PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multicenter observational study on practice of ventilation in brain injured patients: the VENTIBRAIN study protocol
AUTHORS	Robba, Chiara; Citerio, Giuseppe; Taccone, Fabio; Galimberti, Stefania; Rebora, Paola; Vargiolu, Alessia; Pelosi, Paolo

VERSION 1 – REVIEW

REVIEWER	Tardif, Pier-alexandre
REVIEW RETURNED	28-Dec-2020

GENERAL COMMENTS	Thank you for the opportunity to review this study protocol. The authors describe a (colossal) upcoming international multicenter prospective cohort study that will aim to describe ventilator settings and assess its potential associations with pulmonary complications and a given set of outcomes in adult patients with a non-anoxic brain injury admitted to the ICU who required endotracheal intubation and mechanical ventilation. Authors present a compelling rationale for the study and their protocol is usually sound and clear, but some points deserve attention (see major and minor points below). Major points: Background and rationale (I1) First paragraph, last sentence: couldn't the lung injury also be due to a combination of both? (I2) Fourth paragraph, first sentence: «Therefore, the concept of 'protective lung ventilation' has shown to reduce […]». Its not the concept that has reduced the morbidity and mortality of ICU patients, but the practice (intervention). Methods (MM1) Section «Objectives». For secondary objective 4, specify which outcomes will be evaluated in association with ventilator settings. (MM2) Section «Exclusion criteria». Last criteria. It is the first mention of a «7-day period of inclusion» in the manuscript. If this is an inclusion criteria, then it should figure as such in the inclusion criteria section. (MM3) Section «Study procedures and settings». As per the protocol, «Centers will enroll consecutive patients for a minimum period of 3 months to a maximum period of 6 months». What considerations did determine this time frame? Secondary objectives 2 and 4 are not descriptive but analytical (even though they are not causal due to the observational nature of the study as the authors point out); statistical analyses will thus be performed to

	assess the potential associations between ventilator settings and i) pulmonary complications / ii) outcomes (? ought to be specified). With so many potential centers constituting the cohort, are authors confident that this time frame will be sufficient to provide statistical power to undertake robust multilevel regression analyses? Even if the hypotheses are said to be exploratory, internal validity should still be a concern. Various rule of thumbs have been suggested for multilevel analyses; authors specified that the aim is 30 patients per center (a reference to support this would be useful). However, the validity and robustness of analyses using this number is conditional on the number of covariates that will be included in the model (this is not specified) and «30 patients» should be considered as a minimum. What if many centers do not recruit enough patients to reach the minimum requirements or if too many patients have missing data or are lost to follow-up? Will centers with less important volume of patients be excluded and how will authors handle potential selection bias in that regard (have IPCW or multiple imputation been considered)? Do authors already have an idea of the volume of patients roughly meeting their inclusion criteria in some of these centers to ensure feasibility? (MM3) Section «outcomes». An exhaustive list of what will constitute the synthetic outcome «pulmonary complications» should be provided. (MM4) Section «Data collection». In terms of exposition, the authors are interested primarily in the «practice of ventilation». In their protocol, «ventilation settings» is implicitly considered the main exposure and its potential effect(s) will be evaluated relative to pulmonary complications and outcomes (?). «Ventilation settings» is never defined. This is no wonder however, since the primary objective is precisely to describe ventilation settings. The definition of the exposure is thus relegated to later, i.e. after the protocol and the study (recruitment and follow-up) are done. It is not unreasonable to assume that between different recruiting centers, ventilator settings will vary because they are constituted by a given amount of distinct elements. At some point, statistical analyses will be performed to evaluate the associations between ventilator settings and pulmonary complications and outcomes. Whether these associations are significant or not will only provide fragmentary information, especially since we don't know which elements, among the many that constitute a given settings, are responsible for the association (or if the absence of association is due to a mis-categorisation of different settings where distinct elements overlap, when they maybe shouldn't). Under these conditions, there are at least two aspects that should be considered and explicitly described in the protocol: 1) exactly what elements will be considered in order to fully describe the ventilator settings/practices so that the data provided by the current study will be both informative and actionable (for hypothetical interventions in the future); 2) beyond the considerations on low/high tidal volume (which might prove to be important; but authors might also find out some other impactful unexpected characteristics of ventilator settings, if they consider this avenue explicitly), how will ventilator settings be distinguished from one another (based on what elements, how many of them, etc.) and then grouped together (among different centers) in order to avoid potential information biases when performing the regression analyses?

	(MM5) Section «plan of analysis» -The authors specify that ventilator settings will be described according to the type of brain injury and countries, but will associations also be performed using similar stratifications (e.g. TBI vs non-TBI)? Are any other sensitivity analyses planned? -What and how many confounders will be used in the multivariable models? Will they only include factors pertaining to patients, or also to centers and countries (three distinct levels); if so, in addition to the random effects for centers/nations, will multilevel regressions analyses be performed? -Do we expect outcomes (e.g. GOSE, pulmonary complications) to be present in ~10% of patients? If so, why use logistic regressions to obtain odds ratio rather than more straightforward risk ratios? -What statistical method will be used to account for mortality and discharge as competing risks when evaluating the cumulative incidence of pulmonary complications? -More information would be useful to understand the methods planned in the second paragraph describing the longitudinal model on raised intracranial pressure. I am assuming this is a repeated measures regression analysis? With random effects? What potential confounders will be included? -Are any statistical strategies planned (e.g. multiple imputation) to account for missing data (including outcomes due to lost of follow-up) if they reach ~10%? Minor points: Strengths and limitations of the study (SL1) First paragraph, remove «and» in «and ventilator strategies». (SL2) Add a dot «.» at the end of the second paragraph. List of abbreviations and relevant definitions (ABB1) The letter «M» in the acronym «ESICM» has not been defined. (ABB2) The word «Glasgow» is lacking in the acronym «GOSE». (ABB3) Last paragraph, the word «hypothesis» is singular. Do authors mean «a single hypothesis» or potentially many «hypotheses»? On a side note, there are so many acronyms throughout the manuscript that it is sometimes difficult to read, authors could keep them at a minimum without much impact on the article's length. Moreover, some acronyms are defined but not used consistently afterwards (e.g. length of stay). Abstract. (AB1) Section «Methods and analysis», the word «extended» is lacking in the definition of GOSE; in the same sentence, the word «Data» has an unnecessary capital letter. Introduction (I1) Some spaces between words, dots «.» (end of sentences) and references are inconsistent and should be corrected (refs. #12, #13, #14). (I2) Third paragraph, first sentence, remove «also» in «suggest that also» and move to «[…] without ARDS could also benefit». (I3) Last paragraph, last sentence: replace «as suggested by» with «as pointed out by» (or replace «is currently missing» with «is currently needed»).

	Materials and Methods (MM1) Section «Objectives». Ensure consistency in syntax. Sentences for secondary objectives 1&3 end with dots «.» while those for objectives 2&4 don't. Similar considerations apply to all sections of the manuscript since inconsistencies are also found elsewhere (e.g. sections inclusion/exclusion criteria, outcomes, data collection, etc.). (MM2) Ensure consistency relative to spaces (or absence of spaces) between «-» and the first word of the sentences in every enumeration. (MM3) Section «study procedures and settings». The word «medicine» is lacking in the definition of the acronym «ESICM». Lack of capacity and Delayed Consent (LCDC1) First paragraph, 4th line, unnecessary space between «next-» and «of». (LCDC1) Second paragraph, 3th line, space required between «.» and «At». Tables (T1) Remove the unnecessary paragraph in the third row (second column, beginning by «Bilateral opacities […]»). (T2) Table 5. In the title, replace «Terapy» by «Therapy». (T3) Table 5 has no legend for its abbreviations (ICP, CPP, CSF, CO2). (T4) Table 6, the title says «extended» Glasgow Outcome Scale, but the table actually corresponds to the standard GOS (it contains only 5 categories instead of 8 for GOS-E). Figure (F1) The figure has no legend for abbreviations (GOSE, ICU, ABGs). References (R1) Reference #14 Serpa (2012) contains a comment that seems to be addressed to coauthors and not to readers. (R2) Reference #17 Della Torre (2017) differs in style (a part of the title is underlined). (R3) Reference #18 Robba (2020) has been published and is no longer «in press», update required. (R4) Reference #20 Asehnoune (2018) seems to have an unnecessary space between the words «respiratory» and «management». (R5) Reference #27 Karalapillai (2020) is problematic (it contains an unnecessary paragraph).

REVIEWER	Gao, Guo-yi Shanghai Jiao Tong Univ
REVIEW RETURNED	04-Jan-2021

GENERAL COMMENTS	1- The author mentioned later in the part of sample size calculation that 4000 coma patients will be recruited. However, the GCS is absent in the inclusion criteria. 2- The author please consider to include ICP monitoring as the inclusion criteria, as ICP is indicated the major clinical parameter when observing the ventilating policy in this trial. 3- Will the author collect information about the modification of the ventilation policy? Because in the clinical scenario, the fixed

	ventilation model may be adjusted due to the variation of lung/brain status.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Mr. Pier-alexandre Tardif
Comments to the Author:
Thank you for the opportunity to review this study protocol. The authors describe a (colossal) upcoming international multicenter prospective cohort study that will aim to describe ventilator settings and assess its potential associations with pulmonary complications and a given set of outcomes in adult patients with a non-anoxic brain injury admitted to the ICU who required endotracheal intubation and mechanical ventilation. Authors present a compelling rationale for the study and their protocol is usually sound and clear, but some points deserve attention (see major and minor points below).

Answer: We thank the reviewer for his thoughtful suggestions. We agree with the concerned raised, and we have substantially modified the manuscript accordingly.

Major points:
Background and rationale
(I1) First paragraph, last sentence: couldn't the lung injury also be due to a combination of both?

Answer: Thank you, we agree with the reviewer and we better specified this issue in the revised manuscript.

(I2) Fourth paragraph, first sentence: «Therefore, the concept of 'protective lung ventilation' has shown to reduce […]». Its not the concept that has reduced the morbidity and mortality of ICU patients, but the practice (intervention).

Answer: Thank you, this issue has been better specified in the revised version of the manuscript

Methods
(MM1) Section «Objectives». For secondary objective 4, specify which outcomes will be evaluated in association with ventilator settings.

Answer: The outcomes have been specified in this section

(MM2) Section «Exclusion criteria». Last criteria. It is the first mention of a «7-day period of inclusion» in the manuscript. If this is an inclusion criteria, then it should figure as such in the inclusion criteria section.

Answer: We agree with the reviewer and this issue has been modified accordingly. In the revised manuscript, the last criteria have been included in the inclusion criteria, as suggested

(MM3) Section «Study procedures and settings». As per the protocol, «Centers will enroll consecutive patients for a minimum period of 3 months to a maximum period of 6 months». What considerations did determine this time frame?

Answer: Thank you, we considered this timeframe on the basis of our previous experience with other large multicenter observational studies, in order to obtain an equilibrium between the need to include committed centers who routinely manage neurocritical care mechanically ventilated patients and the

feasibility of the study, which requires effort and resources. We better specified this issue in the revised version of the manuscript.

Secondary objectives 2 and 4 are not descriptive but analytical (even though they are not causal due to the observational nature of the study as the authors point out); statistical analyses will thus be performed to assess the potential associations between ventilator settings and i) pulmonary complications / ii) outcomes (? ought to be specified). With so many potential centers constituting the cohort, are authors confident that this time frame will be sufficient to provide statistical power to undertake robust multilevel regression analyses?

Answer: Thank you for this important comment. In the revised version of the manuscript, we have now better specified and defined the outcomes in the objective section as suggested. The time frame is similar to another large observational study that we recently concluded (SYNAPSE ICU, DOI: 10.1136/bmjopen-2018-026552) with the same Network of centers involved. Also, we have sent a survey to the centers with the aim to understand the number of beds, hospital capacity and number of admissions in order to re-evaluate their potentiality of recruitment. Also, authorship is guaranteed for at least 10 patients included, and we expect that the centers involved will be committed. However, we do not ask for a minimum number of patients as we want to have a picture of the status of the art and capacities of mechanically ventilated brain injured patients in all centers. More details regarding statistical methods are provided in the revised version, section MM5.

Even if the hypotheses are said to be exploratory, internal validity should still be a concern. Various rule of thumbs have been suggested for multilevel analyses; authors specified that the aim is 30 patients per center (a reference to support this would be useful).

Answer: Thank you for this comment. We used this target as it has been previously tested in the SYNAPSE study DOI: 10.1136/bmjopen-2018-026552, which is a multicenter observational study regarding ICP practice in brain injured ICU patients. Although the aims are different, the methodology and the Network of centers included is very similar, and we found that the inclusion of this number of patients is feasible provided that the included centers will maintain the same potentiality of recruitment. We added this point and the reference as suggested.

However, the validity and robustness of analyses using this number is conditional on the number of covariates that will be included in the model (this is not specified) and «30 patients» should be considered as a minimum. What if many centers do not recruit enough patients to reach the minimum requirements or if too many patients have missing data or are lost to follow-up?
. Will centers with less important volume of patients be excluded and how will authors handle potential selection bias in that regard (have IPCW or multiple imputation been considered)? Do authors already have an idea of the volume of patients roughly meeting their inclusion criteria in some of these centers to ensure feasibility?
Answer: As previously stated, we have sent a survey to the centers with the aim to understand the number of beds, hospital capacity and number of admissions. Authorship is guaranteed for at least 10 patients included, and we expect that the centers involved will be committed. As previously stated, we do not ask a priori for a minimum number of patients as we want to have a picture of the status of the art and capacities of mechanically ventilated brain injured patients in all centers. Nevertheless, we planned a sensitivity analysis excluding centers with less than 20 patients to evaluate potential selection bias. Regarding missing data, we planned a strict monitoring of data quality during the study. Multiple imputation will be performed when missing data will exceed 10%. This has been better specified in the data management section.

(MM3) Section «outcomes». An exhaustive list of what will constitute the synthetic outcome «pulmonary complications» should be provided.

Answer: Thank you, this has been added, as requested

(MM4) Section «Data collection». In terms of exposition, the authors are interested primarily in the «practice of ventilation». In their protocol, «ventilation settings» is implicitly considered the main exposure and its potential effect(s) will be evaluated relative to pulmonary complications and outcomes (?). «Ventilation settings» is never defined. This is no wonder however, since the primary objective is precisely to describe ventilation settings. The definition of the exposure is thus relegated to later, i.e. after the protocol and the study (recruitment and follow-up) are done. It is not unreasonable to assume that between different recruiting centers, ventilator settings will vary because they are constituted by a given amount of distinct elements. At some point, statistical analyses will be performed to evaluate the associations between ventilator settings and pulmonary complications and outcomes. Whether these associations are significant or not will only provide fragmentary information, especially since we don't know which elements, among the many that constitute a given settings, are responsible for the association (or if the absence of association is due to a mis-categorisation of different settings where distinct elements overlap, when they maybe shouldn't). Under these conditions, there are at least two aspects that should be considered and explicitly described in the protocol: 1) exactly what elements will be considered in order to fully describe the ventilator settings/practices so that the data provided by the current study will be both informative and actionable (for hypothetical interventions in the future); 2) beyond the considerations on low/high tidal volume (which might prove to be important; but authors might also find out some other impactful unexpected characteristics of ventilator settings, if they consider this avenue explicitly), how will ventilator settings be distinguished from one another (based on what elements, how many of them, etc.) and then grouped together (among different centers) in order to avoid potential information biases when performing the regression analyses?

Answer: Thank you for this comment. We have provided details regarding the ventilator settings that will be collected for this study. The fist aim of our study is to assess the differences across different countries of ventilator settings. Together with protective and non protective tidal volume as mentioned, we will explore the role of currently known threshold for other ICU populations of protective Plateau pressure vs non protective Plateau pressure (27-30 cmH20), driving pressure (15 cmH20) and PEEP. However, as in this population no specific thresholds have been defined, we will aim to assess the distribution of these settings and eventually define new threshold for the brain injured population.
We will firstly study the distribution of ventilator setting parameters and their variation in time. In regression analysis the parameters will be initially included as continuous variables, potential categorizations driven by data exploration will be considered as secondary analysis.

(MM5) Section «plan of analysis»
-The authors specify that ventilator settings will be described according to the type of brain injury and countries, but will associations also be performed using similar stratifications (e.g. TBI vs non-TBI)? Are any other sensitivity analyses planned?

Answer: Yes we planned to evaluate associations according to the type of brain injury and we have better specified the strata, i.e. TBI, AIS and SAH. We also added a plan for an analysis according to the presence and severity of lung injury. This has been added in the analysis plan.

-What and how many confounders will be used in the multivariable models? Will they only include factors pertaining to patients, or also to centers and countries (three distinct levels); if so, in addition to the random effects for centers/nations, will multilevel regressions analyses be performed?

Answer: Thank you for pointing this out, we have enriched the section “plan of analysis” accordingly. In the regression models we will include known confounders, such as age, sex, cardiovascular and neurological history, type of injury, the severity of pulmonary and neurological conditions. Beside these clinical relevant variables we will eventually consider additional covariates chosen on the basis of statistical considerations. We confirm that a multilevel regression approach will be performed. We better specified this in the new version of the manuscript.

-Do we expect outcomes (e.g. GOSE, pulmonary complications) to be present in ~10% of patients? If so, why use logistic regressions to obtain odds ratio rather than more straightforward risk ratios?

Answer: Thank you for this comment. We expect an incidence of ARDS in this cohort of 3%.(DOI: 10.1016/j.jcrc.2016.11.010)and 20.4% of VAP (DOI: 10.1016/j.chest.2020.06.064, and unfavourable GOSE in about 60-64% (unpublished data from the synapse study). Most of the outcomes will be evaluated with a Cox model to consider time of event. As far as 6-months GOSE, we planned to use a logistic regression for its computational performance due to the complexity of the setting (multilevel models on longitudinal data). However, we completely agree that risk ratio is indeed a more straightforward measure. We will evaluate the opportunity to apply a relative risk regression model (such as Poisson working model) when ventilator settings during ICU will be summarized in a single measure. More details on the modeling strategy have been specified in the revised manuscript.

-What statistical method will be used to account for mortality and discharge as competing risks when evaluating the cumulative incidence of pulmonary complications?

Answer: We will use the Aalen-Johansen estimator and the cause specific Cox model, we specified them better in the text.

-More information would be useful to understand the methods planned in the second paragraph describing the longitudinal model on raised intracranial pressure. I am assuming this is a repeated measures regression analysis? With random effects? What potential confounders will be included?

Answer: Thank you for this suggestion. We specified it better in the text.
As confounders, among others, we aim to include age, sex, GCS, pupillary reactivity, primary diagnosis, the severity of pulmonary and neurological conditions, cardiovascular and neurological history. These variables will be chosen on the basis of clinical relevance and statistical arguments.

-Are any statistical strategies planned (e.g. multiple imputation) to account for missing data (including outcomes due to lost of follow-up) if they reach ~10%?

Answer: As specified before, a strict monitoring of data quality will be performed during the study with special attention on outcomes and relevant variables. For this reason, we did not except a large amount of missing data and we did not plan a priori multiple imputation. However, we will surely consider multiple imputation when missing data will exceed 10%.

Minor points:
Strengths and limitations of the study
(SL1) First paragraph, remove «and» in «and ventilator strategies».
(SL2) Add a dot «.» at the end of the second paragraph.

List of abbreviations and relevant definitions
(ABB1) The letter «M» in the acronym «ESICM» has not been defined.
(ABB2) The word «Glasgow» is lacking in the acronym «GOSE».
(ABB3) Last paragraph, the word «hypothesis» is singular. Do authors mean «a single hypothesis» or potentially many «hypotheses»?

Answer: Thank you, all these points have been modified/corrected in the revised manuscript

On a side note, there are so many acronyms throughout the manuscript that it is sometimes difficult to read, authors could keep them at a minimum without much impact on the article's length. Moreover, some acronyms are defined but not used consistently afterwards (e.g. length of stay).

Answer: Thank you, we have reduced the number of acronyms and made them consistent thorough the revised manuscript

Abstract.
(AB1) Section «Methods and analysis», the word «extended» is lacking in the definition of GOSE; in the same sentence, the word «Data» has an unnecessary capital letter.

Answer: Thank you, this has been corrected

Introduction
(I1) Some spaces between words, dots «.» (end of sentences) and references are inconsistent and should be corrected (refs. #12, #13, #14).
(I2) Third paragraph, first sentence, remove «also» in «suggest that also» and move to «[…] without ARDS could also benefit».
(I3) Last paragraph, last sentence: replace «as suggested by» with «as pointed out by» (or replace «is currently missing» with «is currently needed»).

Answer: Thank you, this has been corrected in the revised manuscript

Materials and Methods
(MM1) Section «Objectives». Ensure consistency in syntax. Sentences for secondary objectives 1&3 end with dots «.» while those for objectives 2&4 don't. Similar considerations apply to all sections of the manuscript since inconsistencies are also found elsewhere (e.g. sections inclusion/exclusion criteria, outcomes, data collection, etc.).
(MM2) Ensure consistency relative to spaces (or absence of spaces) between «-» and the first word of the sentences in every enumeration.

(MM3) Section «study procedures and settings». The word «medicine» is lacking in the definition of the acronym «ESICM».

Answer: Thank you, this has been corrected in the revised manuscript

Lack of capacity and Delayed Consent
(LCDC1) First paragraph, 4th line, unnecessary space between «next-» and «of».
(LCDC1) Second paragraph, 3th line, space required between «.» and «At».

Answer: Thank you, this has been corrected in the revised manuscript

Tables
(T1) Remove the unnecessary paragraph in the third row (second column, beginning by «Bilateral opacities […]»).
(T2) Table 5. In the title, replace «Terapy» by «Therapy».
(T3) Table 5 has no legend for its abbreviations (ICP, CPP, CSF, CO2).
(T4) Table 6, the title says «extended» Glasgow Outcome Scale, but the table actually corresponds to the standard GOS (it contains only 5 categories instead of 8 for GOS-E).

Answer: Thank you, this has been corrected in the revised manuscript

Figure
(F1) The figure has no legend for abbreviations (GOSE, ICU, ABGs).
Answer: Thank you, the legend for abbreviations has been now added in the revised manuscript, as required.

References
(R1) Reference #14 Serpa (2012) contains a comment that seems to be addressed to coauthors and not to readers.
(R2) Reference #17 Della Torre (2017) differs in style (a part of the title is underlined).
(R3) Reference #18 Robba (2020) has been published and is no longer «in press», update required.
(R4) Reference #20 Asehnoune (2018) seems to have an unnecessary space between the words «respiratory» and «management».
(R5) Reference #27 Karalapillai (2020) is problematic (it contains an unnecessary paragraph).

Answer: Thank you, the references have been corrected

Reviewer: 2
Dr. Guo-yi Gao, Shanghai Jiao Tong Univ
Comments to the Author:
1- The author mentioned later in the part of sample size calculation that 4000 coma patients will be recruited. However, the GCS is absent in the inclusion criteria.

Answer: Thank you. The aim of this study is to assess the ventilator strategies of brain injured patients requiring mechanical ventilation. This could be due to neurological and or respiratory causes

and therefore we did not include a specific threshold of GCS for inclusion criteria, but it is a data which will be collected at admission and daily in the study. This has been better specified in the revised manuscript.

2- The author please consider to include ICP monitoring as the inclusion criteria, as ICP is indicated the major clinical parameter when observing the ventilating policy in this trial.

Answer: Thank you, we agree that ICP monitoring is an important clinical parameter. However, as this is an observational study, we aim to assess the ventilator strategies of all brain injured patients, with and without ICP. As far as the analysis on the presence/absence of high intracranial pressure we included only ICP monitored patients. We added this point in the “plan of analysis” section of the revised manuscript

3- Will the author collect information about the modification of the ventilation policy? Because in the clinical scenario, the fixed ventilation model may be adjusted due to the variation of lung/brain status.

Answer: Thank you for this comment. Yes, daily ventilator settings will be recorded and therefore also the modifications of ventilator settings. As this is an observational study, this study won’t modify the clinical practice regarding ventilator management therefore we will consider the modifications of ventilator strategies during the ICU stay, as suggested.

VERSION 2 – REVIEW

REVIEWER	Tardif, Pier-alexandre
REVIEW RETURNED	06-May-2021

GENERAL COMMENTS	I wish to thank the authors for their detailed response and thoughtful revisions on their study protocol. I am satisfied with their answers/corrections and I do not have any further major comments. Minor edits: -Section Methods/Data Collection, end of the first sentence, revise the syntax. -Section Methods/Plan of analysis: --First paragraph, the acronym GCS has not been defined. --First paragraph, fourth sentence, add «s» to «threshold». --Second paragraph, there’s an unnecessary space at the beginning of the paragraph + add a dot «.» at the end of the sentence. --Second paragraph, second sentence, replace «will be present» by «is present». -Last sentence of the last paragraph, replace «if missing will exceed 10%» by «if missing data exceed 10%».

REVIEWER	Gao, Guo-yi Shanghai Jiao Tong Univ

REVIEW RETURNED	26-Apr-2021

GENERAL COMMENTS	My comments are fully explained. I hope this trial will bring neurocritical care fresh nutrition.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Dr. Guo-yi Gao, Shanghai Jiao Tong Univ

Comments to the Author:

My comments are fully explained. I hope this trial will bring neurocritical care fresh nutrition.

Answer: Thank you for your thoughtful comments, which have importantly improved our manuscript.

Reviewer: 1

Mr. Pier-alexandre Tardif

Comments to the Author:

I wish to thank the authors for their detailed response and thoughtful revisions on their study protocol. I am satisfied with their answers/corrections and I do not have any further major comments.

Answer: Thank you for your thoughtful comments, which have importantly improved our manuscript.

Minor edits:

-Section Methods/Data Collection, end of the first sentence, revise the syntax.

Answer: Thank you, this has been revised

-Section Methods/Plan of analysis:

--First paragraph, the acronym GCS has not been defined.

Answer: Thank you, this has been added

--First paragraph, fourth sentence, add «s» to «threshold».

Answer: Thank you, this has been added

--Second paragraph, there's an unnecessary space at the beginning of the paragraph + add a dot «.» at the end of the sentence.

Answer: Thank you, this has been corrected

--Second paragraph, second sentence, replace «will be present» by «is present».

Answer: Thank you, this has been corrected

-Last sentence of the last paragraph, replace «if missing will exceed 10%» by «if missing data exceed 10%».

Answer: Thank you, this has been corrected