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Title: Recovery from prolonged disorders of consciousness: a dual-center prospective cohort study in China

Dear Editors and Reviewers,

Thank you for your giving us this opportunity to improve our manuscript.

We thank the reviewer for very useful comments. We performed the necessary revision in the article and provided our answers below, with the hope of clarifying all the points. We do hope these revisions are adequate and acceptable.

Thank you for your kind re-consideration of our manuscript.

Should you have any questions, please contact us without hesitation.

PS: The followings are the point to point responds to the questions.

With kind personal regards,

Sincerely yours,

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The followings are the point-by-point answers to the concerns raised by the reviewers and description of the revisions made:

SPECIFIC COMMENTS TO AUTHORS

The authors deal with a intriguing and timely topic, which is the identification and assessment of factors underlying the recovery from prolonged disorders of consciousness (DoC). For this purpose, they performed a dual-center prospective cohort study in China and concluded that even severe DoC patients may recover. Notably, and maybe surprisingly, the recover occurred without distinction for age, etiology, duration, and extent of DoC, as well as even in the presence of strong predictors of poor prognosis. These results, if confirmed by further independent investigations, would shed lights on the clinical and pathohysiological basis of DoC, also providing new diagnostic and prognostic findings not only in Chinese people but also in the population worldwide. Overall, the paper is nicely conceived and designed; the results seem to be consistent and are adequately illustrated and discussed. However, there are some concerns needing attention and revision.

MAJOR

- General: the conclusions reached in this study seem to be quite strong and maybe misleading. I invite the authors to be more cautious in lights of the results of their study and the previous literature. Therefore, Abstract, Core tip, Discussion, and Conclusions should be revised accordingly. Additionally, the possible mechanisms (why and how) accounting for the recovery from severe DoC need to be better highlighted.

Response: Thanks for your comments. We have added these points in the manuscript.

CONCLUSION

Patients with severe DoC, despite having strong predictors of poor prognosis, might recover consciousness after a prolonged time of rehabilitation. An accurate initial diagnosis of patients with DoC is critical for predicting outcome and a long-term regular

follow-up is also important.

Core tip:

Data are lacking regarding the long-term outcomes of patients with disorder of consciousness (DoC) in China. This was a two-center prospective cohort study of inpatients with prolonged DoC for up to 6 years, included 93 patients (62 vegetative state (VS)/unresponsive wakefulness syndrome (UWS) and 31 minimally conscious state (MCS)). The results show that patients with severe DoC, despite having strong predictors of poor prognosis, might recover consciousness after a prolonged time of rehabilitation.

DISCUSSION

Our findings emphasize the clinical importance to follow up patients with DoC. VS/UWS can be considered permanent in TBI patients after 12 months and non-TBI patients after 3 months. This view has been challenged. Avesani et al. described two people diagnosed with VS/UWS who, at respectively 6 and 12 months after their original trauma, had achieved a moderate level of functional independence following a significant motor and cognitive recovery after 5 years and suggested that it is important to conduct regular follow-ups to better evaluate changes and, if it is necessary, to re-adjust the rehabilitation accordingly (Avesani et al., Brain Inj. 2006). Also, our results have been shown that patients admitted to rehabilitation in an unresponsive state can show considerable recovery even after a prolonged time. Although slow regeneration of axons in patients with brain injury could be an intriguing hypothesis as a biological mechanism of delayed recovery, no neurological interpretation of late recovery from VS/UWS has been advanced and early predictors might not apply (Baricich A et al., Funct Neurol. 2017). Our previous study has supported the use of ERP in clinical practice to predict the likelihood of recovery from DoC (Zhang Y et al., Neurosci Lett. 2017). An accurate initial diagnosis of patients with DoC is critical for predicting outcome. Misdiagnosis may lead to a worse prognosis for patients, which may restrict their access to recovery. The adoption of homogeneous assessment procedures will provide valuable and reliable data for investigating clinical issues regarding the diagnosis and prognosis of DoC, as well as the effectiveness of treatment strategies for

long-term clinical progression. At the same time, a decision to conduct or withhold specialized neurorehabilitation in traumatic or non-traumatic DoC survivors should be considered comprehensively.

In conclusion, we present a novel prospective real-world cohort study on the 12-month outcome of patients with a severe condition at two specialized units in Beijing and Nantong with different etiology. The results suggest that patients with severe DoC, despite having strong predictors of poor prognosis, might recover consciousness after a prolonged time of rehabilitation. An accurate initial diagnosis of patients with DoC is critical for predicting outcome and a long-term regular follow-up is also important. This preliminary study indicates that establishing a rehabilitation-based registry for patients with severe DoC after brain injury is feasible and probably relevant to improve patient management.

- Introduction: although the study aim and rationale have been stated, the experimental hypothesis is lacking (i.e. what do you expect for this study and why?).

Response: Thanks for your question. We have added this point in the introduction. It now reads:

The present real-world prospective cohort study aimed to assess the recovery rate of the inpatients with a VS/UWS to a MCS and to analyze and compare the long-term outcomes of patients with prolonged DoC considered in VS/UWS or MCS 1 year after the standard follow-up in the prognostic study, then yearly afterwards up to 6 years, hoping to investigate the factors associated with a higher likelihood of transition to MCS at rehabilitation facilities in China and further our understanding of the rehabilitation potential of the most severely affected patients with DoC. We also hypothesized that there was potential for some level of recovery despite the presence of strong unfavorable prognostic markers. Here we presented the preliminary results six years after the start of the study.

- Materials and Methods (Study design and participants): among the

inclusion/exclusion criteria, the possibility of metabolic, inflammatory/autoimmune, and infectious causes of DoC should be mentioned.

Response: Thanks for your suggestion. According to your comment, we have added the details of inclusion criteria in Materials and Methods (Study design and participants) section. In fact, our study included all types of diseases that cause DoC, but the final patients included were not caused by factors such as metabolism, inflammation, and infection. This may be related to factors that cause prolonged DoC. For example, most metabolic and infectious causes of DoC might be clinically acute coma.

- Materials and Methods (Definition and measure of outcome): in addition to clinical findings, the diagnostic and prognostic role of instrumental exams, especially neurophysiological (i.e. EEG and multimodal evoked potentials), is missing (Daubin C, et al. BMC Cardiovasc Disord 2008). Additionally, motor evoked potentials are useful in the prediction of the post-comatose recovery of motor function (Rohde V, et al. Acta Neurochir 1999), especially when they are adjusted for physical variables (Cantone M, et al. Front Hum Neurosci 2019). Moreover, given their relevant prognostic value, the findings of the neurological examination in DoC should be provided (Sandroni C and D'Arrigo S. Semin Neurol 2017).

Response: Thanks for your suggestion. It is really true as you suggested that an increasing number of studies have addressed the application of new technologies, including EEG, fMRI and ERP on brain state assessment in DOC. And as we mentioned in the supplementary material, neurophysiological such as SEP and ERP, and neuroimaging such as fMRI or PET data were optional because not all patients underwent them based on availability of the tests and on the costs to the patient/family. So we have shown CT/MRI findings of all patients in supplementary table and reported part of ERP and PET results in several papers (Li R, et al. Neural Regen Res 2015 & Neuroreport 2015 and Zhang Y, et al. Neurosci Lett 2017 & Neurol Sci 2020). Neurologic examination was also recorded and we assessed all patients by using the

GCS and CRS-R, which comprise some items in neurologic examination, such as auditory, visual, motor, verbal and communication.

- Results: there is a quite large amount of variability in the different variables considered in the study, e.g. median follow-up (12-37 months), post-injury interval range (28-634 days), CRS-R total score (0-17), mean age (7-85 years), and DoC etiology. Regarding stroke, it seems that ischemic and hemorrhagic strokes have been considered together, despite their significantly different etiology, location, severity, and outcome. I wonder whether this heterogeneity may have affected the reliability and the reproducibility of the results.

Response: Thanks for your suggestion and we have tried to add some data accordingly. But no positive results were found, so we did not show the corresponding data. We did not group CRS-R score and follow-up time, because the CRS-R difference of each group was within an acceptable range and the precise follow-up time related to recovery of consciousness could not be obtained.

The present study only included a small number of patients from only two study centers, which was a limitation of the study. We have present the preliminary results of a DoC cohort and will expand cases and extend the follow-up time later. The statistical data results are as follows:

Table 1. Characteristics of the patients

Characteristic	All (n=93)	Groups		P
		VS/UWS (n=62)	MCS (n=31)	
Age, years, mean±SD	49.8±16.9	49.7±16.4	50.1±18.0	0.897
Maximum	85	80	85	
Minimum	7	7	9	
≤35, n (%)	18 (19.4)	12 (19.4)	6 (19.4)	0.906
>35, ≤65, n (%)	58 (62.3)	39 (62.9)	19 (61.2)	

>65, n (%)	17 (18.3)	11 (17.7)	6 (19.4)	
Post injury days, median (Q_{25},Q_{75})	60 (35,98)	59 (37,95.5)	61 (32,126)	0.446
Maximum	634	496	634	
Minimum	28	28	28	
≤90d, n (%)	65 (69.9)	44 (71.0)	21 (67.7)	0.799
>90d, ≤365d, n (%)	24 (25.8)	15 (24.2)	9 (29.1)	
>365d, n (%)	4 (4.3)	3 (4.8)	1 (3.2)	

Table 2. Characteristics of patients with or without improved responsiveness

Characteristic	Outcome		P
	Unawareness (n=52)	Awareness (n=41)	
Age, years, mean±SD	49.4±16.2	50.3±17.8	0.797
Maximum	79	85	
Minimum	7	13	
≤35, n (%)	9 (17.3)	9 (22.0)	0.597
>35, ≤60, n (%)	33 (63.5)	25 (60.9)	
>60, n (%)	10 (19.2)	7 (17.1)	
Days post injury, median (Q_{25},Q_{75})	65.5 (38.5,136.5)	40.0 (30.0,87.0)	0.006
Maximum	496	634	
Minimum	29	28	
≤90d, n (%)	33 (63.5)	32 (78.0)	0.123
>90d, ≤365d, n (%)	16 (30.7)	8 (19.6)	
>365d, n (%)	3 (5.8)	1 (2.4)	

- Discussion: the authors stated that "patients in MCS and VS/UWS should not be pooled for prognostic purposes." Why? Maybe this would have

disclosed additional findings, possibly remodeling the conclusions.

Response: Thanks for your question. We have added this point in the discussion. It now reads:

In the present study, although the present preliminary data cannot provide definitive diagnostic and prognostic information, they strongly indicate that patients in prolonged DoC should not be pooled for prognostic purposes at admission. Firstly, in all 93patients, we screened out 8 cases of LIS, who should not be classified as prolonged DOC strictly. Secondly, the analysis showed that the potential for unfavorable outcome was significantly greater in VS/UWS than in MCS.

MINOR

- General: please fully write the abbreviations before using the acronyms (e.g. EMCS in the Abstract, HIE in the Results, etc.).

- Discussion: the first two sentences are redundant and, therefore, can be removed.

- Conclusion: please replace "In conclusions, We present…" with "In conclusion, we present…"; few lines below, use "DoC" instead of "DOC".

Response: Thanks for your careful work. We apologize for the language problems in the original manuscript. We carefully checked the entire manuscript and revised them accordingly.