of the patients in our sample recovered FC within eight weeks of rehabilitation admission, and another 16 (9% of the total sample) recovered FC before discharge from rehabilitation. This time interval falls within the broad range reported by previous studies which showed that recovery can continue many months to years after injury."

Reviewer #3: It was a pleasure to read your study, titled "Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury." The objective of this study was

to document the time to recovery of communication in persons with a disorder of consciousness. The authors measured communication response using the CRS-R over a period of at least 8 weeks during inpatient rehabilitation and up to time of discharge in secondary analyses. They authors reported that most (52%) recovery functional communication with a median 49 days postinjury, and a minority of patients who did not achieve functional communication by 8 weeks post-rehabilitation admission eventually did so.

This study had several strengths:

* The topic is important to families of persons with DoC, rehabilitation professionals who treat DoC patients, and brain injury researchers. As well, the topic is likely of interest to readers of Archives of PM&R.
* Although there is a growing body of literature on diagnostic accuracy between vegetative and minimally conscious states, and emergence from MCS, there is scant literature systematically documenting the timing of recovery of functional communication specifically. Ability to reliably communicate has obvious clinical implications.
* This study employed a large sample size relative to the literature with DoC patient samples.
* Study procedures were clearly described and the flow was logical and easy to follow from section to section.

The study also has some weaknesses. The major issues were as follows:

1. The authors should better communicate the impact of their study findings. They report results, but provide little discussion on how their findings compare with the existing literature on the topic, nor do the authors expand on the implications for early decision making and rehabilitation planning which was hinted at in their introduction.

We agree with the reviewers and now link several of our findings with previous ones of the literature (see Discussion section page 10-11). It now reads:

"We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication. More than half (n=91; 52%) of the patients in our sample recovered FC within eight weeks of rehabilitation admission, and another 16 (9% of the total sample) recovered FC before discharge from rehabilitation. This time interval falls within the broad range reported by previous studies which showed that recovery can continue many months to years after injury."

We also now provide some clinical implications in the Conclusion (page 13). It now reads:

"Patients who were admitted to rehabilitation without any sign of communication following severe brain injury, went on to recover communication in 61% of cases overall. Patients with devastating injuries suggestive of a poor prognosis may achieve this highly relevant recovery milestone long after leaving the acute care setting. This finding has important implications for clinicians; referral to rehabilitation therapy

should not be deferred and should be strongly encouraged, even when the initial clinical picture seems hopeless."

2. The authors mention there were other studies on this topic albeit with limitations. The authors are encouraged to summarize those findings (which may inform their discussion).

We agree with the reviewer and have summarized these findings in the introduction. It now reads (page 5):

"Two early studies investigated communication in patients with prolonged DoC and showed that most patients eventually (i.e., between four months and several years after injury) recover this behavior. However, both studies included few patients and relied either on retrospective medical chart review or on unvalidated, non-standardized methods of identifying communication."

3. It is unclear whether their study sample were indeed persons with DoC, which the title and introduction suggests. There is no mention of DoC in the study inclusion criteria "page 4). If they did indeed intend to include only persons with DoC, the authors should describe how this determination was made. Although they may have failed to demonstrate functional communication at admission, they could have demonstrated functional object use, but this information was not presented in the study.

Data were obtained from a database of patients enrolled in a DoC program. The DoC program includes only patients with acquired brain injury. We have clarified this in the methods (page 7) which now reads:

"Inclusion criteria were: 1) acquired severe brain injury determined by medical chart review for a traumatic or non-traumatic neurological event leading to DoC…"

We agree that some patients may have recovered functional object use however for the purpose of the study (i.e., describe the temporal profile of recovering communication) we focused on the communication subscale.

4. The use of different arbitrary time-based cutoffs (8 weeks; by discharge) was not well justified. Also wonder if survival analysis might be a better way to examine this outcome.

We now provide further rationale for using the 8-week observation period for the primary outcome in the Methods section (page 6). It now reads:

"The eight-week cut-off corresponds to the period of the inpatient DoC program during which patients receive standardized assessments and care, even though some patients continue to receive inpatient rehabilitation afterwards. However, the data beyond this period does not accurately reflect the potential to recover communication because of the varying lengths of stay."

We followed the reviewer's suggestion to perform a survival analysis, which returned the survival curve presented below (data up to 1-year post injury). We consulted a biostatistician to help us interpret these results. The biostatistician did not think a survival analysis was a good fit for these data. As illustrated in the figure, the curve is shifted to the left, largely because the data extend out to one-year post-injury and a few subjects had a very protracted time to recovery, then levels off. In addition, the rate of censored data

(i.e., patients for whom the time to recovery of functional communication is unknown) is fairly high- 45%. Interpreting the results will require extensive explanation and may be confusing to readers. An alternative to the survival curve would be to simply provide the percentage of patients who recovered functional communication overall, and at specific time points. To that end, we have revised the text at the end of the Results section (page 10) to read:

"Overall, 52% (n=91) of patients recovered FC within eight weeks of admission to inpatient rehabilitation (i.e., primary endpoint), or within approximately seven weeks of injury. When we combined all of the available data, including recoveries that occurred before and after the close of the eight-week observation period, 61% (n=107) of patients recovered FC, and did so within approximately 15 weeks of injury."

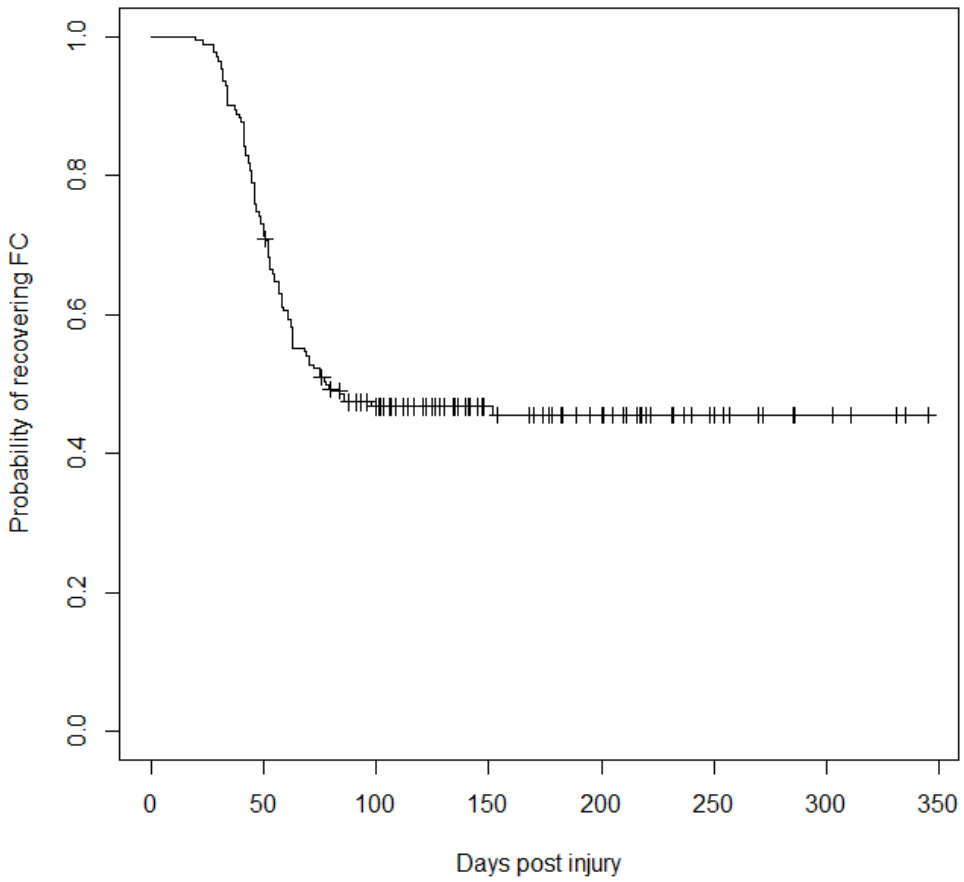

Figure 1: Survival curve (Kaplan-Meier method). Each event represents the recovery of FC. Censored data are indicated with vertical lines. FC=Functional Communication

5. The authors made several ad hoc group comparisons, and restate the results in the discussion, but provide no meaningful discussion about their findings.

Following the reviewer's suggestion, we elaborated on the findings in the Discussion sections. It now reads (page 10-11):

"We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication."

Other minor points:

5. Clarify if the criteria "at least 16 years old" refers to time of injury, time of admission, time of study enrollment, or something else.

We have clarified at the criterion refers to age at admission to rehabilitation.

7. Table 1 is organized in an unusual manner. Typically, groups are represented in columns according to most style guides (AMA, APA, etc).

We have modified the table to present the groups in columns.

8. It is mentioned that the data were housed in an IRB-approved REDCap database, but it is not stated whether this study in particular was IRB-approved (or reviewed but determined to be exempt).

We have specified in the methods (page 6) that the study was approved as part of of the REDCap database. It now reads:

The study was approved by the local Institutional Review Board. Informed consent was not required because all data were retrospectively acquired from the medical record.

Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury

Communication recovery after brain injury

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Figures: 1

Tables: 1

Highlights

- Recovery of communication after severe acquired brain injury was investigated in an inpatient rehabilitation setting
- Half of patients recover functional communication within 7 weeks post injury
- Referral to rehabilitation in severe acute cases should be encouraged as late recovery of communication is possible

Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury

Abstract

Objective: Characterize the temporal profile of recovery of communication after severe brain injury.

Design: Retrospective cohort study.

Setting: Inpatient rehabilitation hospital.

Participants: Patients with severe acquired brain injury and no evidence of communication on the Coma Recovery Scale-Revised (CRS-R).

Main Outcome Measures: Time from injury to recovery of intentional communication (IC, inconsistent yes/no responses) and functional communication (FC, consistent and accurate yes/no responses) on the CRS-R Communication subscale.

Results: 175 patients (Median [IQR]: 48 [27 – 61] years old, 105 males, 28 [21 – 38] days post-injury, 100 traumatic etiology) were included in the primary observation period of the first eight weeks of inpatient rehabilitation. Fifty-four (31%) patients did not recover IC or FC. Thirty (17%) patients recovered IC only (Median [IQR] days from injury to IC= 40 [34 – 54]), 72 (41%) patients recovered IC followed by FC (days from injury to FC= 50 [42 – 61]) and 19 (11%) patients recovered FC without first recovering IC (43 [32 - 63]). The patients who recovered neither IC nor FC within eight weeks of admission were admitted to rehabilitation later than those who recovered IC and/or FC

($p<0.01$). Sixteen patients who did not recover communication within eight weeks of admission to rehabilitation subsequently recovered FC prior to discharge.

Conclusions: In patients with severe brain injury receiving inpatient rehabilitation, discernible yes-no responses emerged approximately six weeks after injury and became reliable one week later. Approximately one in three patients did not demonstrate IC or FC within eight weeks of admission to rehabilitation, although 33% of these individuals recovered communication prior to discharge. In total, 61% of patients recovered FC prior to discharge from rehabilitation.

Abbreviations

CRS-R: Coma Recovery Scale-Revised

DoC: Disorders of Consciousness

FC: Functional Communication

IC: Intentional Communication

IQR: Interquartile Range

Introduction

Patients who sustain severe brain injury may experience prolonged disturbance in consciousness during which they are unable to follow commands or communicate [1]. Recovery of reliable communication is a highly anticipated milestone for both families and clinicians in related diseases states such as locked-in syndrome and stroke [2,3]. The ability to answer questions and express needs are pre-requisites for autonomous decision-making and meaningful social interaction. However, the temporal profile of recovery of communication in patients with disorders of consciousness (DoC) after severe brain injury is not known. Two early studies investigated communication in patients with prolonged DoC and showed that most patients eventually (i.e., between four months and several years after injury) recover this behavior [4,5]. However, both studies included few patients and relied either on retrospective medical chart review [5] or on unvalidated, non-standardized methods [4] of identifying communication. A prospective study of 32 patients in DoC admitted to rehabilitation approximately five

months post-injury used the Coma Recovery Scale-Revised (CRS-R [6], a standardized and validated assessment of behaviors associated with impaired consciousness) to show that eight patients emerged from the minimally conscious state (MCS) within one year of admission to rehabilitation. However, emergence from MCS can be achieved by recovering either functional object use or functional communication, and the results for recovery of communication were not reported separately [7]. Another multi-site study of patients with traumatic DoC admitted to rehabilitation approximately seven weeks post-injury found that 30% (n=29) recovered functional communication on the CRS-R within the following six weeks [8]. Providing clinicians and caregivers with more precise information concerning the time-course to recovery of communication in a larger sample may assist with early decision-making about the need for legal guardianship and promote rehabilitation planning.

Methods

The study was approved by the local Institutional Review Board. Informed consent was not required because all data were retrospectively acquired from the medical record. In this retrospective observational study, we identified patients with a severe brain injury who were admitted to an inpatient rehabilitation facility without any evidence of communication on the CRS-R. To determine the time-course to recovery of communication, we evaluated patients using the CRS-R communication subscale over a period of eight weeks following admission to a specialized inpatient DoC program. The eight-week cut-off corresponds to the period of the inpatient DoC program during which patients receive standardized assessments and care, even though some patients continue to receive inpatient rehabilitation afterwards. However,

the data beyond this period does not accurately reflect the potential to recover communication because of the varying lengths of stay.

Participants

Inclusion criteria were: 1) acquired severe brain injury determined by medical chart review for a traumatic or non-traumatic neurological event leading to DoC ; 2) at least 16 years old at admission; 3) admitted to rehabilitation with no evidence of communication on initial CRS-R administration 4) at least three valid CRS-R assessments within two-weeks of rehabilitation admission; 5) at least an eight-week rehabilitation length of stay, or recovery of functional communication prior to the eighth week. All participants were admitted to a specialized DoC rehabilitation program that is based on a core battery of standardized assessment and systematic, evidence-based treatment approaches. Rehabilitation sessions include serial assessment of level of consciousness and, in conscious patients, identifying volitional movements that can be used to develop a system of communication. For patients who demonstrate the ability to volitionally control movements or to verbally respond to questions, treatment sessions are focused on establishing reliable communication and expressing basic needs.

Measures

The CRS-R is a standardized neurobehavioral assessment measure designed to monitor recovery after severe brain injury across multiple domains of function.[6] The communication subscale includes three items organized by cognitive complexity. Functional communication (FC), defined as accurate responses to six consecutive "yes/no" questions concerning situational orientation, is the most difficult item on the

CRS-R[9], 2) Intentional communication (IC) is scored when there are clearly-discernible yes-no responses to at least two of six situational orientation questions (regardless of accuracy) and 3) No communication (None) is scored when there are no discernible verbal or gestural yes-no responses at any time.

Procedures

We analyzed demographic and clinical data acquired from 323 patients admitted to an inpatient DoC rehabilitation program. Data were housed in an Institutional Review Board approved REDCap database (www.projectredcap.org)[10]. The CRS-R was administered twice weekly by trained clinicians. Patients who met the inclusion criteria were divided into four groups based on the level of communication observed during the first eight weeks of the rehabilitation course: 1) no communication (Group 1: -IC-FC), 2) recovered IC but not FC (Group 2: +IC-FC), 3) recovered IC followed by FC (Group 3: +IC +FC) and 4) recovered FC without prior evidence of IC (Group 4: -IC+FC). For groups 2-4, the time to recovery of IC or FC was defined as the length of time from injury to the first instance of communicative behavior on the CRS-R.

In a secondary analysis, we explored the time to recovery of IC and FC in patients who recovered either of these behaviors after week 8 but before rehabilitation discharge. For this analysis, communication status was also determined using scores on the CRS-R communication subscale.

Statistical Analysis

We used descriptive statistics (medians, interquartile ranges [IQR]) to summarize demographic and clinical characteristics. Non-parametric analyses (Kruskal-Wallis

Rank-sum Test, Chi-squared Test, Fisher's Exact Test, R 3.5.3 5 (R Core Team, Austria)[11] were used to compare groups. Post-hoc pairwise comparisons of the four communication groups were conducted using Wilcoxon Rank-sum and Fisher's Test. Bonferroni corrections were applied to adjust for multiple comparisons (corrected significance $p<0.01$).

Results

Of 323 patients (Median [IQR] days post-injury: (27 [19 – 36]) in the database admitted between June 2012 and August 2017, 148 (46%) did not meet inclusion criteria (73 admitted with IC or FC, 43 followed for fewer than eight weeks without recovery of FC, 26 did not complete at least three consecutive valid assessments and six were not assessed within the eight-week observation period). The 43 excluded patients did not significantly differ from the final study sample in terms of gender ($p=0.8$), age ($p=0.93$), days between injury to admission to rehabilitation ($p=0.18$) or etiology ($p=0.76$). Among the remaining 175 patients, 54 (31%) did not recover IC or FC within eight weeks of admission (Group 1: -IC-FC). Thirty (17%) recovered IC, but not FC (Group 2: +IC-FC); 72 (41%) recovered IC before FC (Group 3: +IC+FC), and 19 (11%) recovered FC without prior evidence of IC (Group 4: -IC+FC) (see Figure 1). Demographic and clinical characteristics, time to recovery of IC and FC and post-hoc pairwise comparisons are presented in Table 1. Briefly, gender; age; time from injury to rehabilitation admission and etiology differed significantly between the groups ($p<0.05$). Most notably, the Group 1 (-IC-FC) was admitted to rehabilitation significantly later post-injury than the two groups that recovered FC (Groups 3: +IC+FC and 4: -IC+FC). The Group 3 (+IC+FC), comprising the largest number of subjects, recovered IC within a median [IQR] of 37 days [32-47] post-injury, and FC within 50

days [42-61] post-injury. This group also had the shortest length of stay of the four groups. After controlling for multiple comparisons, we found that patients in Group 1 (-IC-FC) were younger than Group 2 (+IC-FC), had longer acute length of stay than Groups 3 (+IC+FC) and 4 (-IC+FC) and longer rehab length of stay than Group 3 (+IC+FC). In addition, patients who recovered IC but not FC within eight weeks (Group 2: +IC-FC) had longer rehab lengths of stay than patients who recovered IC and then FC within eight weeks (Group 3: +IC+FC).

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Secondary analyses were performed on 75 patients who did not recover FC by the end of the eight-week observation period (49 patients who did not recover IC or FC and 26 who recovered IC but not FC). Among these 75 patients, 16 (21%) recovered FC within 15 [13 – 19] weeks; nine (12%) recovered only IC within 16 [13 – 18] weeks and 50 (67%) recovered neither IC nor FC by discharge.

Overall, 52% (n=91) of patients recovered FC within eight weeks of admission to inpatient rehabilitation (i.e., primary endpoint), or within approximately seven weeks of injury. When we combined all of the available data, including recoveries that occurred before and after the close of the eight-week observation period, 61% (n=107) of patients recovered FC, and did so within approximately 15 weeks of injury.

INSERT FIGURE 1 AROUND HERE

Discussion

In this retrospective study, we used CRS-R assessments to determine the time-course of emergence of communication in patients with severe brain injury. We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not [7]. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome [12]. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication. More than half (n=91; 52%) of the patients in our sample recovered FC within eight weeks of rehabilitation admission, and another 16 (9% of the total sample) recovered FC before discharge from rehabilitation. This time interval falls within the broad range reported by previous studies which showed that recovery can continue many months to years after injury[7,8,13]. Most patients recovered IC first followed by FC. The time between recovery of the first sign of communication and reliable yes-no responses was approximately 10 days, suggesting that IC may be a harbinger of FC. Among those who failed to recover IC or FC within the eight-week observation window, a third

recovered IC or FC. Although it is possible that rehabilitation interventions contributed to recovery of communication in our study sample, the current study did not include patients who did not receive inpatient rehabilitation, and therefore was not designed to empirically answer this question. Even though there is no literature to support that our approach to assessment and treatment promotes recovery of communication, it seems that earlier rehabilitation may improve functional outcome [14]. Future studies employing comparative effectiveness methods are needed to determine whether rehabilitation promotes or accelerates recovery of communication after severe brain injury and the optimal time to initiate therapy. It will also be important to identify the aspects of communication that are most valuable for families and patients. This has been studied in other disease-states such as locked-in syndrome and stroke [2,3,15,16], but not in DoC.

Study limitations

This study has some important limitations to consider. First, our sample was comprised entirely of patients admitted to inpatient rehabilitation. Thus, our subjects may have had more favorable prognoses than patients who did not receive authorization for admission. That said, all were severely injured as none were able to communicate on admission. Our sample also did not include acutely-hospitalized patients, some of whom would be expected to experience earlier recovery of communication, or patients who recovered communication after discharge from rehabilitation. Regarding the latter group, there is evidence that as many as 36% of patients admitted to rehabilitation unable to follow commands recover communication as late as two to five years after injury[17]. Finally, our operational definitions of intentional and functional communication were based on the CRS-R Communication

subscale, which relies on situational orientation questions. Other definitional criteria may have produced different results[13]. Nonetheless, the findings from this study provide inpatient rehabilitation clinicians with parameters for recovery of communication, a highly-valued outcome in the eyes of caregivers.

Conclusion

Patients who were admitted to rehabilitation without any sign of communication following severe brain injury, went on to recover communication in 61% of cases overall. Patients with devastating injuries suggestive of a poor prognosis may achieve this highly relevant recovery milestone long after leaving the acute care setting. This finding has important implications for clinicians; referral to rehabilitation therapy should not be deferred and should be strongly encouraged, even when the initial clinical picture seems hopeless.

References

1. Laureys, S., Owen, A. M. & Schiff, N. D. Brain function in coma, vegetative state, and related disorders. *Lancet Neurol* **3**, 537–546 (2004).

2. Krishnan, S. *et al.* Needs of Stroke Survivors as Perceived by Their Caregivers: A Scoping Review. *Am. J. Phys. Med. Rehabil.* **96**, 487–505 (2017).

3. Lugo, Z., Pellas, F., Blandin, V., Laureys, S. & Gosseries, O. Assessment of needs, psychological impact and quality of life in families of patients with locked-in syndrome. *Brain Inj.* **31**, 1590–1596 (2017).

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5. Andrews, K. Recovery of patients after four months or more in the persistent vegetative state. *BMJ* **306**, 1597–600 (1993).

6. Giacino, J. T., Kalmar, K. & Whyte, J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* **85**, 2020–2029 (2004).

7. Noé, E. *et al.* Behavioral recovery in disorders of consciousness: A prospective study with the Spanish version of the coma recovery scale-revised. *Arch. Phys. Med. Rehabil.* **93**, 428-433.e12 (2012).

8. Giacino, J. T. *et al.* Behavioral Recovery and Early Decision Making in Patients with Prolonged Disturbance in Consciousness after Traumatic Brain Injury. *J. Neurotrauma* neu.2019.6429 (2019). doi:10.1089/neu.2019.6429

9. La Porta, F. *et al.* Can We Scientifically and Reliably Measure the Level of Consciousness in

Vegetative and Minimally Conscious States? Rasch Analysis of the Coma Recovery Scale-Revised. *Arch. Phys. Med. Rehabil.* **94**, 527-535.e1 (2013).

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11. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. (2008).

12. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (2). *N Engl J Med* **330**, 1572–1579 (1994).

13. Nakase-Richardson, R., Yablon, S. A., Sherer, M., Nick, T. G. & Evans, C. C. Emergence from minimally conscious state: Insights from evaluation of posttraumatic confusion. *Neurology* **73**, 1120–1126 (2009).

14. Königs, M., Beurskens, E. A., Snoep, L., Scherder, E. J. & Oosterlaan, J. Effects of Timing and Intensity of Neurorehabilitation on Functional Outcome After Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *Arch. Phys. Med. Rehabil.* **99**, 1149-1159.e1 (2018).

15. Wallace, T. & Bradshaw, A. Technologies and strategies for people with communication problems following brain injury or stroke. *NeuroRehabilitation* **28**, 199–209 (2011).

16. Bucki, B., Spitz, E. & Baumann, M. Emotional and social repercussions of stroke on patient-family caregiver dyads: Analysis of diverging attitudes and profiles of the differing dyads. *PLoS One* **14**, e0215425 (2019).

17. Whyte, J. *et al.* Functional Outcomes in Traumatic Disorders of Consciousness: 5-Year Outcomes From the National Institute on Disability and Rehabilitation Research Traumatic Brain Injury Model Systems. *Arch. Phys. Med. Rehabil.* **94**, 1855–1860 (2013).

Figure 1: Timeline of the recovery of communication after injury. Days are reported using medians. Group 1 (-IC-FC): Patients who did not recover communication within the eight weeks primary observation period; Group 2 (+IC-FC): Patients who recovered IC but not FC within eight weeks; Group 3 (+IC+FC): Patients who recovered IC and then FC within eight weeks; Group 4 (-IC+FC): Patients who recovered FC (without prior evidence of IC) within eight weeks.

Temporal profile of recovery of communication in patients with disorders of consciousness following severe brain injury

Abstract

Objective: Characterize the temporal profile of recovery of communication after severe brain injury.

Design: Retrospective cohort study.

Setting: Inpatient rehabilitation hospital.

Participants: Patients with severe acquired brain injury and no evidence of communication on the Coma Recovery Scale-Revised (CRS-R).

Main Outcome Measures: Time from injury to recovery of intentional communication (IC, inconsistent yes/no responses) and functional communication (FC, consistent and accurate yes/no responses) on the CRS-R Communication subscale.

Results: 175 patients (Median [IQR]: 48 [27 – 61] years old, 105 males, 28 [21 – 38] days post-injury, 100 traumatic etiology) were included in the primary observation period of the first eight weeks of inpatient rehabilitation. Fifty-four (31%) patients did not recover IC or FC. Thirty (17%) patients recovered IC only (Median [IQR] days from injury to IC= 40 [34 – 54]), 72 (41%) patients recovered IC followed by FC (days from injury to FC= 50 [42 – 61]) and 19 (11%) patients recovered FC without first recovering IC (43 [32 - 63]). The patients who recovered neither IC nor FC within eight weeks of admission were admitted to rehabilitation later than those who recovered IC and/or FC

(p<0.01). Sixteen patients who did not recover communication within eight weeks of admission to rehabilitation subsequently recovered FC prior to discharge.

Conclusions: In patients with severe brain injury receiving inpatient rehabilitation, discernible yes-no responses emerged approximately six weeks after injury and became reliable one week later. Approximately one in three patients did not demonstrate IC or FC within eight weeks of admission to rehabilitation, although 33% of these individuals recovered communication prior to discharge. In total, 61% of patients recovered FC prior to discharge from rehabilitation.

Abbreviations

CRS-R: Coma Recovery Scale-Revised

DoC: Disorders of Consciousness

FC: Functional Communication

IC: Intentional Communication

IQR: Interquartile Range

Introduction

Patients who sustain severe brain injury may experience prolonged disturbance in consciousness during which they are unable to follow commands or communicate [1]. Recovery of reliable communication is a highly anticipated milestone for both families and clinicians in related diseases states such as locked-in syndrome and stroke [2,3]. The ability to answer questions and express needs are pre-requisites for autonomous decision-making and meaningful social interaction. However, the temporal profile of recovery of communication in patients with disorders of consciousness (DoC) after severe brain injury is not known. Two early studies investigated communication in patients with prolonged DoC and showed that most patients eventually (i.e., between four months and several years after injury) recover this behavior [4,5]. However, both studies included few patients and relied either on retrospective medical chart review [5] or on unvalidated, non-standardized methods [4] of identifying communication. A prospective study of 32 patients in DoC admitted to rehabilitation approximately five

months post-injury used the Coma Recovery Scale-Revised (CRS-R [6], a standardized and validated assessment of behaviors associated with impaired consciousness) to show that eight patients emerged from the minimally conscious state (MCS) within one year of admission to rehabilitation. However, emergence from MCS can be achieved by recovering either functional object use or functional communication, and the results for recovery of communication were not reported separately [7]. Another multi-site study of patients with traumatic DoC admitted to rehabilitation approximately seven weeks post-injury found that 30% (n=29) recovered functional communication on the CRS-R within the following six weeks [8]. Providing clinicians and caregivers with more precise information concerning the time-course to recovery of communication in a larger sample may assist with early decision-making about the need for legal guardianship and promote rehabilitation planning.

Methods

The study was approved by the local Institutional Review Board. Informed consent was not required because all data were retrospectively acquired from the medical record. In this retrospective observational study, we identified patients with a severe brain injury who were admitted to an inpatient rehabilitation facility without any evidence of communication on the CRS-R. To determine the time-course to recovery of communication, we evaluated patients using the CRS-R communication subscale over a period of eight weeks following admission to a specialized inpatient DoC program. The eight-week cut-off corresponds to the period of the inpatient DoC program during which patients receive standardized assessments and care, even though some patients continue to receive inpatient rehabilitation afterwards. However,

the data beyond this period does not accurately reflect the potential to recover communication because of the varying lengths of stay.

Participants

Inclusion criteria were: 1) acquired severe brain injury determined by medical chart review for a traumatic or non-traumatic neurological event leading to DoC ; 2) at least 16 years old at admission; 3) admitted to rehabilitation with no evidence of communication on initial CRS-R administration 4) at least three valid CRS-R assessments within two-weeks of rehabilitation admission; 5) at least an eight-week rehabilitation length of stay, or recovery of functional communication prior to the eighth week. All participants were admitted to a specialized DoC rehabilitation program that is based on a core battery of standardized assessment and systematic, evidence-based treatment approaches. Rehabilitation sessions include serial assessment of level of consciousness and, in conscious patients, identifying volitional movements that can be used to develop a system of communication. For patients who demonstrate the ability to volitionally control movements or to verbally respond to questions, treatment sessions are focused on establishing reliable communication and expressing basic needs.

Measures

The CRS-R is a standardized neurobehavioral assessment measure designed to monitor recovery after severe brain injury across multiple domains of function.[6] The communication subscale includes three items organized by cognitive complexity. Functional communication (FC), defined as accurate responses to six consecutive "yes/no" questions concerning situational orientation, is the most difficult item on the

CRS-R[9], 2) Intentional communication (IC) is scored when there are clearly-discernible yes-no responses to at least two of six situational orientation questions (regardless of accuracy) and 3) No communication (None) is scored when there are no discernible verbal or gestural yes-no responses at any time.

Procedures

We analyzed demographic and clinical data acquired from 323 patients admitted to an inpatient DoC rehabilitation program. Data were housed in an Institutional Review Board approved REDCap database (www.projectredcap.org)[10]. The CRS-R was administered twice weekly by trained clinicians. Patients who met the inclusion criteria were divided into four groups based on the level of communication observed during the first eight weeks of the rehabilitation course: 1) no communication (Group 1: -IC-FC), 2) recovered IC but not FC (Group 2: +IC-FC), 3) recovered IC followed by FC (Group 3: +IC +FC) and 4) recovered FC without prior evidence of IC (Group 4: -IC+FC). For groups 2-4, the time to recovery of IC or FC was defined as the length of time from injury to the first instance of communicative behavior on the CRS-R.

In a secondary analysis, we explored the time to recovery of IC and FC in patients who recovered either of these behaviors after week 8 but before rehabilitation discharge. For this analysis, communication status was also determined using scores on the CRS-R communication subscale.

Statistical Analysis

We used descriptive statistics (medians, interquartile ranges [IQR]) to summarize demographic and clinical characteristics. Non-parametric analyses (Kruskal-Wallis

Rank-sum Test, Chi-squared Test, Fisher's Exact Test, R 3.5.3 5 (R Core Team, Austria)[11] were used to compare groups. Post-hoc pairwise comparisons of the four communication groups were conducted using Wilcoxon Rank-sum and Fisher's Test. Bonferroni corrections were applied to adjust for multiple comparisons (corrected significance $p<0.01$).

Results

Of 323 patients (Median [IQR] days post-injury: (27 [19 – 36]) in the database admitted between June 2012 and August 2017, 148 (46%) did not meet inclusion criteria (73 admitted with IC or FC, 43 followed for fewer than eight weeks without recovery of FC, 26 did not complete at least three consecutive valid assessments and six were not assessed within the eight-week observation period). The 43 excluded patients did not significantly differ from the final study sample in terms of gender ($p=0.8$), age ($p=0.93$), days between injury to admission to rehabilitation ($p=0.18$) or etiology ($p=0.76$). Among the remaining 175 patients, 54 (31%) did not recover IC or FC within eight weeks of admission (Group 1: -IC-FC). Thirty (17%) recovered IC, but not FC (Group 2: +IC-FC); 72 (41%) recovered IC before FC (Group 3: +IC+FC), and 19 (11%) recovered FC without prior evidence of IC (Group 4: -IC+FC) (see Figure 1). Demographic and clinical characteristics, time to recovery of IC and FC and post-hoc pairwise comparisons are presented in Table 1. Briefly, gender; age; time from injury to rehabilitation admission and etiology differed significantly between the groups ($p<0.05$). Most notably, the Group 1 (-IC-FC) was admitted to rehabilitation significantly later post-injury than the two groups that recovered FC (Groups 3: +IC+FC and 4: -IC+FC). The Group 3 (+IC+FC), comprising the largest number of subjects, recovered IC within a median [IQR] of 37 days [32-47] post-injury, and FC within 50

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Secondary analyses were performed on 75 patients who did not recover FC by the end of the eight-week observation period (49 patients who did not recover IC or FC and 26 who recovered IC but not FC). Among these 75 patients, 16 (21%) recovered FC within 15 [13 – 19] weeks; nine (12%) recovered only IC within 16 [13 – 18] weeks and 50 (67%) recovered neither IC nor FC by discharge.

Overall, 52% (n=91) of patients recovered FC within eight weeks of admission to inpatient rehabilitation (i.e., primary endpoint), or within approximately seven weeks of injury. When we combined all of the available data, including recoveries that occurred before and after the close of the eight-week observation period, 61% (n=107) of patients recovered FC, and did so within approximately 15 weeks of injury.

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Discussion

In this retrospective study, we used CRS-R assessments to determine the time-course of emergence of communication in patients with severe brain injury. We identified four different patterns of communication recovery, with significantly different injury characteristics between these groups. In general, these findings suggest that patients who have shorter acute and rehab lengths of stay are more likely to recover communication. This is in line with previous findings showing a shorter acute length of stay in patients recovering communication as compared to those who did not [7]. Shorter acute and rehabilitation length of stay may reflect a less severe injury, which may, not surprisingly, be associated with an increased likelihood of recovering communication abilities. Surprisingly, patients who did not recover communication (Group 1; -IC-FC) were significantly younger, which contradicts with prior reports associating younger age with better outcome [12]. This suggests that even though age might be a prognostic factor, it does not consistently influence recovery of communication. More than half (n=91; 52%) of the patients in our sample recovered FC within eight weeks of rehabilitation admission, and another 16 (9% of the total sample) recovered FC before discharge from rehabilitation. This time interval falls within the broad range reported by previous studies which showed that recovery can continue many months to years after injury[7,8,13]. Most patients recovered IC first followed by FC. The time between recovery of the first sign of communication and reliable yes-no responses was approximately 10 days, suggesting that IC may be a harbinger of FC. Among those who failed to recover IC or FC within the eight-week observation window, a third

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References

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2. Krishnan, S. *et al.* Needs of Stroke Survivors as Perceived by Their Caregivers: A Scoping Review. *Am. J. Phys. Med. Rehabil.* **96**, 487–505 (2017).

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12. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (2). *N Engl J Med* **330**, 1572–1579 (1994).

13. Nakase-Richardson, R., Yablon, S. A., Sherer, M., Nick, T. G. & Evans, C. C. Emergence from minimally conscious state: Insights from evaluation of posttraumatic confusion. *Neurology* **73**, 1120–1126 (2009).

14. Königs, M., Beurskens, E. A., Snoep, L., Scherder, E. J. & Oosterlaan, J. Effects of Timing and Intensity of Neurorehabilitation on Functional Outcome After Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *Arch. Phys. Med. Rehabil.* **99**, 1149-1159.e1 (2018).

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Figure 1

Click here to access/download;Figure;Figure1.tif

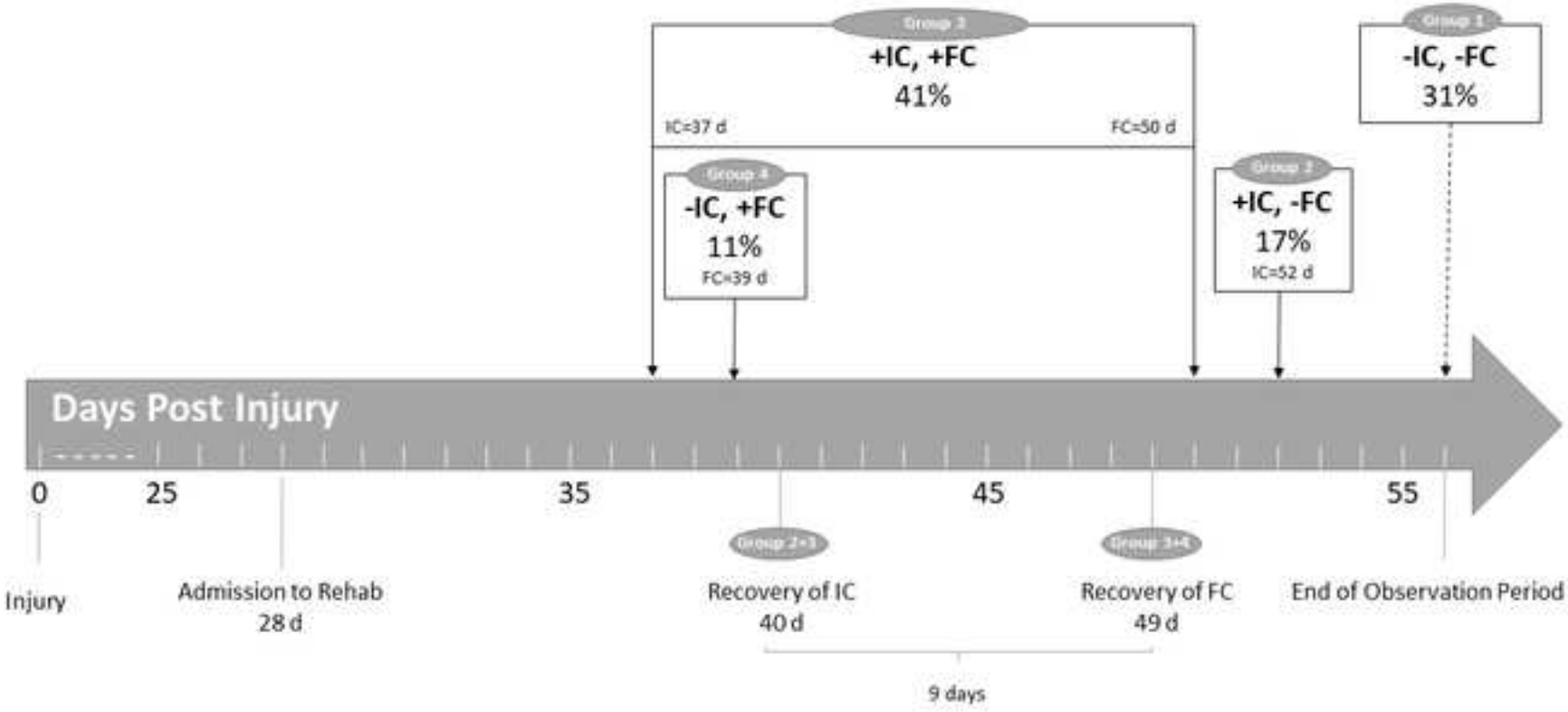

Table 1

	Study sample n=175	Group 1 (-IC, -FC) n=54	Group 2 (+IC, -FC) n=30	Group 3 (+IC, +FC) n=72	Group 4 (-IC, +FC) n=19	p value [c]
Gender (% male)	60%	31	12	53	9	**p=0.008**
Age (years)	48 [27 – 61]	34 [25 – 52]	55 [37 – 64]	52.5 [27 – 66]	53 [40 – 59]	**p=0.023**
Days between injury and admission	28 [21 – 38]	33.5 [27 – 51]	29 [20 – 34]	26 [20 – 33]	23 [21 – 29]	**p=0.0004**
Etiology (% TBI)	57%	32	11	48	9	**p=0.034**
Days of rehabilitation admission	94 [67 – 152	131 [87 – 198]	100 [78 – 157]	75 [57 – 113]	98 [58 – 121]	**p=0.00003**
Days from injury to recovery of IC	40 [34 – 54] [a]	NA	52 [38 – 67]	37 [32 – 47]	NA	**p=0.0004**
Days from injury to recovery of FC	49 [41 – 61] [b]	NA	NA	50 [42 – 61]	43 [32 – 63]	p=0.106
Post-hoc pairwise comparisons [d]						
	Group 1 vs. 2	Group 1 vs. 3	Group 1 vs. 4	Group 2 vs. 3	Group 2 vs. 4	Group 3 vs. 4
Gender	p=0.136	p=0.99	p=0.629	p=0.018	p=0.650	p=0.99
Age	**p=0.007**	p=0.020	p=0.032	p=0.557	p=0.538	p=0.953
Days between injury and admission	p=0.016	**p=0.00009**	**p=0.0029**	p=0.515	p=0.366	p=0.513
Etiology	p=0.466	p=0.775	p=0.370	p=0.450	p=0.141	p=0.370
Days of rehabilitation admission	p=0.157	**p=0.000004**	p=0.041	**p=0.005**	p=0.388	p=0.353

Table 1: Demographics, clinical characteristics, and time to recovery of communication. Data are median [IQR] unless indicated. Group Definitions- Group 1: patients who did not recover communication within 8 weeks or prior to discharge from rehabilitation, Group 2: patients who recovered IC but not FC within 8 weeks, Group 3: patients who recovered IC and then FC within 8 weeks, Group 4: patients who recovered FC (without prior evidence of IC) within 8 weeks

[a] includes 102 patients in Group 2 + Group 3 who recovered IC;

[b] includes 91 patients in Group 3 + Group 4 who recovered FC.

[c] Pearson's Chi-squared test for dichotomous variables and Kruskal-Wallis Rank Sum Test for continuous variables.

[d] Fisher's test for dichotomous variables and Wilcoxon Rank-sum test for continuous variables. Bonferonni's corrected threshold for multiple comparisons= 0.05/6 ($p<0.0083$). p values in bold depict significant differences at $p<0.0083$

Abbreviations: TBI= Traumatic Brain Injury; IC=Intentional Communication; FC=Functional Communication. Post-hoc pairwise comparisons were performed using Fisher's exact test for dichotomous variables and Wilcoxon rank-sum test for continuous variables.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6,7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7
Bias	9	Describe any efforts to address potential sources of bias	9,10
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8,9
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.