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Title page

Serum Acylcarnitine and Long-term Functional Prognosis after Traumatic Brain Injury with Intracranial Injury: A Multicenter Prospective Study

Authors:

Stephen Gyung Won Lee, MD

Department of Emergency Medicine, Seoul National University Boramae Medical Center, Seoul, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

Email: Leestephengyungwon@gmail.com

Young Sun Ro, MD, DrPH

Department of Emergency Medicine, Seoul National University Hospital, Seoul, Korea

Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

Email: Ro.youngsun@gmail.com

Eujene Jung, MD, PhD

Department of Emergency Medicine, Chonnam National University Hospital, Gwangju, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

Email: 81823ej@hanmail.net

Sung Bae Moon, MD

Department of Emergency Medicine, School of Medicine Kyungpook National University and Kyungpook National University Hospital, Daegu, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

Email: moon@knu.ac.kr

Gwan Jin Park, MD

Department of Emergency Medicine, Chungbuk National University Hospital, Cheongju, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

Email: pkj83531@naver.com

Hanna Yoon, MD

Department of Emergency Medicine, Seoul National University Hospital, Seoul, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

Email: noonup@naver.com

Jeong Ho Park, MD, PhD

Department of Emergency Medicine, Seoul National University Hospital, Seoul, Korea

Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

Email: timthe@gmail.com

Sang Do Shin, MD, PhD

Department of Emergency Medicine, Seoul National University Hospital, Seoul, Korea

Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

Email: sdshin@snu.ac.kr

: For Pan-Asia Trauma Outcomes Study for Traumatic Brain Injury (PATOS-TBI) research network

Address for Correspondence:

Young Sun Ro, MD, DrPH

Department of Emergency Medicine, Seoul National University Hospital, Seoul, Korea

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Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Korea

Laboratory of Emergency Medical Services, Seoul National University Hospital Biomedical Research Institute, Seoul, Korea

101 Daehak-Ro, Jongno-Gu, Seoul 03080, Korea

Phone: +82-2-2072-1800

Fax: +82-2-741-7855

E-mail: Ro.youngsun@gmail.com

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Author Contributions

Drs. Ro and Lee had full access to all of the data in the study and take responsibility for the integrity of the data as well as the accuracy of the data analysis.

Conceptualization: Dr. Lee and Dr. Ro

Data curation: Dr. Lee, Dr. Jung, Dr. Moon, Dr. Park (GJP), Dr. Yoon, and Dr. Park (JHP)

Formal analysis: Dr. Lee

Funding acquisition: Dr. Ro

Investigation: Dr. Ro, Dr. Jung, Dr. Moon, Dr. Park (GJP), and Dr. Yoon

Methodology: Dr. Lee, and Dr. Ro, and Dr. Shin

Software: Dr. Lee,

Supervision: Dr. Ro, Dr. Park (JHP), and Dr. Shin

Validation: Dr. Jung, Dr. Moon, Dr. Park (GJP), and Dr. Yoon

Visualization: Dr. Lee

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Writing - original draft: Dr. Lee

Writing - review & editing: Dr. Ro and Dr. Shin

Approval of final manuscript: all authors.

Data availability

The data for the study were obtained from the National Research Foundation of Korea (NRF) but restrictions apply to the availability of these data and so are not publicly available.

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of all participating hospitals (IRB no.: SNUH-1806-078-951; CNUH-2018-297; KNUH-2018-10-014-007; CBNUH-2018-09-018; BMC-30-2018-85)

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ABSTRACT

Serum biomarkers have potential to help predict prognosis of traumatic brain injury (TBI). The objective of this study was to evaluate the association between serum acylcarnitine levels and functional outcomes at 1-month/6-months after injury for TBI patients with intracranial hemorrhage or diffuse axonal injury.

This study is a multicenter prospective cohort study in which adult TBI patients with intracranial injury visiting the emergency departments (ED) from December 2018 to June 2020 were enrolled. Serum acylcarnitine levels at the time of ED arrival were categorized into 4 groups: low (1.2–5.5 μmol/L), low-normal (5.6–10.0 μmol/L), high-normal (10.1–14.5 μmol/L), and high (1.4.6–56.6 μmol/L). The study outcome was set as poor functional recovery at 1-month/6-months after injury (Glasgow Outcome Scale score, 1–3). Multilevel logistic regression analyses were conducted to estimate association between serum acylcarnitine and functional outcomes.

Among total of 549 patients, poor functional recovery at 1-month and 6-months after injury were observed in 29.1% (160/549) and 29.1% (158/543, follow-up loss n=6). The odds for 1-month poor functional outcome increased in the high-normal and the high groups (AORs (95% CIs): 1.56 (1.09–2.23) and 2.47 (1.63–3.75), compared to the low-normal group) and also as a continuous variable (1.05 (1.03–1.07) for each 1 μmol/L). Regarding 6-months mortality, the high group had significantly higher odds when compared to the low-normal group (AOR (95% CI): 2.16 (1.37–3.40)).

Higher serum acylcarnitine levels are associated with poor functional outcomes at 1-month/6-months after injury for TBI patients with intracranial injury.

Keywords: Traumatic Brain Injury; Acylcarnitine; Prognosis

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INTRODUCTION

Traumatic brain injury (TBI) is a serious health problem and is a leading cause of death and disability. Approximately 50 million new TBI cases occur annually worldwide, and the mortality rate has been estimated to 30-40%.[1,2] Even though the widespread use of brain imaging has helped in diagnosing TBI and predicting neurological outcomes of those patients,[3] prediction of prognosis after TBI based solely on radiological findings remains challenging.[4,5] Previous studies have suggested that serum biomarkers such as S100B, glial fibrillary acidic protein (GFAP), and neuron-specific enolase (NSE) have potential to help predict prognosis of patients with TBI.[6-8]

The role of serum acylcarnitine as a prognostic biomarker has previously been reported for out-of-hospital cardiac arrest, sepsis, hemodialysis, and angina pectoris, where elevated acylcarnitine levels were associated with poorer patient prognosis.[9-12] L-carnitine is a naturally occurring endogenous compound that transports fatty acids into the mitochondria for beta-oxidation.[13] The process results in esterification of L-carnitine to form acylcarnitine derivatives, where L-carnitine is thereafter present in the human body as both free carnitine and acylcarnitine.[14] In TBI, an increase in serum acylcarnitine could be the result of mitochondrial dysfunction and disruption of cellular metabolism after injury.[15,16] Because of the potential neuroprotective effect of the L-carnitine, previous studies evaluated the effect of administration of exogenous L-carnitine on human and animal cases with TBI.[17,18] However, few studies have investigated the association between serum carnitine levels, including acylcarnitine levels, and clinical outcomes after severe TBI.

We hypothesized that increased serum acylcarnitine levels would be associated with short- and long-term poor functional and survival outcomes in TBI patients with intracranial hemorrhage and diffuse axonal injury. The objective of this study was to evaluate the association between serum acylcarnitine levels and functional and survival outcomes at 1-month/6-months after injury for TBI patients with intracranial injury visiting the emergency department (ED).

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METHODS

Study design and setting

We evaluated data from the Pan-Asia Trauma Outcomes Study for Traumatic Brain Injury (PATOS-TBI) study, an ongoing multicenter prospective cohort study that started in 2018 at 5 participating university hospitals throughout Korea (ClinicalTrials.gov, ID: NCT04718935).[19] The PATOS-TBI study aims to identify nutritional and metabolic biomarkers that are related to prognosis of TBI and to develop a prediction model of good prognosis with long-term follow-up funded by the National Research Foundation of Korea. The PATOS-TBI study prospectively enrolls adult TBI patients who were transported by emergency medical services (EMS) to participating hospitals' ED within 72 hours after injury and who had intracranial injury defined as intracranial hemorrhage or diffuse axial injury. Based on radiological examination in the ED including computer tomography (CT) and magnetic resonance imaging (MRI), TBI patients who were diagnosed with intracranial injury were included after informed consent from the patients or patients' next of kin in cases of unconsciousness. Patients with penetrating brain injury, those who have had pre-diagnosed neurological diseases, psychological diseases, or terminal cancer, those who were pregnant, and patients transferred to participating hospitals' ED after surgery at other hospitals were excluded from the study.

The PATOS-TBI study registry included patients' demographics, injury characteristics, clinical findings including vital signs, neurological exam results, laboratory test results, brain imaging findings, diagnoses and in-hospital treatment, and survival/functional outcomes at time of hospital discharge and follow-up. Upon confirmation of intracranial injury and consent to enrollment to the study, blood samples of biomarkers were obtained for analysis in the ED. Patient long-term outcome variables were investigated by telephone interview, and survival/functional outcomes at 1 and 6 months after injury were collected. For quality assurance of the PATOS-TBI registry, a trained data entry researcher was designated for each participating hospital, and quality control of entered data was performed by the PATOS-TBI data quality control team on a monthly basis.[19]

Study population

The study enrolled adult TBI patients 18 years or older between December 2018 to June 2020. Patients with TBI diagnosed with intracranial injury confirmed by brain CT or MRI

were included. Patients with unknown information on the serum acylcarnitine level or the Glasgow Outcome Scale (GOS) score at 1-month follow-up were excluded.

Outcome measures

The main study outcomes were functional recovery at 1-month and 6-months after injury. Poor functional outcome was defined as GOS score of 1 (death), 2 (persistent vegetative state), or 3 (severe disability).[20] The secondary outcomes were functional recovery at hospital discharge, and in-hospital, 1-month and 6-months mortality.

Analysis of serum biomarkers

Upon confirmation of intracranial injury on brain imaging and patient consent to study enrollment in the ED, 24 mL of blood was drawn via venipuncture. Within 60 minutes after having been drawn, the samples were centrifuged for 10 minutes at 3000 rpm at room temperature for separation of serum. The separated serum was frozen at -20°C and analyzed within 7 days for serum biomarkers.

Serum acylcarnitine level was calculated by subtracting free carnitine level from total carnitine level. Serum total carnitine and free carnitine levels were measured by liquid chromatography with electrospray ionization tandem mass spectrometry.[21] To 150 µL of the aliquoted serum, 30 µL of 400µmol/L solution of internal standard D3-carnitine was added. Followed by vortex mixing, 30µL of the mixture was applied to cotton fiber filter paper to be used for free carnitine quantification. The remaining mixture was hydrolyzed with 10 µL of 1 mol/L KOH and incubated at 65°C for 15 minutes, followed by neutralization by 10µL of 1 mol/L HCl. The mixture was then applied to cotton fiber filter paper for quantification of total carnitine. The specimens were incubated at 40°C for 30 minutes and extracted with 200 µL of 80% Methanol. Aliquots of the samples (5 µL) were injected into the electrospray ion source of the tandem mass spectrometer for data acquisition. Serum concentrations of carnitine was calculated using the ratio of signals of carnitine to its internal standard (carnitine, m/z 162 → m/z 85; internal standard, m/z 165 → m/z 85).

Exposure and variables

The main exposure was serum acylcarnitine level, which was categorized into 4 groups according to reference range of acylcarnitine (5.6–14.4 µmol/L) derived from healthy

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adults reported in a previous study: low (1.2–5.5 μmol/L), low-normal (5.6–10.0 μmol/L), high-normal (10.1–14.5 μmol/L), and high (14.6–56.6 μmol/L).[22]

We included data regarding patients' demographics (age, sex, body mass index (BMI), and comorbidities (diabetes mellitus, renal disease, hemodialysis, liver disease, heart failure, cancer, and coagulation abnormality), injury characteristics (mechanism of injury and injury severity score), clinical findings (initial vital signs and Glasgow coma scale (GCS) scores at ED, type of intracranial injury found on brain imaging, need for surgery, and disposition after ED treatment), and patients' outcomes at time of hospital discharge and follow-up.

Statistical analysis

Descriptive analysis was conducted to compare the characteristics of study population. Categorical variables were reported as number (percentage) and were compared using the chi-squared test or Fisher's exact test. Continuous variables were reported as median (interquartile range, IQR) and compared using the Wilcoxon rank sum test.

Multilevel logistic regression analysis was used to investigate whether serum acylcarnitine level was related to the study outcomes, after adjusting for hospital clustering. The adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated for study outcomes after adjusting for age, sex, obesity (BMI ≥25), diabetes mellitus, renal disease or hemodialysis, other comorbidities, and injury severity score.[23]

Sensitivity analyses were conducted for study population groups based on time period between the injury and the blood sample collection during which time-dependent changes in acylcarnitine levels could have occurred, to assess whether the associations between serum acylcarnitine level and study outcomes were maintained in patients for whom blood samples were collected within 24, 12, 6, 3 hours after TBI.[24]

All tests were two-tailed and p-values of <0.05 were considered statistically significant. All statistical analyses were performed using the SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

Ethics statement

The study was approved by the Institutional Review Board of all participating hospitals (IRB no.: SNUH-1806-078-951; CNUH-2018-297; KNUH-2018-10-014-007; CBNUH-2018-09-018; BMC-30-2018-85). Informed consent was obtained from the patient or a family

member/legal representative of an unconscious patient. Patient information was anonymized prior to analysis.

RESULTS

Among 606 patients with intracranial injury in the PATOS-TBI study, 549 patients fulfilled the inclusion criteria, excluding cases with unknown information on the serum acylcarnitine level (n=1) and the GOS score at 1-month after injury (n=56). The characteristics of the excluded population with unknown GOS scores at 1-month can be found in Table S1.

Table 1 presents the patients' characteristics and outcomes according to level of serum acylcarnitine. The median (IQR) of serum acylcarnitine was 12.5 (8.5–17.1) µmol/L and time from injury to blood sample collection was 3.0 (1.5–5.7) hours. Poor functional recovery at 1-month after injury was observed in 29.1% (160/549), and 1-month mortality was 18.8% (103/549). Among 543 patients who were followed up to 6-months after injury, 29.1% (158/543) had poor functional recovery and 20.6% (112/543) died. The proportions of poor functional recovery at 6-month after injury were 28.9% (11/38) for the low group, 21.2% (31/146) for the low-normal group, 25.9% (42/162) for the high-normal group, and 37.4% (76/203) for the high group, respectively (p=0.096).

In Figure 1, patients with poor functional recovery at 1-month after injury had significantly higher serum acylcarnitine levels, compared to patients with favorable functional outcomes (15.8 vs 13.2 µmol/L ($p<0.001$). The acylcarnitine cutoff value of 10.0 µmol/L resulted in sensitivity of 75.2% and specificity of 35.7% while cutoff value of 14.5 µmol/ L resulted in sensitivity of 47.4% and specificity of 66.5%.

Table 2 presents the associations between serum acylcarnitine levels and study outcomes. The adjusted odds for poor functional recovery at 1-month after injury increased in the high-normal and the high groups (adjusted ORs (95% CIs) when compared with the low-normal group: 1.56 (1.09–2.23) for the high-normal group and 2.47 (1.63–3.75) for the high group). When acylcarnitine was analyzed as a continuous variable, each 1 µmol/L increase in serum acylcarnitine level was associated with significant increase in odds for poor 1-month functional outcome (adjusted OR (95% CI): 1.05 (1.03–1.07)). When 543 patients who were followed up to 6-months were analyzed, the high group had statistically significantly higher odds of poor functional recovery at 6-months after injury (adjusted OR

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(95% CI): 2.16 (1.37–3.40)) and 6-month mortality (adjusted OR (95% CI): 2.86 (1.91–4.28)) when compared to the low-normal group.

Sensitivity analysis

Among total population, 494 (90.0%) patients with intracranial injury had blood sample collected within 24 hours after TBI. Compared with the low-normal acylcarnitine group, the high-normal and the high groups had higher odds for poor functional recovery at 1-month (adjusted ORs (95% CIs): 1.68 (1.24–2.28) and 2.58 (1.78–3.73)) as well as 1-month mortality (adjusted ORs (95% CIs): 1.73 (1.06–2.84) and 3.53 (2.41–5.17)) (Table 3). These associations showed a similar trend in patients with blood samples collected within 12 (n=463), 6 (n=420) and 3 (n=281) hours after injury.

DISCUSSION

Using the multicenter prospective PATOS-TBI registry, this study evaluated the association between serum acylcarnitine levels and short- and long-term functional/survival prognoses of adult TBI patients with intracranial hemorrhage or diffuse axonal injury. There was an association between serum acylcarnitine levels and 1-month poor functional recovery (adjusted OR (95% CI) when compared with the low-normal group: 1.56 (1.09–2.23) for the high-normal group and 2.47 (1.63–3.75) for the high group). Regarding long-term functional outcome at 6-months, there was an association between serum acylcarnitine levels and poor functional recovery (adjusted OR (95% CI) when compared to the low-normal group: 2.16 (1.37–3.40) for the high group). A similar trend was observed in patients with blood samples collected within 24 (n=494), 12 (n=463), 6 (n=420) and 3 (n=281) hours after injury. These results suggest serum acylcarnitine as a potential biomarker related to the prognosis of TBI with intracranial injury.

Carnitine is an essential factor in cellular metabolism and is also known to have neuroprotective effects.[25,26] Acylcarnitine derivatives are formed by esterification of L-carnitine during the process of transporting fatty acids into the mitochondria for beta-oxidation.[13] Previous human and animal studies have reported that severe TBI triggers hypermetabolic state of the brain which increases glucose utilization.[27,28] Enhanced fatty acid oxidation to supply energy for the brain is resulted in a decrease in free carnitine and increase of acylcarnitine.[26,29,30] Among serum acylcarnitine, long chain acylcarnitines, palmitoylcarnitine and oleoylcarnitine were overexpressed in brain tissues only after injury

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in rats with TBI which suggested acylcarnitine as injury related biomarkers.[31,32] In another study, a combination of branched-chain amino acid metabolites (2-methylbutyrylcarnitine, propionylcarnitine and 4-methyl-2-oxopentanoate) were utilized for predicting increased intracranial pressure in patients with severe TBI.[33] As shown, the results of this study that higher levels of serum acylcarnitine are associated with poor prognosis is in line with previous studies.

In Korea, more than 100,000 TBI patients visit the emergency department (ED) every year, and about 4,000 patients die due to TBI.[34] Determining the prognosis of severe TBI patients based solely on brain imaging and demographic factors has limitations,[3-5] and previous studies have suggested that serum biomarkers could be helpful in predicting prognostication.[1,6-8] Acylcarnitine profile has been traditionally utilized for screening of inborn errors such as long-chain acyl-CoA dehydrogenase deficiency and propionyl-CoA carboxylase deficiency.[25] In this study, serum acylcarnitine could be utilized as a biomarker for prognostication of TBI patients with intracranial hemorrhage or diffuse axonal injury. As has been previously reported for biomarkers S100B, GFAP, and NSE,[6-8] further studies are needed investigating the efficacy of serum acylcarnitine in combination with other biomarkers in assisting prediction of functional/survival outcomes of patient with TBI.[35,36]

This study has several limitations. First, the blood-based protein biomarker concentration would be affected by elapsed time from injury. However, blood samples in this study were collected only at the time of ED arrival and therefore missing data on kinetics of serum acylcarnitine level. The kinetics of acylcarnitine over time after TBI is yet to be studied and further studies considering serial follow up are needed. Second, this study only evaluated total acylcarnitine levels and not specific carnitine components, although serum acylcarnitine is composed of short-, medium- and long-chain acylcarnitine that have different chemical and metabolic properties.[12,14,25] Third, there was no available data for diet diaries and/or nutritional status, which would be related to serum carnitine levels.[37] Fourth, the acylcarnitine levels could have been affected by accompanied trauma other than brain injury such as orthopedic, spinal cord or myocardial injury[9,33,38] which was not considered in the analysis and were only adjusted with injury severity score. Fifth, even though the study population was classified according to the reference range of acylcarnitine level in healthy adults, the study lacks serum acylcarnitine levels in age- and

sex-matched controls. Lastly, selection bias may arise because the patients with unknown GOS scores at 1-month were excluded. Caution should be taken when interpreting this study results given the significant limitations.

CONCLUSIONS

The higher serum acylcarnitine levels are associated with short- and long-term poor functional and survival outcomes for TBI patients with intracranial injury. This study suggests that serum acylcarnitine may be a potential biomarker for predicting the prognosis of patients with TBI with intracranial hemorrhage or diffuse axonal injury when utilized in combination with other biomarkers.

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Figure legends

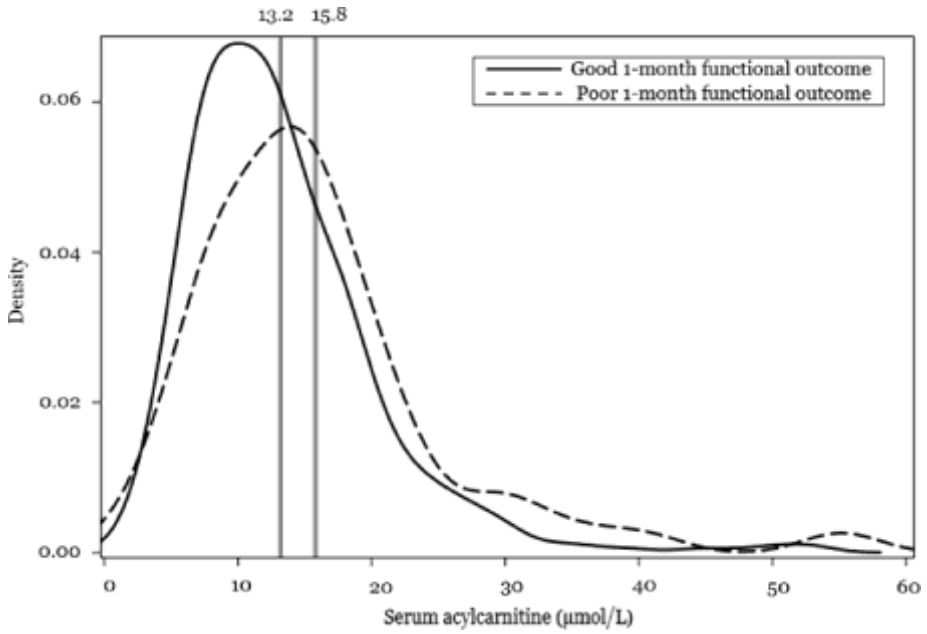

Figure 1. Kernel density plots of serum acylcarnitine according to functional recovery at 1-month after injury. Poor functional outcome defined as Glasgow outcome scale score of 1 (death), 2 (persistent vegetative state), or 3 (severe disability).

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Table 1. Characteristics of study population by serum acylcarnitine level

	Total	Serum acylcarnitine level (μmol/L)				
		Low (1.2–5.5)	Low-normal (5.6–10.0)	High-normal (10.1–14.5)	High (14.6–56.6)	P-value
	N (%)	N (%)	N (%)	N (%)	N (%)	
Total	549	38	146	162	203	
Acylcarnitine, μmol/L, median (IQR)	12.5 (8.5–17.1)	4.7 (3.6–5.0)	7.8 (7.0–8.8)	12.3 (11.3–13.4)	18.8 (16.7–23.3)	<0.001
Total carnitine, μmol/L, median (IQR)	49.6 (39.7–61.1)	38.0 (26.6–44.3)	42.4 (34.8–49.7)	48.0 (39.7–58.4)	60.0 (50.7–74.0)	<0.001
Free carnitine, μmol/L, median (IQR)	36.8 (28.7–45.9)	34.4 (21.2–40)	34.8 (26.9–42.1)	35.9 (27.7–45.8)	40.0 (32.0–50.3)	<0.001
Time from injury to blood sample collection, hour, median (IQR)	3.0 (1.5–5.7)	3.6 (2.3–6.2)	2.8 (1.4–5.7)	3.5 (1.8–6.9)	2.8 (1.5–4.7)	0.107
Demographics						
Age, year, mean (SD)	64.4 (16.9)	71.9 (13.5)	67.7 (15.8)	63.5 (16.6)	61.2 (17.7)	<0.001
Age, ≥65 years old	305 (55.6)	36 (94.7)	103 (70.5)	82 (50.6)	84 (41.4)	<0.001
Male sex	376 (68.5)	20 (52.6)	95 (65.1)	103 (63.6)	158 (77.8)	0.002
Body mass index, ≥25 kg/m^2	114 (20.8)	7 (18.4)	21 (14.4)	37 (22.8)	49 (24.1)	0.144
Education, >12 years	100	2 (5.3)	23 (15.8)	32 (19.8)	43 (21.2)	0.10

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	(18.2)					207
Comorbidities						
Diabetes mellitus	141 (25.7)	14 (36.8)	41 (28.1)	41 (25.3)	45 (22.2)	0.236
Renal disease	34 (6.2)	2 (5.3)	8 (5.5)	11 (6.8)	13 (6.4)	0.960
Hemodialysis	20 (3.6)	2 (5.3)	4 (2.7)	8 (4.9)	6 (3.0)	0.643
Liver disease	24 (4.4)	0 (0.0)	7 (4.8)	9 (5.6)	8 (3.9)	0.488
Heart failure	11 (2.0)	0 (0.0)	4 (2.7)	3 (1.9)	4 (2.0)	0.753
Cancer	23 (4.2)	2 (5.3)	6 (4.1)	5 (3.1)	10 (4.9)	0.831
Coagulation abnormality	13 (2.4)	2 (5.3)	6 (4.1)	2 (1.2)	3 (1.5)	0.180
Mechanism of injury						0.643
Road traffic injury	223 (40.6)	12 (31.6)	65 (44.5)	59 (36.4)	87 (42.9)	
Fall/slip down	238 (43.4)	18 (47.4)	62 (42.5)	74 (45.7)	84 (41.4)	
Others	88 (16.0)	8 (21.1)	19 (13.0)	29 (17.9)	32 (15.8)	
Injury severity score						
Score, median (IQR)	22 (13–29)	21.5 (16–29)	17 (12–25)	22 (13–29)	22 (14–30)	0.274
Score, ≥16	389 (70.9)	29 (76.3)	100 (68.5)	112 (69.1)	148 (72.9)	0.662
Initial ED vital signs, median (IQR)						
Systolic blood pressure,	133	140	140	130	131.5	0.02

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mmHg	(115–152)	(130–160)	(120–160)	(110–150)	(110–150)	214
Diastolic blood pressure, mmHg	80 (70–90)	80 (70–90)	80 (70–93)	80 (70–90)	80 (69–90)	0.100
Heart rate, per min	84 (72.5–96)	80 (73–86)	80.5 (71–97)	80 (70.5–92)	88 (76–100)	<0.001
Respiratory rate, per min	20 (18–20)	20 (18–20)	20 (18–20)	20 (18–20)	20 (20–20)	0.020
Oxygen saturation, %	97 (96–98)	97 (95–98)	97 (96–98)	97 (96–98)	97 (96–98)	0.571
Initial GCS						0.006
3–8	121 (22.0)	6 (15.8)	19 (13.0)	36 (22.2)	60 (29.6)	
9–13	71 (12.9)	4 (10.5)	22 (15.1)	19 (11.7)	26 (12.8)	
14–15	344 (62.7)	28 (73.7)	104 (71.2)	106 (65.4)	106 (52.2)	
Score, mean (SD)	12.1 (4.3)	13.1 (3.6)	13.1 (3.5)	12.2 (4.2)	11.1 (4.7)	<0.001
Intracranial injury						
Subdural hemorrhage	411 (74.9)	30 (78.9)	114 (78.1)	115 (71.0)	152 (74.9)	0.487
Subarachnoid hemorrhage	215 (39.2)	13 (34.2)	50 (34.2)	70 (43.2)	82 (40.4)	0.374
Intracerebral hemorrhage	121 (22.0)	12 (31.6)	31 (21.2)	34 (21.0)	44 (21.7)	0.534
Epidural hemorrhage	80 (14.6)	5 (13.2)	10 (6.8)	33 (20.4)	32 (15.8)	0.009
Diffuse axonal injury	36 (6.6)	6 (15.8)	7 (4.8)	11 (6.8)	12 (5.9)	0.103

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Intraventricular hemorrhage	47 (8.6)	4 (10.5)	10 (6.8)	14 (8.6)	19 (9.4)	22 0.825
Operation						
Any operation	160 (29.1)	7 (18.4)	42 (28.8)	49 (30.2)	62 (30.5)	0.491
Neurosurgery	109 (19.9)	6 (15.8)	30 (20.5)	30 (18.5)	43 (21.2)	0.839
ICU admission	330 (60.1)	19 (50.0)	77 (52.7)	107 (66.0)	127 (62.6)	0.050
Survival outcomes						
In-hospital mortality	56 (10.2)	2 (5.3)	7 (4.8)	10 (6.2)	37 (18.2)	<0.001
1-month mortality	103 (18.8)	6 (15.8)	19 (13.0)	24 (14.8)	54 (26.6)	0.004
6-month mortality (n=543)	112 (20.6)	7 (18.4)	21 (14.7)	26 (16.4)	58 (29.0)	0.003
GOS score at discharge						<0.001
1	56 (10.2)	2 (5.3)	7 (4.8)	10 (6.2)	37 (18.2)	
2	23 (4.2)	2 (5.3)	4 (2.7)	7 (4.3)	10 (4.9)	
3	59 (10.7)	5 (13.2)	9 (6.2)	22 (13.6)	23 (11.3)	
4	57 (10.4)	3 (7.9)	20 (13.7)	13 (8.0)	21 (10.3)	
5	354 (64.5)	26 (68.4)	106 (72.6)	110 (67.9)	112 (55.2)	
Poor functional recovery at discharge	138 (25.1)	9 (23.7)	20 (13.7)	39 (24.1)	70 (34.5)	<0.001
GOS score at 1-month after injury						0.044
1	103 (18.8)	6 (15.8)	19 (13.0)	24 (14.8)	54 (26.6)	

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2	8 (1.5)	0 (0.0)	1 (0.7)	4 (2.5)	3 (1.5)	
3	49 (8.9)	5 (13.2)	11 (7.5)	14 (8.6)	19 (9.4)	
4	43 (7.8)	3 (7.9)	11 (7.5)	12 (7.4)	17 (8.4)	
5	346 (63.0)	24 (63.2)	104 (71.2)	108 (66.7)	110 (54.2)	
Poor functional recovery at 1-month	160 (29.1)	11 (28.9)	31 (21.2)	42 (25.9)	76 (37.4)	0.096
GOS score at 6-month after injury						0.142
1	112 (20.4)	7 (18.4)	21 (14.4)	26 (16.0)	58 (28.6)	
2	9 (1.6)	1 (2.6)	3 (2.1)	4 (2.5)	1 (0.5)	
3	37 (6.7)	4 (10.5)	8 (5.5)	11 (6.8)	14 (6.9)	
4	38 (6.9)	1 (2.6)	9 (6.2)	13 (8.0)	15 (7.4)	
5	347 (63.2)	25 (65.8)	103 (70.5)	107 (66.0)	112 (55.2)	
Follow-up loss	6 (1.1)	0 (0.0)	2 (1.4)	1 (0.6)	3 (1.5)	
Poor functional recovery at 6-month	158 (29.1)	12 (31.6)	32 (22.4)	41 (25.8)	73 (36.5)	0.021

IQR, Interquartile range; SD, Standard deviation; TBI, Traumatic brain injury; ED, emergency department; ICU, Intensive care unit; GCS, Glasgow coma scale; GOS, Glasgow outcome scale

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Table 2. Multilevel logistic regression analysis of serum acylcarnitine level category for study outcomes

Outcomes	Outcome, n/N (%)	Model 1	Model 2	Model 3
		OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Poor functional recovery at 1-months after injury				
Low (1.2–5.5)	11/38 (28.9)	1.09 (0.71–1.66)	0.95 (0.59–1.53)	0.90 (0.56–1.45)
Low-normal (5.6–10.0)	31/146 (21.2)	Reference	Reference	Reference
High-normal (10.1–14.5)	42/162 (25.9)	1.36 (0.97–1.91)	1.54 (1.05–2.25)	1.56 (1.09–2.23)
High (14.6–56.6)	76/203 (37.4)	2.09 (1.53–2.85)	2.45 (1.65–3.65)	2.47 (1.63–3.75)
Continuous (per 1 µmol/L increase)	160/549 (29.1)	1.04 (1.03–1.05)	1.05 (1.04–1.06)	1.05 (1.03–1.07)
Poor functional recovery at 6-months after injury				
Low (1.2–5.5)	12/38 (31.6)	1.14 (0.59–2.20)	1.03 (0.57–1.87)	0.99 (0.52–1.86)
Low-normal (5.6–10.0)	32/144 (22.2)	Reference	Reference	Reference
High-normal (10.1–14.5)	41/161 (25.5)	1.18 (0.80–1.76)	1.36 (0.82–2.27)	1.37 (0.84–2.25)
High (14.6–56.6)	73/200 (36.5)	1.87 (1.36–2.57)	2.16 (1.39–3.35)	2.16 (1.37–3.40)
Continuous (per 1 µmol/L increase)	158/543 (29.1)	1.04 (1.03–1.06)	1.05 (1.04–1.06)	1.05 (1.04–1.07)
Poor functional recovery at discharge				

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Low (1.2–5.5)	9/38 (23.7)	1.18 (0.68–2.06)	1.06 (0.63–1.78)	1.00 (0.56–1.76)
Low-normal (5.6–10.0)	20/146 (13.7)	Reference	Reference	Reference
High-normal (10.1–14.5)	39/162 (24.1)	2.00 (1.28–3.13)	2.40 (1.35–4.24)	2.39 (1.41–4.04)
High (14.6–56.6)	70/203 (34.5)	2.96 (1.99–4.39)	3.64 (2.26–5.88)	3.61 (2.25–5.80)
Continuous (per 1 μmol/L increase)	138/549 (25.1)	1.05 (1.04–1.06)	1.06 (1.05–1.07)	1.06 (1.05–1.08)
In-hospital mortality				
Low (1.2–5.5)	2/38 (5.3)	0.55 (0.38–0.81)	0.48 (0.29–0.80)	0.44 (0.29–0.69)
Low-normal (5.6–10.0)	7/146 (4.8)	Reference	Reference	Reference
High-normal (10.1–14.5)	10/162 (6.2)	1.12 (0.37–3.41)	1.41 (0.44–4.51)	1.37 (0.43–4.32)
High (14.6–56.6)	37/203 (18.2)	3.36 (2.04–5.53)	4.61 (2.19–9.68)	4.48 (2.21–9.07)
Continuous (per 1 μmol/L increase)	56/549 (10.2)	1.06 (1.03–1.10)	1.08 (1.06–1.10)	1.08 (1.06–1.10)
1-month mortality				
Low (1.2–5.5)	6/38 (15.8)	0.87 (0.58–1.29)	0.71 (0.44–1.14)	0.67 (0.43–1.05)
Low-normal (5.6–10.0)	19/146 (13.0)	Reference	Reference	Reference
High-normal (10.1–14.5)	24/162 (14.8)	1.12 (0.69–1.83)	1.40 (0.81–2.40)	1.41 (0.84–2.38)
High (14.6–56.6)	54/203 (26.6)	2.03 (1.54–2.68)	2.71 (1.71–4.30)	2.74 (1.76–4.27)
Continuous (per 1 μmol/L	103/549	1.04 (1.02–	1.05 (1.04–	1.05 (1.04–

increase)	(18.8)	1.05)	1.06)	1.06)
6-month mortality				
Low (1.2–5.5)	7/38 (18.4)	0.79 (0.54–1.16)	0.65 (0.42–1.02)	0.62 (0.40–0.95)
Low-normal (5.6–10.0)	21/144 (14.6)	Reference	Reference	Reference
High-normal (10.1–14.5)	26/161 (16.1)	1.14 (0.73–1.80)	1.40 (0.83–2.34)	1.41 (0.86–2.33)
High (14.6–56.6)	58/200 (29.0)	2.13 (1.66–2.73)	2.81 (1.83–4.30)	2.86 (1.91–4.28)
Continuous (per 1 μmol/L increase)	112/543 (20.6)	1.05 (1.02–1.07)	1.06 (1.05–1.08)	1.06 (1.05–1.08)

OR, odds ratio; CI, confidence interval

Model 1: unadjusted logistic regression

Model 2: adjusted for hospital, demographics (age, sex, and obesity) and comorbidities (diabetes mellitus, renal disease or hemodialysis, and other comorbidities)

Model 3: adjusted for variables in the Model 2, and injury severity score

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Table 3. Sensitivity analysis for study population based on time periods between the injury and the blood sample collection

Outcomes	Outcome, n/N (%)	Model 1	Model 2	Model 3
		OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Sample collection within 24 hours after injury (N=494)				
Poor functional recovery at 1-months after injury				
Low (1.2–5.5)	8/33 (24.2)	1.02 (0.59–1.77)	0.88 (0.48–1.60)	0.83 (0.44–1.57)
Low-normal (5.6–10.0)	27/130 (20.8)	Reference	Reference	Reference
High-normal (10.1–14.5)	40/145 (27.6)	1.50 (1.10–2.05)	1.69 (1.22–2.34)	1.68 (1.24–2.28)
High (14.6–56.6)	72/186 (38.7)	2.19 (1.59–3.03)	2.59 (1.87–3.58)	2.58 (1.78–3.73)
Continuous (per 1 μmol/L increase)	147/494 (29.8)	1.04 (1.03–1.05)	1.05 (1.04–1.06)	1.05 (1.04–1.07)
1-month mortality				
Low (1.2–5.5)	4/33 (12.1)	1.09 (0.62–1.93)	0.85 (0.45–1.60)	0.82 (0.44–1.54)
Low-normal (5.6–10.0)	15/130 (11.5)	Reference	Reference	Reference
High-normal (10.1–14.5)	23/145	1.37	1.72 (1.04–	1.73 (1.06–

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	(15.9)	(0.84–2.23)	2.83)	2.84)
High (14.6–56.6)	53/186 (28.5)	2.52 (1.90–3.35)	3.49 (2.41–5.06)	3.53 (2.41–5.17)
Continuous (per 1 μmol/L increase)	95/494 (19.2)	1.04 (1.02–1.07)	1.06 (1.04–1.07)	1.06 (1.05–1.07)
Sample collection within 12 hours after injury (N=463)				
Poor functional recovery at 1-months after injury				
Low (1.2–5.5)	8/31 (25.8)	1.07 (0.64–1.77)	0.93 (0.54–1.60)	0.87 (0.47–1.59)
Low-normal (5.6–10.0)	26/124 (21.0)	Reference	Reference	Reference
High-normal (10.1–14.5)	37/137 (27.0)	1.45 (1.09–1.94)	1.67 (1.22–2.31)	1.65 (1.21–2.26)
High (14.6–56.6)	68/171 (39.8)	2.36 (1.69–3.28)	2.79 (1.97–3.93)	2.80 (1.94–4.03)
Continuous (per 1 μmol/L increase)	139/463 (30.0)	1.04 (1.03–1.05)	1.05 (1.04–1.06)	1.05 (1.04–1.07)
1-month mortality				
Low (1.2–5.5)	4/31 (12.9)	1.18 (0.72–1.91)	0.93 (0.55–1.59)	0.89 (0.49–1.59)

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Low-normal (5.6–10.0)	14/124 (11.3)	Reference	Reference	Reference
High-normal (10.1–14.5)	21/137 (15.3)	1.32 (0.80–2.16)	1.69 (1.03–2.76)	1.70 (1.03–2.82)
High (14.6–56.6)	52/171 (30.4)	2.86 (2.15–3.81)	3.93 (2.69–5.75)	4.03 (2.78–5.85)
Continuous (per 1 µmol/L increase)	91/463 (19.7)	1.04 (1.02–1.07)	1.06 (1.05–1.08)	1.06 (1.05–1.07)
Sample collection within 6 hours after injury (N=420)				
Poor functional recovery at 1-months after injury				
Low (1.2–5.5)	7/28 (25.0)	0.99 (0.54–1.82)	0.89 (0.47–1.68)	0.85 (0.42–1.73)
Low-normal (5.6–10.0)	24/114 (21.1)	Reference	Reference	Reference
High-normal (10.1–14.5)	31/116 (26.7)	1.49 (1.11–2.00)	1.69 (1.14–2.49)	1.68 (1.18–2.38)
High (14.6–56.6)	67/162 (41.4)	2.55 (1.73–3.78)	2.98 (2.11–4.22)	2.96 (2.01–4.37)
Continuous (per 1 µmol/L increase)	129/420 (30.7)	1.05 (1.04–1.07)	1.06 (1.06–1.07)	1.06 (1.05–1.07)
1-month mortality				

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Low (1.2–5.5)	3/28 (10.7)	0.97 (0.55–1.72)	0.80 (0.44–1.42)	0.76 (0.40–1.47)
Low-normal (5.6–10.0)	13/114 (11.4)	Reference	Reference	Reference
High-normal (10.1–14.5)	18/116 (15.5)	1.41 (0.89–2.26)	1.81 (1.14–2.89)	1.88 (1.19–2.96)
High (14.6–56.6)	51/162 (31.5)	2.97 (2.09–4.23)	4.16 (2.73–6.35)	4.23 (2.75–6.53)
Continuous (per 1 µmol/L increase)	85/420 (20.2)	1.05 (1.02–1.09)	1.07 (1.05–1.09)	1.07 (1.06–1.09)
Sample collection within 3 hours after injury (N=281)				
Poor functional recovery at 1-months after injury				
Low (1.2–5.5)	4/14 (28.6)	1.12 (0.41–3.06)	0.96 (0.37–2.48)	0.87 (0.33–2.31)
Low-normal (5.6–10.0)	17/78 (21.8)	Reference	Reference	Reference
High-normal (10.1–14.5)	23/74 (31.1)	1.79 (1.31–2.43)	2.00 (1.39–2.89)	1.89 (1.34–2.68)
High (14.6–56.6)	47/115 (40.9)	2.24 (1.67–3.01)	2.71 (1.90–3.89)	2.56 (1.71–3.85)
Continuous (per 1 µmol/L	91/281	1.04	1.05 (1.03–	1.05 (1.03–

increase)	(32.4)	(1.02–1.05)	1.06)	1.06)
1-month mortality				
Low (1.2–5.5)	1/14 (7.1)	0.67 (0.40–1.11)	0.53 (0.34–0.81)	0.49 (0.32–0.75)
Low-normal (5.6–10.0)	8/78 (10.3)	Reference	Reference	Reference
High-normal (10.1–14.5)	14/74 (18.9)	2.14 (1.28–3.56)	2.81 (1.67–4.71)	2.71 (1.59–4.62)
High (14.6–56.6)	35/115 (30.4)	3.06 (2.08–4.50)	4.50 (2.53–7.98)	4.25 (2.35–7.69)
Continuous (per 1 μmol/L increase)	58/281 (20.6)	1.04 (1.00–1.08)	1.06 (1.03–1.09)	1.06 (1.03–1.08)

OR, odds ratio; CI, confidence interval

Model 1: unadjusted logistic regression

Model 2: adjusted for hospital, demographics (age, sex, and obesity) and comorbidities (diabetes mellitus, renal disease or hemodialysis, and other comorbidities)

Model 3: adjusted for variables in the Model 2, and injury severity score

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