PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Evaluating Glial and Neuronal Blood Biomarkers GFAP and UCH-L1 as Gradients of Brain Injury in Concussive, Subconcussive and Nonconcussive Trauma: a Prospective Cohort Study
AUTHORS	Papa, Linda; Zonfrillo, Mark; Welch, Robert; Lewis, Lawrence; Braga, Carolina; Tan, Ciara; Ameli, Neema; Lopez, Marco; Haeussler, Crystal; Mendez Giordano, Diego; Giordano, Philip; Ramirez, Jose; Mittal, Manoj

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Rachel Hilliam Institution and Country: The Open University, UK Competing interests: None
REVIEW RETURNED	10-Mar-2019

GENERAL COMMENTS	This is a very well written paper with appropriate statistical tests for the data which are well explained. I think it would help if table 1 was split between children and adults within each of the three groups. Particularly as the focus of the journal is paediatrics. The limitations of the study in terms of data in the later time points are well noted in the paper and the multiple testing accounted for. There are a couple of small typing errors to the paper would benefit from a final read.

REVIEWER	Reviewer name: Julian Bailes Institution and Country: NorthShore University HealthSystem, University of Chicago Pritzker School of Medicine United States Competing interests: None
REVIEW RETURNED	13-Apr-2019

GENERAL COMMENTS	The authors present a prospective cohort study of blood biomarkers of subconcussion and concussion in level one trauma centers in the United States over time. The main finding is that GFAP was the more sensitive at detecting concussion than others tested. The study is well designed and of interest. Comments: Although these was no significant findings please elaborate more on the role and importance of subconcussion in this population and relevance of biomarkers in this population. A good reference is Bailes et al. J Neurosurg 2013. What is the potential for future saliva tests? This can be done without blood sampling?

	Was there any accounting for past concussion history or contact sports participation? Do authors believe that GFAP could be s stand-alone test for the future?

REVIEWER	Reviewer name: Jovany Cruz Navarro Institution and Country: Baylor College of Medicine Competing interests: None
REVIEW RETURNED	24-Apr-2019

GENERAL COMMENTS	Another nicely executed work by Dr. Papa and colleagues. The authors should be congratulated for a nicely developed study design. The paper is readable and relatively easy to follow. No grammar concerns. I only have a few comments/suggestions: Table 1. Might want to add female patients in demographics Table 1. Regarding CT scan. Did patients with intracranial lesions had performance levels of GFAP and UCH-L1 significantly different compared to patients without intracranial lesions? If information is available, probably should be included in the manuscript. Page 14 - Line 45-60 - Could develop a table indicating sampling time and n=value rather than plain text. Figure 1. Number of children in table does not match values within text. 175 vs. 176 and 371 vs. 372

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1)   COMMENT: I think it would help if table 1 was split between children and adults within each of the three groups. Particularly as the focus of the journal is paediatrics.

RESPONSE: As suggested, we have split the table to include each of the three groups in children and adults separately.

2)   COMMENT: There are a couple of small typing errors to the paper would benefit from a final read.

RESPONSE: As suggested, the manuscript has been reviewed and typographical errors corrected.

Reviewer: 2

3)   COMMENT: Although there were no significant findings please elaborate more on the role and importance of subconcussion in this population and relevance of biomarkers in this population. A good reference is Bailes et al. J Neurosurg 2013.

RESPONSE: As suggested, this reference has been added and the discussion expanded. The following additions to the discussion have been made:

"Emerging data have demonstrated that significant alterations in brain function can occur in the absence of clinically obvious symptoms following even a single head trauma. Given the lack of concussive symptoms acutely, biomarkers (such as GFAP and UCH-L1) could provide a more objective measure of injury and potentially identify those at risk for neurocognitive problems."

"To date, there is a lack of studies addressing the effects of subconcussive head impacts following head trauma in an emergency department population. Acute biomarkers may have a role in assessing these patients if the markers can be shown to correlate with long-term neurocognitive dysfunction. Most recently, microRNA biomarkers measured pre and post-season in collegiate football players were associated with worsening neurocognitive functioning over the course of a season in those with no concussions."

4)   COMMENT: What is the potential for future saliva tests? This can be done without blood sampling?

RESPONSE: Ongoing studies are evaluating the potential of saliva testing to replace blood testing.

5)   COMMENT: Was there any accounting for past concussion history or contact sports participation?

RESPONSE: About 5% of patients reported prior concussions. About half of these were due to contact sports.

6)   COMMENT: Do authors believe that GFAP could be a stand-alone test for the future?

RESPONSE: GFAP appears to be among the strongest acute brain injury biomarkers to date. Whether it can be a "stand-alone test" needs further validation. Although the FDA has approved GFAP and UCH-L1 as a panel for use in mild-to-moderate TBI for detecting intracranial lesions on CT scan in adults within 12 hours of injury, it has not been approved to diagnose concussion.

Reviewer: 3

7)   COMMENT: Table 1. Might want to add female patients in demographics

RESPONSE: As suggested, we have added female patients to the demographics.

8)   COMMENT: Table 1. Regarding CT scan. Did patients with intracranial lesions had performance levels of GFAP and UCH-L1 significantly different compared to patients without intracranial lesions? If information is available, probably should be included in the manuscript.

RESPONSE: As suggested, we have added the following statement, "There were significantly higher levels of GFAP and UCH-L1 in those with intracranial lesions on CT, therefore, we excluded the 36 (8%) patients with CT lesions and found similar results (Figure 4)."

9)   COMMENT: Page 14 - Line 45-60 - Could develop a table indicating sampling time and n=value rather than plain text.

RESPONSE: The numbers (n) for each of the sampling times are summarized in Table 4.

10)   COMMENT: Figure 1. Number of children in table does not match values within text. 175 vs. 176 and 371 vs. 372.

RESPONSE: This was a typographical error and has been corrected.