Peer Review File

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## REPLY TO REVIEWER A

**1)** In line 115-116 is written 'We reviewed presenting arterial glucose levels, serum lactate and pH levels as well as their subsequent peak values recorded in the PICU…'. In the limitations is written: '…the frequency of monitoring of these metabolic markers, and thresholds for intervention were likely to differ across sites and some confounders may not be known'. How many samples were available per patient? What about outliers? Was a single value enough to be classified as 'hyperglycemia'? This needs to be clarified in the Methods.

**Response**

**We thank the reviewer for this comment. Being a non-interventional study, we did not standardize the frequency of blood-taking and we recognize variability in clinical practices and TBI protocols among study sites. We have clarified this in the methods:**

**Changes in the text**

***Methods; Variables and Definitions (Paragraph 1, Pages 5-6 Lines 116-120):***

**"We reviewed presenting (initial) arterial glucose levels, serum lactate and pH levels as well as peak values recorded at 0-24 hours, 24-48 hours and 48-72 hours. Being an observational study, we did not standardize the frequency of blood-taking. Hyperglycemia was defined as a single glucose reading > 11.1 mmol/L and hypoglycemia was defined as glucose < 4.0 mmol/L (3,14)."**

**2)** 'On page. 6 is written: 'Among these 108 patients with early hyperglycemia, 15 (13.8%) received insulin therapy within the first 24 hours'. However, on page 4 (Variables and definitions) was not given that these data was collected. What about the remaining 93 patients? Could it be that patients were classified in the group 'throughout the first 72 hours', because limited attempts were made to restore the laboratory values? What was the clinical management protocol in the centers?

**Response**

**Thank you for your comment. We did collect data on the administration of insulin therapy throughout the first 72 hours of PICU admission, including data on which time point insulin therapy was initiated in the first 72 hours. We recognize that individual centers' threshold to initiate insulin would have differed, and this may have affected the glucose levels that were documented.**

**Changes in the text**

***Methods; Variables and Definitions (Paragraph 1, Page 6, Line 126):***

**"We also recorded the presence of insulin administration in the first 72 hours."**

**3)** The statistical analysis needs some clarification. In line 143-144 is written: "We performed an univariate logistic regression analysis to determine if each laboratory marker predicted for unfavorable outcome." However, statistical results are shown for demographics as well. Please, clarify these statistics. In addition, in the statistical section is written: 'Categorical data were summarized by percentages', but for clarity please add '…frequencies and percentages'.

**Response**

**Thank you for your feedback. The manuscript now reads:**

**Changes in the text**

***Methods, Statistical Analysis (Paragraph 1, Page 7, Lines 143-147)***

**"Categorical data were summarized by frequencies and percentages, while continuous variables were expressed as median with interquartile range (IQR). We performed a univariate logistic regression analysis to determine if specific demographic factors, such as gender and age, alongside each laboratory marker – glucose, lactate and pH – predicted for unfavorable outcome."**

**4)** 'Statistics on line 222 – 224 are not clear to me. In Table 5 are separate groups for the clinical outcome reported (Good, mild etc.) and not UO/FO. Which statistics were applied? (individual outcomes or UO/FO?)

**Response**

**Thank you for highlighting the above. We have clarified the statement.**

**Changes in the text**

***Results, Association of Lactatemia and Acidosis with Clinical Outcome (Paragraph 1, Page 10, Lines 225-229)***

**"Table 5 shows clinical outcomes between children with high lactate > 2.0mmol/L in the first 24 hours compared to those without. There was a greater proportion with moderate disability, severe disability, vegetative state or coma, and death cumulatively in those with high lactate compared to those without (74/130, 56.9% compared to 53/121, 43.8%, $p < 0.001$) (Table 5).**

**5)** P. 4/line 111. '..or who had minor injuries were excluded'. Please, clarify 'minor'?

**Response**

**Thank you for your suggestion. We have clarified our inclusion criteria and patient population as below.**

**Changes in the text**

***Methods, Study design, Setting and Population (Paragraph 1, Page 5, Lines 106-112):***

**"We included patients with both isolated TBI and TBI in the presence of poly-trauma – defined as the presence of other extracranial injuries including intra-thoracic, intra-abdominal injuries and long bone fractures. Following the initial publication, we aimed to investigate early post traumatic seizures in children (cite EPTS paper here), as well as biochemical alterations in TBI. Among the 10 centers, 8 centers responded to our call and were able to provide further data on existing patients. Data were obtained using a standardized electronic REDCap data collection form."**

**6)** STROBE. The page numbers in the document do not correspond to the article page numbers. In addition, item 10 (sample size) is not described in the article. Did the authors perform a power analysis?

**Response**

**We thank the reviewer for highlighting the above. We have rectified the STROBE checklist prior to re-submission. This was a secondary analysis of a retrospective multi-center TBI cohort, hence, we did not perform a power analysis to determine the sample size for the study.**

**7)** P. 4 line 104/105 '..with variables determined a priori'. Please, clarify.

**Response**

**The phrase 'with variables determined a priori' was intended to explain that the variables were agreed upon by the primary investigating team before data collection started in all sites. In view that this is confusing, we have removed it. We explained the specific variables that were collected in the paragraphs that follow.**

**Changes in the text**

***Methods, Study design, Setting and Population (Paragraph 1, Page 5, Lines 111-112):***

**"Data were obtained using a standardized electronic REDCap data collection form."**

**8)** P.3 line 87-88 Please, clarify morbidity in this sentence in relation to the references.

**Response**

**Thank you for your comments. We have elaborated on our statement**

**Changes in the text**

***Introduction (Paragraph 3, Page 4, Lines 88-90):***

**"Furthermore, while lactate and acidosis in adult multisystem trauma are associated with massive hemorrhage and prolonged ICU admission (16,17), there is a paucity of literature examining their roles as prognostic markers in pediatric TBI (2,4)."**

**9)** Who assessed the PCPC score. Was this in each center similar?

**Response**

**Thank you for your question. The PCPC score was assessed by intensivists in the PICU at each center. We have rectified the manuscript to include this.**

**Changes in the text**

***Methods, Study design, Outcome Measures (Paragraph 1, Page 6, Lines 131-133):***

**"Our primary outcome of interest was functional outcome on discharge from the PICU, measured by the Pediatric Cerebral Performance Category (PCPC), assigned by intensivists in each PICU."**

**10)** The total percentage of missing values was 2.2% (given in the limitations). Could the authors report the number of missing values in the table per variable?

**Response**

**Thank you for your suggestion. We clarify that there were 2.2% of patients from our original cohort of 313 children enrolled into our study, who were excluded due to incomplete PCPC outcomes. Amongst 305 patients analyzed for the study, there were 2.2% (7/305) of patients with missing glucose values, 18.6% (57/305) with missing lactate values and 1.9% (6/305) of patients with missing pH values. We have detailed these into the tables accordingly.**

**Changes in the text**

***Results, Patient Demographic (Paragraph 1, Page 8, Lines 170-172):***

**"Amongst the 305 children analyzed for the study, there were 2.2% (7/305) with incomplete glucose values, 18.6% (57/305) with missing lactate values and 1.9% (6/305) with missing pH values."**

**11)** Table 1. The value 'persistent hyperglycemia > 11.1 mmol/L beyond 48 hours' is 108 (36.2) in the table, but 108 (36.3) in the text. Please, check the correct value.

**Response**

**Thank you for highlighting this. We have corrected the error in the manuscript.**

**Changes in the text**

***Results, Association of Hyperglycemia with Clinical Outcome (Paragraph 1, Page 8, Lines 182-183):***

**"There were 108 patients (36.2%) with early hyperglycemia within the first 24 hours of PICU admission (Table 1)."**

**12)** Figure 1. Could the authors report the number of patients per category in the figure. In addition, could the authors add to the y-axis 'PCPC Score at ICU discharge'.

**Response**

**We thank the reviewer for his suggestion. We have amended Figure 1 accordingly.**

**Changes in the text**

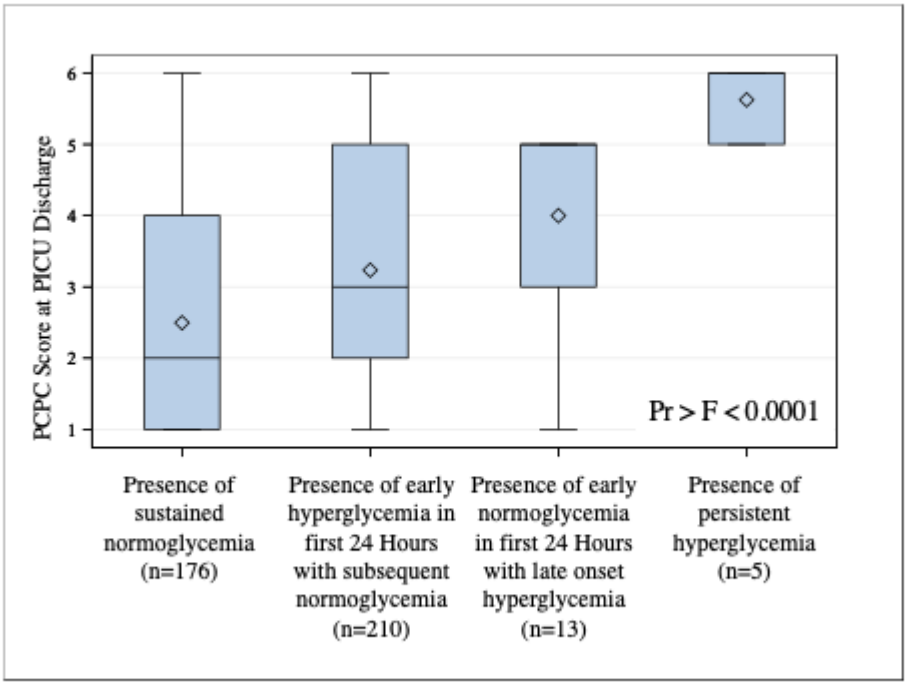


**Figure 1** PCPC – Pediatric Cerebral Performance Category; PICU – Pediatric Intensive Care Unit

Scores assigned as (1) Good (2) Mild Disability (3) Moderate Disability (4) Severe Disability (5) Vegetative state or coma (6) Death; with unfavorable PCPC outcome defined as Moderate Disability, Severe Disability, Vegetative state or coma, Death

**13)** Table 1. What is meant by 'non-accidental injury'? Violence?

**Response**

**We define non-accidental injury as injury that is purposefully inflicted onto the child. This includes any violent, physical act performed to the child.**

**Changes in the text**

**Table 1: Patient demographics, clinical characteristics and metabolic markers**

| | **Total (n= 305)** | **Patients with favorable [a] PCPC[1] outcome (n = 169)** | **Patients with unfavorable [b] PCPC outcome (n= 136)** | **P-value[+]** |
|---|---|---|---|---|
| **Age (years), median (IQR)** | 4.2 (1.8, 8.8) | 4.3 (1.8, 8.6) | 3.6 (1.8, 9.0) | 0.807 |
| **Gender (males), *n* (%)** | 207 (67.9) | 121 (71.6) | 86 (63.2) | **0.029** |
| **Severe TBI[2] with Glasgow Coma Scale </= 8, *n (%)*** | 169 (55.4) | 67 (39.6) | 102 (75.0) | **<0.001** |
| **Mechanism of Injury, *n* (%)** | | | | 0.054 |
| **Road Traffic Accident** | 133 (43.6) | 64 (37.9) | 69 (50.7) | - |
| **Fall** | 133 (43.6) | 81 (47.9) | 52 (38.3) | - |
| **Non-accidental Injury*** | 22 (7.2) | 13 (7.7) | 9 (6.6) | - |
| **Others** | 17 (5.6) | 11 (6.5) | 6 (4.4) | - |
| **Presence of Polytrauma, *n (%)*** | 174 (57.0) | 80 (47.3) | 94 (69.1) | **<0.001** |
| **First Presenting Glucose (mmol/L), median (IQR[3])** | 8.4 (6.5, 12.1) | 7.9 (6.3, 9.6) | 9.5 (6.9, 14.8) | **<0.001** |
| **Admission Hyperglycemia > 11.1 mmol/L, *n* (%)** | 76 (24.9) | 19 (11.2) | 57 (41.9) | **<0.001** |
| **Early Hyperglycemia > 11.1mmol/L in first 24 Hours, *n* (%)** | 108 (36.2) | 33 (19.5) | 75 (55.1) | **<0.001** |
| **Presence of Persistent Hyperglycemia > 11.1mmol/L throughout first 72 Hours, *n* (%)** | 5 (1.6) | 0 (0.0) | 5 (3.7) | 0.179 |

| | | | | |
|---|---|---|---|---|
| **Presence of Late-Onset Hyperglycemia > 11.1mmol/L beyond 48 Hours, *n* (%)** | 13 (4.3) | 1 (0.6) | 12 (8.8) | 0.239 |
| **Admission Lactate (mmol/L), median (IQR[3])** | 2.2 (1.3, 4.0) | 1.9 (1.2, 3.4) | 2.7 (1.5, 5.2) | **<0.001** |
| **Presence of Early Hyperlactatemia > 2 mmol/L in the first 24 Hours, *n* (%)** | 130 (42.3) | 56 (32.5) | 74 (54.4) | **0.013** |
| **Admission pH, median (IQR[3])** | 7.30 (7.27, 7.41) | 7.35 (7.31, 7.40) | 7.31 (7.23, 7.43) | **0.003** |
| **Presence of Early Acidosis pH < 7.35 in first 24 Hours, *n* (%)** | 163 (53.4) | 78 (46.1) | 85 (62.5) | **0.003** |

[1] PCPC – Pediatric Cerebral Performance Category (PCPC)

[2] TBI – Traumatic Brain Injury

[3] IQR – Interquartile Range

[a] Favorable PCPC outcome defined as PCPC categories of good function and mild disability

[b] Unfavorable PCPC outcome defined as PCPC categories of moderate disability, severe disability, vegetative state or coma or brain death

[+] Statistical significance taken at $p < 0.05$

*Non-accidental injury is defined as injury that is purposefully inflicted onto the child, including any violent physical act.

**14)** The reference to Table 1 in line 185-186 (p.6) seems incorrect.

**Response**

**We thank the reviewer for highlighting this erroneous reference. We have rectified our manuscript to exclude the above.**

**15)** Please, reorder or rewrite sentence 189-190.

**Response**

**We have restructured the paragraph for further clarity as below.**

**Changes in the text**

***Results, Association of Hyperglycemia with Clinical Outcome (i) Early Hyperglycemia and Clinical Outcome (Paragraph 1, Page 8-9, Lines 187-192):***

**"The presence of early hyperglycemia in the first 24 hours of PICU admission was associated with unfavorable PCPC outcome (75/108, 69.4% vs 59/187, 31.5%, p < 0.001) compared to the group with normoglycemia (Table 2). The cohort with early hyperglycemia had increased length of ICU stay compared to those with normoglycemia (8.5 days, IQR 4, 14 vs. 6 days, IQR 3,10; p = 0.004) (Table 2)."**

**16)** Please, reorder or rewrite sentence 234-235. For example: "In our multivariable analysis - after adjusting for gender, presence of polytrauma and presence of admission - hyperglycemia, hyperlactatemia and acidosis were not associated with unfavorable outcomes"

**Response**

**We have amended the concluding statement of our results section as below.**

**Changes in the text**

***Results, Association of Lactatemia and Acidosis with Clinical Outcome (Paragraph 2, Page 10, Lines 238-240):***

**"In our multivariable analysis, after adjusting for gender, presence of polytrauma and concomitant presence of admission hyperglycemia, hyperlactatemia and acidosis were not associated with unfavorable outcomes (Supplementary Table 2, 3)."**

**17)** Typing mistakes
- Please, check the word multicenter / muti-center throughout the paper for consistency
- Gender should be replaced for sex
- P.3 line 76 'altercations' replace for 'alterations'
- Please check the word 'unfavorable functional outcome' and 'unfavorable outcome' for consistency

**Response**

**We thank the reviewer. We have reviewed the above and made the necessary adjustments for consistency throughout our manuscript.**

**REPLY TO REVIEWER B**

1) Critique of sections:
   Abstract:
   Clear, though I do think it is necessary to add in L 40-41 that "unfavourable outcome at the time of ICU discharge as Paedatric…" is what constitutes unfavorable outcome.

**Response**

**We thank the reviewer for your feedback. We have edited our abstract as follows.**

**Changes in the text**

***Abstract, Background (Page 2, Lines 40-43):***

**"To study the association in moderate and severe pediatric traumatic brain injury (TBI) between hyperglycemia, hyperlactatemia, acidosis and unfavorable outcome, as assessed by Pediatric Cerebral Performance Category (PCPC) on discharge from the pediatric intensive care unit (PICU)."**

2) Methods:
   Subject selection: I struggled with comparison of the present cohort with the Chong et al 2020 cohort. It would be helpful to revise this section by highlighting the differences of the present cohort with the Chong et al 2020 cohort. Variable definitions relevant to the present study (L 113-136) are clear. Statistical analysis and ethics sections were clear.

**Response**

**Thank you for your comment. Our study cohort was a subset of the TBI cohort studied in Chong et al. 2020. We have clarified this under the methods section.**

**Changes in the text**

***Methods, Study design, Setting and Population (Paragraph 1, Page 5, Lines 102-112):***

**"We performed a secondary analysis of the retrospective, multi-center Pediatric Acute and Critical Care Medicine Asian Network (PACCMAN) TBI data set, involving 10 pediatric intensive care units from January 2014 to October 2017 (20). This was a multi-national population that included 380 children < 16 years old with a Glasgow Coma Scale (GCS) Score ≤ 13, and who presented within 24 hours of head injury. We included patients with both isolated TBI and TBI in the presence of poly-trauma – defined as the presence of other extracranial injuries including intra-thoracic, intra-abdominal injuries and long bone fractures. Following the initial publication, we aimed to investigate early post traumatic seizures in children (cite EPTS paper here), as well as biochemical alterations in TBI. Among the 10 centers, 8 centers responded to our call and were able to provide further data on existing patients. Data were obtained using a standardized electronic REDCap data collection form."**

3) Results:
Subheadings would make it easier to appreciate the importance of the results.

**Response**

**Thank you for your suggestion. We have edited the results section to include subheadings of 'Patient Demographic', 'Association of Hyperglycemia with Clinical Outcome' with further subheadings of '(i) Early Hyperglycemia and Clinical Outcome' and '(ii) Late Onset Hyperglycemia and Clinical Outcome', and 'Association of Lactatemia and Acidosis with Clinical Outcome'.**

4) There are too many tables with overlapping information, and sometimes text descriptions overlap as well.

In the text descriptions, for example, L 177-180 are repeated at line 188-190 to give an odds ratio for early hyperglycemia and poor outcome, to add another risk factor (longer ICU stay), as well as to note the fact that duration of ventilation and duration of hospitalization did not impact outcome. All this information about the predictive value of early hyperglycemia could be combined in one location. Similarly, information about the odds ratio and predictive value of late onset hyperglycemia (L 203-204) could be combined with the earlier section (L 183-185). It would be clearer if all the PCPC scores were listed with their variable of interest (e.g., persistent hyperglycemia), rather than listed repetitively later on. Then L 210-213 follow nicely.

**Response**

**Thank you for your advice. We have rectified the manuscript to consolidate our results in a more succinct manner.**

**Changes in the text**

***Results, Association of Hyperglycemia with Clinical Outcome; Early Hyperglycemia and Clinical Outcome (Paragraph 1, Pages 8-9, Lines 187 –197):***

**"The presence of early hyperglycemia in the first 24 hours of PICU admission was associated with unfavorable PCPC outcome (75/108, 69.4% vs 59/187, 31.5%, p < 0.001) compared to the group with normoglycemia (Table 2). The cohort with early hyperglycemia was also found to have an increased length of ICU stay compared to those with normoglycemia (8.5 days, IQR 4, 14 vs. 6 days, IQR 3,10; p = 0.004) (Table 2). Early hyperglycemia in the first 24 hours however, was not associated with a longer duration of ventilation (5 days, IQR 2, 9 vs. 4 days, IQR 2, 8; p = 0.186) or duration of hospitalization (23 days, IQR 9, 35 vs. 14 days, IQR 8, 29; p = 0.233) compared to the normoglycemia group (Table 2). In our sensitivity analysis, we found a consistent association between early hyperglycemia (when defined within the first 48 hours) and unfavorable outcome (Supplementary Table 1)."**

***Results, Association of Hyperglycemia with Clinical Outcome; Late-onset Hyperglycemia and Clinical Outcome (Paragraph 1, Page 9, Lines 205 –210):***

**"Amongst 13 patients who developed late-onset hyperglycemia at 48-72 hours of admission, 12 (92.3%) had unfavorable outcome. We found that the presence of late-onset**

**hyperglycemia was associated with unfavorable outcome (aOR 13.30, 95% CI 1.64 – 107.8, p = 0.015) (Table 4). We were unable to perform multivariable analyses for the subgroup with persistent hyperglycemia as all progressed to have unfavorable outcomes."**

5) For the tables: Fig 1 is important and clear. Information in Tables 2-6 could be presented differently. The demographic data could be shown in one table. Clarification in the text as to how the present cohort differs from that presented in the Chong et al paper could be made (if that is not covered in the subject selection section). Some of the data in Tables 2-6 are presented in text and that might be sufficient, with the remainder available in a single supplementary table. Presentation of the ROC as Supplementary Fig 1 is clear. Supplementary Table 2 might be able to be combined with other data from Tables 2-6.

**Response**

**Thank you for your comment. We have endeavored to clarify differences between the present cohort and the cohort in our primary analysis as below. We thank the reviewer for his/her suggestion on revising our tables. Our rationale for drawing up Tables 2-6 is that each table presents data on a different main risk factor of interest – hyperglycemia, lactatemia and acidosis. Therefore we had chosen to present each biochemical marker separately in each table for clarity.**

**Changes in the text**

***Methods, Study design, Setting and Population (Paragraph 1, Page 5, Lines 102 – 112):***

**"We performed a secondary analysis of the retrospective, multi-center Pediatric Acute and Critical Care Medicine Asian Network (PACCMAN) TBI data set, involving 10 pediatric intensive care units from January 2014 to October 2017 (20). This was a multi-national population that included 380 children < 16 years old with a Glasgow Coma Scale (GCS) Score ≤ 13, and who presented within 24 hours of head injury. We included patients with both isolated TBI and TBI in the presence of poly-trauma – defined as the presence of other extracranial injuries including intra-thoracic, intra-abdominal injuries and long bone fractures. Following the initial publication, we aimed to investigate early post traumatic seizures in children (cite EPTS paper here), as well as biochemical alterations in TBI. Among the 10 centers, 8 centers responded to our call and were able to provide further data on existing patients. Data were obtained using a standardized electronic REDCap data collection form."**