Burns & Trauma, 2020, 8, tkaa034
doi: 10.1093/burnst/tkaa034
Letter to Editor

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Assessment of plasma 12(S)-Hydroxyeicosatetraenoic acid as a biomarker to predict mortality in adults with severe trauma

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To the Editor

Identification upon admission of a group of patients with severe traumatic injury presenting with a higher risk of death is crucial in designing personalized treatment strategies [1]. However, there are as yet limited biomarkers for the prediction of mortality in patients with traumatic injury. 12(S)-Hydroxyeicosatetraenoic acid (12(S)-HETE), as a classic metabolite of arachidonic acid, was suggested to be a potential biomarker in brain injury [2] or subarachnoid hemorrhage [3]. Here we report on a prospective observational analysis of the biomarker 12(S)-HETE in plasma samples collected from 76 adult patients with traumatic injury admitted to the emergency department (ED) (within the first 48 h post-trauma) and 25 healthy adults from two tertiary teaching hospitals in Chongqing between October 2018 and October 2019.

The baseline demographics and clinical characteristics of traumatic subjects ($n = 76$) were collected at admission and are presented in Table 1. The average age was 50.8 ± 15.8 years and the majority (73.7%) was male, with no significant differences compared with the control group ($n = 25$). For all trauma subjects, the interval from injury to blood extraction was 17 (11–29) h. The injury types were divided into isolated intracranial lesions (IL, 13.2%) or isolated extracranial lesions (EL, 50.0%) or a combination of both lesion types (IL + EL, 36.8%). Based on the injury severity score (ISS), traumatic patients were classified into two subgroups: mild trauma patients (ISS< 16, $n = 23$) and severe trauma patients (ISS≥ 16, $n = 53$). Admission levels of plasma 12(S)-HETE were markedly elevated in the severe group compared with the mild group (severe vs. mild: 4.26 [1.27–7.40] vs. 1.54 [0.24–2.71] ng/ml, $p = 0.005$) or control group (severe vs. control: 4.26 [1.27–7.40] vs. 0.55 [0.13–1.13] ng/ml, $p < 0.001$) while there was no significant difference between the mild and control groups. The endpoint was defined as death. Patients who died at any point during their initial hospitalization were considered as meeting the mortality outcome. In our study, non-surviving patients ($n = 8$) showed significantly higher admission levels of plasma 12(S)-HETE than survivors ($n = 68$) (non-survivor vs. survivor: 11.17 [7.24–13.10] vs. 2.10 [0.71–5.40] ng/ml, $p < 0.001$). Spearman's correlation analysis showed admission 12(S)-HETE levels were correlated with ISS ($\rho = 0.419$, $p < 0.001$), acute physiology and chronic health evaluation II (APACHE II) ($\rho = 0.499$, $p < 0.001$), revised trauma score (RTS) ($\rho = -0.477$, $p < 0.001$) and trauma and injury severity score (TRISS) ($\rho = -0.508$, $p < 0.001$). Multivariate linear regression revealed five factors independently related to admission 12(S)-HETE levels, including APACHE II scores at admission, hypoxia at admission, external abbreviated injury score (AIS), head and neck AIS and time from injury to first blood extraction (Table 2).

To investigate whether 12(S)-HETE levels are useful in predicting mortality in traumatic patients, a binary logistic regression was conducted. Of note, elevated 12(S)-HETE predicted mortality even after adjustment for gender, age, injury severity, cause of injury and injury types. Receiver operating characteristic (ROC) curves were conducted (Figure 1) using 12(S)-HETE, APACHE II, RTS and TRISS, of which the last three are the common clinical predictors in severe trauma [4]. Mortality ROC for 12(S)-HETE revealed an area under the curve (AUC = 0.936; 95% CI: 0.878–0.993) for non-survivor detection that was higher than the AUC for APACHE II (AUC = 0.923; 95% CI: 0.842–1.000),

Table 1. Basic demographics and clinical characteristics of traumatic patients

Variables	Overall (n = 76)	Subgroups		Mild trauma vs. Severe trauma *P* value
		Mild trauma (n = 23)	Severe trauma (n = 53)	
Demographics				
Age, years	50.8 ± 15.8	49.1 ± 13.8	51.6 ± 16.7	$p = 0.544$
Gender, male, n (%)	56(73.7)	13(56.5)	43(81.1)	$p = 0.025$
Time (h)	17(11–29)	16(12–23)	18(11–31)	$p = 0.353$
Medical history, n (%)				
Hypertension	5(6.6)	1(4.3)	4(7.5)	$p = 1.000$
Diabetes	1(1.3)	1(4.3)	0(0)	$p = 0.303$
Cause of injury, n (%)				
Traffic accidents	30(39.5)	12(52.2)	18(34.0)	
Falls	29(38.2)	6(26.1)	23(43.4)	$p = 0.278$
Other	17(22.4)	5(21.7)	12(22.6)	
Injury types, n (%)				
IL	10(13.2)	0(0)	10(18.9)	
EL	38(50.0)	20(87)	18(34.0)	$p = 0.178$
IL + EL	28(36.8)	3(13)	25(47.2)	
Systemic injury severity				
ISS	20.4 ± 10.2	8.6 ± 3.6	25.5 ± 7.6	$p < 0.001$
APACHEII	9(5–14)	5(2.0–11.0)	9(6–16)	$p = 0.002$
RTS	7.84(6.73–7.84)	7.84(7.84–7.84)	7.11(5.97–7.84)	$p = 0.006$
TRISS	0.96(0.87–0.99)	0.99(0.97–1.00)	0.92(0.75–0.97)	$p < 0.001$
Secondary insults, Present, n (%)				
Hypotension at admission	9(11.8)	2(8.7)	7(13.2)	$p = 0.715$
Hypoxia at admission	28(36.8)	2(8.7)	26(43.4)	$p = 0.001$
Biomarkers				
12(S)-HETE (ng/ml)	2.59(0.87–6.46)	1.54(0.24–2.71)	4.26(1.27–7.40)	$p = 0.005$
Clinical data				
Hospital length of stay (days)	26(11–51)	27(8–57)	26(13–44)	$p = 1.000$
ICU length of stay (days)	3(0–11)	0(0–3)	6(2–14)	$p < 0.001$
Laboratory characteristics				
WBC (×109/L)	10.9 (8.5–14.1)	10.6(7.5–13.5)	11.5 (8.7–15.1)	$p = 0.212$
CRP (mg/L)	22.1(13.4–79.4)	23.8(13.8–80.8)	21.1(12.6–81.2)	$p = 0.935$
PCT (ng/ml)	0.63(0.28–2.20)	0.34(0.23–0.53)	0.97(0.29–2.75)	$p = 0.037$

Data normally distributed were reported as mean ± SD, non-normally distributed were reported as median (IQR). Categorical variables are presented as numbers and percentages. Normal distribution was compared using the *t*-test for independent samples. Significance for intergroup differences of non-normal distribution variables was assessed by the Mann-Whitney *U* test. Chi-square tests or Fisher exact tests were used to compare categorical variables. The severity of Traumatic Injury was assessed by ISS: mild (ISS < 16) and severe (ISS ≥ 16). Time: time from injury to blood extraction. Hypotension was defined as the presence or absence of any episode of systolic blood pressure < 90 mmHg within the first 48 h after the trauma event. Hypoxemia was established as a $PaO_2 \leq 60$ mmHg or oxygenation index (PaO_2/FiO_2) <300. *ISS* injury severity score, *IL* isolated intracranial lesions, *EL* isolated extracranial lesions, *IL + EL* a combination of IL and EL, *APACHE II* acute physiology and chronic health evaluation II score, *RTS* revised trauma score, *TRISS* trauma and injury severity score, *ICU* intensive care unit, *WBC* white blood cell, *CRP* C-reactive protein, *PCT* procalcitonin, *IQR* interquartile range

RTS (AUC = 0.874; 95% CI: 0.780–0.968) or TRISS (AUC = 0.922; 95% CI:0.837–0.971). However, there is no significant statistical difference in the AUC among these four predictors. Moreover, 12(S)-HETE showed 100% sensitivity and 83.8% specificity for mortality prediction.

A variety of risk prediction scores, including the RTS and the TRISS, have been used widely to predict mortality after traumatic injury. The APACHE II scoring system is widely used to determine disease severity and predict outcomes in critically ill patients [5] and showed good prognostic value in predicting outcomes in trauma patients [1, 4]. Nonetheless, these scores use so many biochemical variables that they become non-practical for rapid evaluation of the severity of disease in the ED. In our study, 12(S)-HETE showed good prognostic value in classifying mortality during hospitalization of trauma patients and it has the potential to become a prognostic biomarker in addition to the risk prediction scores used in the ED.

Echoing the studies of Westcott *et al*. [6] and Farias *et al*. [2] that elevated levels of 12(S)-HETE could be observed in human cerebrospinal fluid following severe brain injury, we found that the admission plasma 12(S)-HETE level was positively correlated with the degree of consciousness disorder at admission in our subgroup analysis. However, significantly elevated plasma 12(S)-HETE levels were also observed in patients with severe isolated extracranial trauma. We failed

Table 2. Factors independently related to 12(S)-HETE levels (multivariate analysis, linear regression)

Parameters	B	SE	Beta adjusted	*P* value	R^2 change	Multicollinearity	
						Tolerance	VIF
APACHE II at admission	0.229	0.055	0.434	0.000	0.351	0.714	1.401
Hypoxia at admission	3.103	0.843	0.367	0.001	0.076	0.777	1.288
External AIS	2.440	0.841	0.289	0.005	0.060	0.775	1.290
Head and neck AIS	0.588	0.213	0.281	0.008	0.047	0.749	1.336
Time (h)	0.067	0.029	0.209	0.024	0.042	0.954	1.048

AIS in six body regions (head and neck, face, thorax, abdomen, extremities and external) were collected at admission. ISS is equal to the sum of the squares of the three maximum AIS scores. Time: time from injury to blood extraction. $R = 0.759$; $R^2 = 0.575$; R^2 adjusted = 0.537, $p < 0.001$. AIS abbreviated injury score, SE standard error, VIF variance inflation factor, 12(S)-HETE 12(S)-Hydroxyeicosatetraenoic acid. "B" is regression coefficient in regression equation

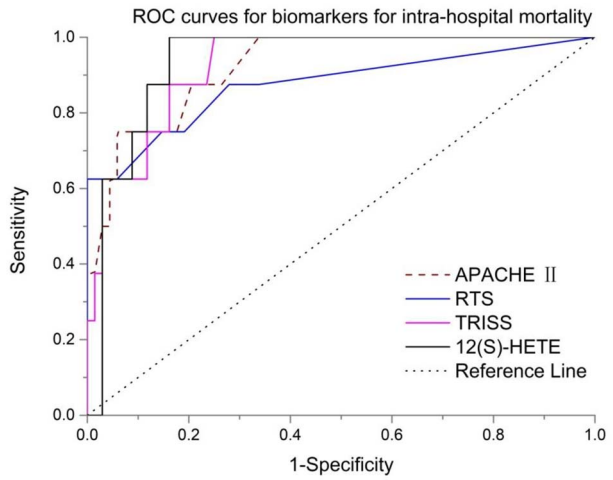

Figure 1. ROC curves for biomarkers of intra-hospital mortality. The AUCs for 12(S)-HETE, APACHE II, RTS and TRISS were 0.936, 0.923, 0.874 and 0.922 respectively. For 12(S)-HETE concentrations, a cut-off value of 6.415 ng/ml showed 100% sensitivity and 83.8% specificity for mortality prediction. For APACHE II score, a cut-off value of 13.5 reached 87.5% sensitivity and 79.4% specificity, while the cutoff (4.09) of RTS discriminated mortality with a sensitivity of 62.5% and a specificity of 100%. For TRISS, J index identified the best cutoff at 0.91 (sensitivity: 100%, specificity: 75%). ROC receiver operating characteristic, AUCs area under curve, 12(S)-HETE 12(S)-Hydroxyeicosatetraenoic acid, APACHE II acute physiology and chronic health evaluation II score, RTS revised trauma score, TRISS trauma and injury severity score

to find significant differences of 12(S)-HETE in injury types. Therefore, 12(S)-HETE is not a specific marker of craniocerebral injury, but rather a marker of systemic response.

Severe trauma can cause complex changes in human immune function at an early stage. This post-traumatic immune inflammatory response is a physiological process needed for tissue repair and healing. However, the release of a large number of inflammation-related mediators can induce a cascade of immune and inflammatory responses, leading to systemic inflammatory response syndrome. 12(S)-HETE is often considered a pro-inflammatory cytokine playing a role in various diseases, and was first reported as a potent chemoattractant for neutrophils in 1975 [7]. Not only that, 12(S)-HETE can also promote the generation of monocyte chemokine protein-1 and induce inflammatory cell infiltration [8]. Besides, it has been reported that 12(S)-HETE can also enhance the phagocytic function of macrophages and promote the secretion of inflammatory factors by macrophages, such as interleukin-6 (IL-6), tumor necrosis factor α, IL-1 and IL-12 [9, 10]. In this study, it was found that the plasma level of 12(S)-HETE was significantly increased in patients with severe trauma upon admission, which may be the result of the post-traumatic immune-inflammatory response initiated by the body in the early stage of severe trauma. As an intermediary mediator of the inflammatory response, 12(S)-HETE plays an important role in regulating inflammatory cells and inflammatory factors. The absence of significant changes of 12(S)-HETE in mild trauma patients may also be associated with a slight inflammatory response.

In conclusion, plasma 12(S)-HETE in the first 48 h was elevated in patients with severe trauma and correlated with the severity of systemic injury. Determining plasma 12(S)-HETE concentrations at the early stage of post-trauma was of great value in distinguishing severe trauma from mild trauma and predicting in-hospital mortality in adult patients with severe trauma. These findings encourage larger multicenter studies aimed at exploring the clinical value of circulating 12(S)-HETE to help early clinical decision-making in human trauma.

Abbreviations

12(S)-HETE: 12(S)-hydroxyeicosatetraenoic acid; AIS: abbreviated injury score; APACHE II: acute physiology and chronic health evaluation II; AUC: area under the curve; CI: confidence interval; CRP: C-reactive protein; EL: isolated extracranial lesions; IL: isolated intracranial lesions; IQR: interquartile range; ISS: injury severity score; PCT: procalcitonin; ROC: receiver operating characteristic; RTS: revised trauma score; SD: standard deviation; TRISS: trauma and injury severity score; VIF: variance inflation factor; WBC: white blood cell

Ethics approval and consent to participate

This study was approved by Daping Hospital, Army Military Medical University and The First Affiliated Hospital of Chongqing Medical University, China. The registration number is ChiCTR1800018496. Written informed consent

obtained from all patients or their legal representatives where appropriate.

Supplementary data

Supplementary data is available at *Burns & Trauma Journal* online.

Availability of data and materials

All relevant datasets are available from the corresponding author upon reasonable request.

Authors' contributions

HL and YL conceived and designed the study. LY was the primary author and editor of the manuscript, with QC as the lead clinical investigator. All authors contributed to the enrolment of patients and sample collection. QH provided statistical advice and analyzed the data. All authors critically reviewed and approved the final manuscript.

Funding

This study was supported by the National Nature Science Foundation of China (No. 81901956) and the Innovation Project in Military Medicine (NO.18CXZ002).

Competing interests

None declared.

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