Author’s response to reviews

Title: Outcome prediction in disorders of consciousness: the role of coma recovery scale revised

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To Samson Awili Gwer
Editor in Chief
BMC Neurology

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Outcome prediction in disorders of consciousness: the role of coma recovery scale revised

Dear Editor

In the attached reply to the reviewer, we outlined our responses to each of its comments. We feel that our manuscript is strongly improved by incorporating their suggestions.
The data have not been published previously and are not under consideration for publication elsewhere. The first author, Dr. Lucia Lucca declares that he had full access to all of the data in the study and he takes responsibility for the integrity of the data and the accuracy of the data analysis. The methods employed were approved by the Local Research Ethics Committee, and are in accord with the Declaration of Helsinki. There are no conflicts of interest in this work requiring declaration. All authors gave substantial contribution to conception and experimental design, as well as data analysis, interpretation and drafting of the manuscript. The submission of this paper has been approved by all of the authors.

We look forward to hearing from you in due course.

Yours sincerely,

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Reviewers' comments:
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Reviewer: 1

Ronny Beer (Reviewer 1): The manuscript by Lucca and co-workers addresses the utility of a clinical rating scale, i.e. CRS-r, in combination with a set of other prognostic indicators to predict regain of consciousness/ responsive wakefulness in a mixed cohort of patients having sustained acute brain injuries (severe TBI, HIE & cerebrovascular catastrophies). According to the authors' statistical analyses, the clinical rating scale performed best in predicting a meaningful functional improvement in patients with ABI despite a rather short neurological rehabilitation treatment of app. 2 months. Interestingly, in the studied patient cohort, 1 out of 3 patients with a serious DoC experienced a full recovery. Though the results of this study are interesting to the providers of neurocritical care as well as neurorehabilitation, several limitations must be taken into consideration, some of which are also admitted by the authors. Importantly, the following, additional points should be elaborated in greater detail by the authors:

1. In fact, this is a retrospective study analyzing data that have been collected prospectively (see 2.2. Design and Procedure, page 4, first paragraph), and therefore, suffers from the inherent limitations of this study design - please amend.

Reply: As required by this reviewer we include a new paragraph reporting the main limitation of retrospective study design.

Please see pag. 8. “Finally, the employment of a retrospective study design is more subject to confounding. For instance, other risk factors may be present that were not measured, such as EEG evaluations. Indeed it has been demonstrated that EEG coherence might have a diagnostic value in the prognosis of recovery from VS [38], its inclusion might have been improved the strength of our predictive model
Concerning treatment, the authors are encouraged to provide information on neuropharmacological interventions, which - at least in the cohort of patients with prolonged unresponsiveness after severe TBI - are established in the field of neurorehabilitation (e.g. amantadine). Some of the patients might have received centrally acting medications to mitigate states of sympathetic hyperactivity in the early post ICU period which could have negatively influenced recovery from DoC.

Reply: We are perfectly aware of the elegant work made by Giacino et al., on New England Journal of Medicine (2012) where authors demonstrated that Amantadine accelerated the pace of functional recovery during active treatment in patients with post-traumatic disorders of consciousness. Unfortunately, our retrospective study set off in 2010, thus before this seminal study. Therefore, our patients were not assigned to receive this stimulant medication.

Overall, in agreement with Seel et al., (Arch Phys Med Reh 2013), we did not apply a uniform neuropharmacological intervention for all patients with DoC. Our main interest concerns basic care and secondary medical conditions that can emerge during neurorehabilitation period. For instance, dysautonomia crises are common and can be difficult to treat, thus requiring multimodal interventions. 14% of DoC patients showed Paroxysmal Sympathetic Hyperactivity signs, which were treated with beta-blockers, baclofen, clonidine, gabapentin which, however, did not worse the responsiveness of patients. Other neurological complications (eg, hydrocephalus, infections, epileptic attacks) can be detected and were immediately treated appropriately to reduce the risk of further disability.

We included this additional information at pag. 5

In addition, more data on the evolution of neurophysiological, especially EEG, examinations are needed, which should have been performed regularly for the objective assessment of reactivity to exogenous stimuli. Did the authors also perform f- or rsfMRI to rule out or detect clinically not identifiable recovery from coma or UWS?

Reply: We would like to thank this reviewer for highlighting the importance of fMRI analysis in DOC patients, but unfortunately, our Institute is not equipped with this costly neuroimaging method. As you can image fMRI examination of 180 DoC patients could be extremely labor-intensive.

On the other hand, standard qualitative visual EEG analysis was performed, but only for medical treatment purpose. Indeed this was used to evaluate the gradual decalage of pharmacological intervention (i.e. anti-epileptic drugs). However, we’ve amended this important suggestion in the limitation section in order to inspire further investigations comparing EEG evaluations against CRS values. Please see pag. 8

Could the authors provide some reason to limit data analysis to the relatively short neurorehabilitation period of app. 2 months. Several experts in the field recommend rehabilitation times of at least 3 months for HIE or 6 (up to 12 months) after severe TBI before designating an unfavorable outcome. What happened to the patients who did not show signs of emergence from unresponsiveness during the respective period of time? Were these patients discharged to skilled nursing facilities or granted additional weeks of neurorehabilitation?

Reply: As already admitted in the limitation section, the short outcome period employed in this study cannot be considered as definitive. For statistical purpose (in order to delineate a more powerful predictive clinical model) we chose to employ this target because this represents the minimum guaranteed period where all patients were continuously monitored, thus providing a more homogenous dataset. Since the most severe patients with no signs of emergence from unresponsiveness were discharged from the rehabilitation in the period between the 8th and 12th week after admission, there could be the possibility to violate the assumption of “non-informative censoring” in our survival model, since the distribution of censoring time (discharge time) among severe (particularly for HIE) and mild patients (traumatic) was different.
5. Language editing could help to streamline the flow of information, e.g. "patients of traumatic nature" should read patients with TBI or "autonomy of respiration" is better described as spontaneous breathing or fully weaned from mechanical ventilation. The same holds true for the phrase "longitudinal papers" (the authors rather refer to longitudinal studies) etc. What do you mean by "inpatient recovery period"?
Reply: All required revisions have been performed. With “inpatient recovery period” we meant the period of intensive rehabilitation during hospitalization.

6. Feed administration should be changed to route of feeding. Surprisingly, some of the patients in UWS were feed orally; the interested reader might ask whether one could achieve adequate nutrition goals?
Reply: We would like to thank this reviewer for highlighting this typo. In the first row of the feed administration, it must have been reported “parenteral feeding”, instead of “oral feeding”. This mistake has been now corrected in table 1. Thanks again for your help and support.

Minor points:
• Page 3, first paragraph: MSC should read MCS.
Reply: Done
• Please specify the cerebrovascular patient cohort in greater detail, do you refer to patients with (malignant) ischemic stroke, poor grade SAH and/or ICH?
Reply: The cerebrovascular cohort was divided into 4 subgroups: ischemic stroke: 13%; poor grade of subarachnoid hemorrhage: 27%; Intraparenchymal hemorrhage: 52%; subdural hemorrhage: 8%. Please see pag. 5 last paragraph.

Reviewers n°2
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Rana Alnasser Alsukhni, M.D (Reviewer 2): The research compares the predictability of CRS-r in DOC outcome with other clinical and non-clinical parameters.

Although it is not completely original, it is a well written paper highlighting the utility of CRS-r scale in a specific subgroups of coma patients to predict their long-term results which is compatible with the body of available research.

1. The conclusion drawn included minor inaccuracy "We demonstrated in a large Italian sample that 35% of severe DoC patients achieve a full functional improvement by the end of inpatient rehabilitation", I think "severe" is inaccurate as patients with deep coma or DoC of other aetiologies or age groups were excluded.
Reply: In accordance with the reviewer’s suggestion the word “severe” has been removed

2. The language is good and appropriate. I could hardly find lingual mistakes.
Page 2 line 35: This was done in order to determine: algorithmic approaches to patient treatment; ii) the optimal clinical care and setting to improve outcomes. Ad "i)" before algorithmic.
Reply: Done

Page 8 line 31: "However, it should bear in mind that". It should be borne in mind or one should bear
in mind that..
Reply: Done