Author’s response to reviews

Title: Mild Traumatic Brain Injury with CT scan abnormality: which patients are safe for discharge? A protocol for the development of a prediction model in a retrospective cohort

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Dear Editor of Diagnostic and Prognostic Research,

Thank you for the time that the reviewers have taken in considering our manuscript and their useful comments. We outline how we have addressed their comments below and have highlighted the changes to the manuscript using track changes.

Yours sincerely,

Carl Marincowitz
Reviewer 1

Main issues:

- In exclusion criteria, why do you exclude patients that are transferred from other EDs when they diagnosed an injury? Or you doing this as to avoid having more "severe" TBIs in your group?

The prognostic model that we are attempting to derive is aimed at helping clinicians in the emergency department assess whether alert patients that have traumatic brain injuries identified by CT imaging on first presentation need hospital admission.

Patients transferred to neurosurgery centres (such as the 2 sites at which data collection is occurring) for admission under specialist neurosurgical care are not first presentation and represent a different and more severely injured population of patients. Their inclusion therefore would make the derived model less applicable to the population of interest.

- Why "intravenous therapy" as an outcome metric? What is "intravenous therapy" here? Osmotic agents to reduce intracranial pressure or are we talking about nutrition? I know many centers who have it as standard therapy of fasting patients with TBI as they "might" need surgery, is this why? Please elaborate.

We agree that intravenous therapy is too general and that the use of osmotic agents is clinically variable. We have therefore removed this from our outcome measure.

- Marshall CT classification was constructed on patients that were unconscious when they arrived to the hospital (thus not optimal for your study), and is not an ordinal score that is suitable for outcome prediction. If you are thinking of including the rather outdated Marshall, I would strongly include other CT classification systems such as the Rotterdam-, Helsinki- and Stockholm CT scores as they have shown to be better outcome predictors (PLoS Med 2017; 14(8):e1002368).
We need a CT classification system that can be derived from the available written CT reports to include in the modelling in order to assess the prognostic value of injury severity. Study investigators have been trained in abbreviated injury scale coding of injuries on CT brain scans by the Trauma Audit and Research Network, which is an accredited trainer, to ensure a reliable and reproducible injury scale coding of CT reports. We have added to the section entitled “Research Team Undertaking Screening and Data Extraction” to emphasise this. There is an established method of mapping from brain injury scale coding to the Marshall Classification system derived from the UK trauma registry.1 We are unaware of an equivalent method for mapping between injury severity coding and other CT classification systems. To apply a different CT classification system, therefore, the CT scans would have to be re-assessed and reported again with a classification score assigned. This is beyond the resources available for this study. However, we will consider how the assigned brain injury scale codes and severity scores map to the Rotterdam and Helsinki scores during the study and see if they improve the prognostic model.

Although the Marshall classification was derived in patients with lower GCS scores than in our study it was used as a common CT scoring system in the validation of the IMPACT and CRASH prognostic studies, both of which included patients that were conscious, and is well validated.2 The use of the Marshal Classification as an ordinal prognostic scale has been described in the literature.3 We are collecting data on the additional factors, such as the presence of traumatic subarachnoid haemorrhage, found to improve the predictive value of newer but less widely validated classification systems.4

- You are likely to have problems scoring "frailty" index in these patients, with a lot of missing variables (similar with Charlson Comorbiditiy Index). There is also a strong likelihood that there will be confounding factors towards patients that were admitted for a longer period of time or that have comorbidities requiring previous hospitalization to have notes that will allow you to calculate these scores. Younger patients with no or little time spent in the emergency department will probably have a lot of missing/uncertain data here. Will you do a subcohort analysis of elderly patients for your frailty index?

The standard care for all patients with brain injuries identified by CT imaging in the UK currently is inpatient hospital admission for a period of observation. Therefore, for the vast majority of patients an inpatient hospital clerking is available and this contains both an assessment of comorbidities and functional status. This will allow an assessment of frailty on almost all patients. Missing data will prevent an assessment only for the small number of patients that self-discharge or are discharged erroneously from the Emergency Department.
It is true that more information to make an assessment of frailty may be available for (frailer) patients with more frequent recent hospital admissions. This may result in there being more accurate frailty scoring of frail patients with increased admissions. However, we don’t believe that this confounds the relationship between frailty and the outcomes of interest which are independent of such previous hospital admissions.

- I would recommend that a special group of investigators assess the CT scans and that this group is blinded to outcome, as this would increase the quality and decrease the risk of bias in the study.

The CT scans have all been reported by neuro-radiologists at the time of injury for clinical purposes. The reporting radiologists, therefore, were in effect blinded to the outcomes that we are interested in. The CT scans are not being re-assessed for the purposes of this study. The use of available CT reports is pragmatic as it is directly applicable to information available during clinical care. Any variability in the accuracy of clinical CT reports will introduce random error (rather than bias) and will potentially lead to more conservative estimates of effect.5 We are reassured by a recent Cochrane review assessing the value of central study adjudication which found little deviation between treatment effect estimates for subjective outcomes derived local assessors and those assigned by central study adjudicators.6 We also do not have the resources to undertake the re-assessment of all CT scans included in the study.

Minor issues:

Abstract: Page 2, Line 14: Remove "and" (or "so").

This change has been made.

Introduction: Page 3, Line 19: I would include in regards to clinical deterioration "due primarily to intracranial hematoma progression"
This change has been made.

M&M: Page 5, Line 17: "whist" = whilst

This change has been made.


This sentence has been changed to: This may underestimate deterioration following discharge especially if patients die in the community or deteriorate and are readmitted to a different hospital.

Reviewer 2

1) In the inclusion criteria please elaborate on the definition of traumatic brain injury. Be more specific about the mechanism of trauma and the CT findings that were deemed eligible. Also you mention in the exclusion criteria that you excluded spontaneous intracranial hemorrhage. How was that ascertained? Moreover, please give more details on which type of pre-existing brain pathologies you excluded.

We have amended the sections entitled inclusion and exclusion criteria to make these definitions more specific. In the section entitled inclusion criteria we explicitly state that all patients with brain injuries identified by CT that can only be traumatic in origin are included. In the section entitled exclusion criteria we now outline that patients with intracranial bleeds that could either be spontaneous or traumatic in aetiology without a documented mechanism of injury that could result in head trauma or without physical evidence of head injury are excluded on the basis that they have spontaneous bleeds. In the section entitled exclusion criteria we now list the pre-existing brain pathologies that we exclude if they prevent the timing of injury.
2) In the study outcome you mention as part of the composite endpoint "intravenous therapy whilst an inpatient". Please clarify what type of treatment that includes eg antibiotics, antiepileptic medication.

In light of this comment and a similar comment from Reviewer 1 we have removed as an outcome measure.

3) Page 8, line 2 : you mention that predictors that you will retain in the multivariate model prediction having great clinical relevance. Do you mean that this is true even if they don't fulfill the p-value criterion? What is your rationale for that?

Our sample size and estimated prevalence of outcomes means that we can assess up to 20 factors in a multivariable model. We are collecting data on more than 20 factors and will have to choose which factors to assess in the multivariable model to undergo backward elimination. This will be in part determined by the univariable associations that we find but we will also initially include factors that are clinically relevant, irrespective of univariable statistical significance. They will not be retained following backward elimination if they are not statistically predictive of the outcomes of interest. The second paragraph of the section entitled model development has been changed to clarify this.

4) You mention that according to your sample size and the expected prevalence of the outcome that allows the model to include 20 variables. However this is a very big number of variables for a model to allow application in acute care settings. A prediction model that is intended for use in the emergency department should include a small number of factors, that are easily and quickly measured.

The quoted 20 variables that can be included in the model simply represents the largest number of variables that be included in the modelling process at the same time and have enough statistical power based on our sample size calculation.
We agree that a parsimonious model that includes the smallest number of easily obtained factors would be desirable and the most practically applicable within the clinical context of the Emergency Department. We will include up to 20 factors as our starting point and then reduce the number of included variables whilst optimising the prognostic model’s sensitivity to the outcome of interest.

5) Please specify the method you will use for imputation of missing values

Missing data will be addressed based on a missing at random assumption using multiple imputation using STATA. The exact methods will be determined by the amount, type and distribution of missing data and therefore we cannot describe the methods precisely until data collection is complete. However, we will adhere to guidelines published in the BMJ regarding the use and reporting of methods to deal with missing data. The section entitled missing data has been modified to clarify this.

6) If you have access in the Italian cohort why not perform external validation then? Why did you decide to compare results only?

The Italian cohort represents a modestly sized group (approximately 700) of eligible patients in which not all the factors that we are assessing have been measured. We therefore felt that it may not be possible to validate the model in this cohort and if it were possible the estimated precision would be limited by the sample size. We therefore decided to only undertake the outlined exploratory analysis and plan to validate the derived model in larger and more comprehensive Center TBI study data.
7) Page 10, paragraph 2nd of limitations please rephrase the paragraph, it is very difficult to comprehend

This paragraph has been rephrased as follows:

“Outcomes will only be assessed during hospital admission and for those who re-attend the study hospitals following discharge. This may underestimate deterioration following discharge especially if patients die in the community or deteriorate and are readmitted to a different hospital. We will estimate the effect of this possible bias by conducting a sensitivity analysis using data for the sub-set of patients registered on the Trauma and Audit Network Database where complete data following discharge is available.”

8) Figure 1: I would propose one column with the factors and group them by source of inclusion

Table 1 has been modified accordingly

9) Comment on midline shift and size of bleed are two factors that suffer greatly from lack of interobserver agreement. How will this be assessed, qualitatively or quantitatively?

The size of the largest bleed and presence of midline shift will be taken from the written CT reports provided by a neuro-radiologist at the time of injury. We agree there may be some inter-observer variation between individual neuro-radiologists in assessing these factors that may introduce random error. This reflects real clinical practice and so makes the use of variables derived in this way more practically applicable. Random error may reduce the effect estimates but will not bias the results.5

10) When you mention CT head report as a factor what do you mean? How is that assessed?

This was included in error and has been removed.
11) GCS as a variable in the final model is dependent on the eligibility criteria you set and has low variability. I would propose to omit it as a variable.

In our recently published systematic review assessing prognostic factors in GCS13-15 patients with injuries identified by CT imaging we found that even in this small range initial GCS was highly predictive of clinical deterioration so we think it should be retained initially.9 If it does not add significant independent predictive value then it will be removed from the model.

12) Please add in table 1 for each candidate factor how it will be handled (as a categorical or continuous variable)

Table 1 has been amended accordingly.


