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Serum glial fibrillary acidic protein and ubiquitin C-terminal hydrolase-L1 for diagnosis of sepsis-associated encephalopathy and outcome prognostication

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ABSTRACT

Purpose: We investigated the role of serum Glial Fibrillary Acidic Protein (GFAP) and Ubiquitin C-Terminal Hydrolase-L1 (UCH-L1) in diagnosis of sepsis-associated encephalopathy(SAE), predicting prognosis and long-term quality of life with patients of sepsis.

Materials and methods: This is a prospective single center study entailed 105 patients whosuffered from sepsis from Jan 2015 to Aug 2016. Serum concentrations of GFAP and UCH-L1 for diagnosis of SAE and predicting prognosis and long-term quality of life with patients of sepsis were analyzed.

Results: The serum concentrations of GFAP and UCH-L1 were higher in SAE group than in no-SAE group ($p < .001$). GFAP and UCH-L1 produced an AUC of 0.824 and 0.812 respectively for diagnosis of SAE with optimal cut-off values 0.532 ng/ml and 7.72 ng/ml respectively. The optimal cut-off values of GFAP and UCH-L1 to distinguish patients with survivors from non-survivors were 0.536 ng/ml and 8.06 ng/ml with an area under the curve of 0.773 and 0.746. Patients with a higher GFAP levels had worse long-term usual activities and patients with a higher UCH-L1 levels had more long-term pain ($P = .026$).

Conclusions: Serum concentrations GFAP and UCH-L1 early elevated and associated with sepsis-associated encephalopathy, poor prognosis and quality of life.

1. Introduction

Sepsis is redefined as a life-threatening organ dysfunction due to a dysregulated host response to infection [1], and the brain is one of the organs that has been accidentally injured. Acute cerebral dysfunction was reported in >50% of patients with sepsis [2,3] and associated with increased mortality as well as long-term neurocognitive impairments and poor quality of life in survivors [3-6].

The mechanistic pathways for sepsis-associated encephalopathy (SAE) and poor long-term outcomes are incompletely understood. Several pathogenic mechanisms have been put forwarded [7-9], among these the blood-brain barrier (BBB) injury and endothelial dysfunction may be an important link [10-13], which lead to neuroinflammation [14] and microcirculation disturbance [15] and then result in neuronal injury. Circulating neuronal and glial biomarkers of brain damage that are commonly used for diagnosis of injury to the central nervous system (CNS), because they can capture the underlying neuropathophysiology and molecular processes. Currently, there are several difficulties in the diagnosis of SAE, consciousness assessment methods, such as Glasgow Coma Scale (GCS), the confusion assessment method for the diagnosis of delirium in the ICU (CAM-ICU), are usually used for its clinical diagnosis [3,16]. However, these consciousness score system may be subjective and affected by sedation and analgesia, tracheal intubation and sleep disorder. Circulating neuronal and glial biomarkers of brain damage would be valuable tools to complement currently available clinical data and aid in medical decision-making [17]. Previous studies have showed that the elevated serum levels of S100B and neuron-specific enolase (NSE) were associated with brain injury in sepsis patients [18-20]. The potential neuronal and glial biomarkers of brain injury including glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase L1(UCH-L1) have been demonstrated that they were faithful markers for brain injury in traumatic brain injury [21], stroke [22], hypoxic-ischemic encephalopathy [23]. So far there are not studies to explore the role of serum GFAP and UCH-L1 with adult SAE.

Therefore, we hypothesis that elevated serum concentrations of GFAP and UCH-L1 may well reflect the encephalopathy activity, poor prognosis and long-term poor quality of life in sepsis.

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2. Methods

2.1. Subjects

All aspects of this prospective cohort study were approved by the Xiangya Hospital, Central South University Institutional Review Board, and the informed consent was obtained from patients or legal representatives. The principles of the Declaration of Helsinki was well abided by our study. In this study, patients admitted to the comprehensive ICU who suffered from sepsis were enrolled from Jan 2015 to Aug 2016.

Exclusion criteria included were as follows: age < 18 yrs.; primary brain injury (such as head trauma, cerebral stroke, cardiac arrest, intracranial infection, epilepsy, Alzheimer's disease, Parkinson's disease etc.); acute mental deterioration secondary to non-septic metabolic disorders with organ dysfunction(hepatic encephalopathy, pulmonary encephalopathy, severe electrolyte imbalance, severe blood glucose disorders etc.); pregnancy or nursing state; severe burns, trauma, and neurosurgery, sepsis associated with forthcoming death.

2.2. At time presentation

Sepsis is defined according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3): organ dysfunction can be represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more. In all the patients who enter the ward, we assessed the level of consciousness and delirium. Glasgow Coma Scale (GCS) was evaluated before sedation. Up to ICU discharge, the Confusion Assessment Method for the ICU (CAM-ICU) was assessed together with the Richmond Agitation Sedation Scale (RASS) twice per day by the nurse or the physician in charge of the patient. For patients who have been sedated before ICU admission, the assumed GCS scores, i.e., the scores measured before any administration of sedative/relaxant drug were used for analyzing [25]. For postoperative patients, the GCS scores measured before surgery was used.

Patients with a GCS score of <15, or at least one positive CAM-ICU assessment were thought to have cerebral dysfunction. SAE was defined as cerebral dysfunction in the presence of sepsis and in the absence of any of the exclusion criteria. Spontaneous awakening trials were performed daily for patients who were sedated. The longest evaluating time after stopping sedation in spontaneous awakening trials was 24 h. In this evaluation period, patients should be awake to evaluate their mental status, and they were diagnosed of SAE if the patients were not awake. Auxiliary examination method, such as the electroencephalograph(EEG), the somatosensory evoked potential, and the transcranial doppler ultrasonography were performed for helping diagnosis of SAE in sedation patients. EEG was performed to clarify seizures. After hemodynamically recovered, the septic patients were sill disorder of consciousness, CT or MRI was performed to exclude cerebral hemorrhage or cerebral infarction after successful detaching from the ventilator.

Within 24 h after first arrived at ICU and after severe hypotension corrected, blood was drawn for the detection of GFAP and UCH-L1. The demographic and clinical characteristics data, bacteriological information, biochemical indicators, source of infection, length of ICU stay, hospital mortality, 180-day mortality were recorded, and GCS scores, the Acute Physiology and Chronic Health Evaluation (APACHE) II scores, SOFA scores based on the information retrieved within the first 24 h of ICU admission. The 180-day follow-up was mainly carried out by telephone. The return visit ranged from the onset until the fifth to seventh month. The survival outcomes and overall prognosis were recorded by the EuroQol 5-dimension questionnaire health scale(EQ-5D), which was completed by the patients or their representatives. “GFAP+” represents GFAP levels > the optimal cut-off values of serum GFAP levels for diagnosis of SAE; “GFAP-” represents GFAP levels ≤ the optimal cut-off values of serum GFAP levels for diagnosis of SAE; “UCH-L1+” represents UCH-L1 levels >the optimal cut-off values of serum UCH-L1 levels for diagnosis of SAE; “UCH-L1-” represents UCH-L1 levels ≤ the optimal cut-off values of serum UCH-L1 levels for diagnosis of SAE. The differences in demographic, clinical, biological, prognosis parameters and EQ-5D scores were assessed between GFAP+ group and GFAP- group, UCH-L1+ group and UCH-L1- group.

2.3. Blood sample collection and processing

At admission, 2 ml blood samples of septic patients were collected with EDTA anticoagulative tubes, then centrifuged at 5000 RPM for 10 min within 15 to 60 min after blood collection. Serum was removed, and separated in single vials and then stored at −70 °C until the time of analysis.

2.4. Enzyme-linked immunosorbent assay

Serum UCH-L1 and GFAP were measured using a standard sandwich ELISA protocol. GFAP protein was analyzed using a commercially available ELISA kit (Elabscience, *E*-EL-H2377c) polyclonal two-side immunoluminometric assay according to the manufacturer's instructions. A standard curve was constructed by plotting absorbance values versus GFAP concentrations of calibrators. UCH-L1 concentrations in the serum samples were measured by ELISA with reagents from (Elabscience, *E*-EL-H1888).

2.5. Statistical analyses

Statistical analyses were performed with SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA). Data were assessed for equality of variance and distribution. The normality of our data was assessed with Kolmogorov–Smirnov test and by visual inspection of histograms. For normal distribution of quantitative data, the results were presented as mean ± standard deviation (SD). For abnormal distribution of quantitative data, the results were presented as median (quartile range). For normally distributed continuous variables, independent-samples *t*-test was used. Chi square test was used for categorical data (When the theoretical frequency is <5, the continuous correction method is adopted. When the theoretical frequency is <1, the exact probability method is adopted) and Mann-Whitney test for abnormal distribution continuous variables. Receiver operating characteristic (ROC) curves were used to evaluate the ability of GFAP and UCH-L1 for diagnosing SAE and predicting the 28-day mortality. Kaplan-Meier survival curves were created and compared using the log-rank test. Binary logistic regression was used to identify the variables associated with higher serum GFAP or UCH-L1 levels in patients with sepsis. All statistical tests were two-tailed, and $P < .05$ was considered statistically significant.

3. Results

3.1. Demographics

A total of 134 septic patients were consecutively enrolled, and ruled out 29 patients, including 8 patients with head trauma or stroke, 3 patients with Alzheimer's disease, 1 patient with Parkinson's disease, 1 patient with intracranial infection, 1 patient with pregnancy; 2 patients with hepatic encephalopathy, 1 patient with pulmonary encephalopathy, 2 patients with electrolyte disturbance, 2 patients with cardiopulmonary resuscitation, 1 patient with psychosis; 7 patients' plasma not available or hemolyzed plasma, finally 105 patients involved in the study. The primary diseases included severe pneumonia, abdominal infections, urinary tract infections, severe cholangitis, skin or soft tissue infection and so on. 58 patients were diagnosed with SAE, the rest of 47 patients were divided into the Non-SAE group. Baseline demographic clinical, and biological parameters at admission in patients between the SAE group and the Non-SAE group are listed in Supplementary Table 1. Baseline demographic clinical, and biological

Table 1
Serum concentrations of GFAP and UCH-L1 in patients with SAE and Non-SAE.

Parameters	All Patients	SAE group	Non-SAE group	p[a]
	($n = 105$)	($n = 58$)	($n = 47$)	
GFAP ng/ml	0.544 (0.428–0.764)	0.696 (0.540–0.871)	0.436 (0.316–0.532)	<0.001
UCH-L1 ng/ml	7.042 (6.317–8.079)	7.968 (7.018–8.736)	6.396 (5.771–6.977)	<0.001

Data are given as median (interquartile range).
[a] Mann-Whitney *U* test.

parameters at admission in patients between the Survivors group($n = 72$) and the Non-survivors group($n = 33$) are showed in Supplementary Table 2.

3.2. Serum Concentrations of GFAP and UCH-L1 in patients with SAE

Both GFAP and UCH-L1 levels in SAE patients were significantly higher than in Non-SAE patients [0.696 (IQR 0.540–0.871) ng/ml vs. 0.436 (IQR 0.316–0.532) ng/ml; 6.396 (IQR 5.771–6.977) ng/mL vs. 7.968 (IQR 7.018–8.736) ng/mL, $P < .001$]. This section refers to data in Table 1.

Serum GFAP and UCH-L1 levels at ICU admission correlated with GCS scores ($r = -0.446$, $p < .001$; $r = -0.474$, $p < .001$, respectively).

The serum levels of GFAP and UCH-L1 can distinguish patients with SAE from non-SAE with optimal cut-off values 0.532 ng/ml and 7.72 ng/ml (AUC 0.824 [95% CI 0.738 to 0.892], 0.812[95% CI 0.724 to 0.881] respectively)(Fig. 1a). The sensitivity of GFAP and UCH-L1 was 77.6(64.7–87.5)% and 62.1(48.4–74.5)% respectively, the specifcity was 76.6(62.0–87.7)% and 93.6(82.5–98.7)%, respectively, the positive likelihood ratio (+LR) was 3.32(1.9–5.7) and 9.72(3.2–29.6) respectively, the negative likelihood ratio (−LR) was 0.29(0.2–0.5) and 0.41 (0.3–0.6) respectively.

3.3. Serum Concentrations of GFAP and UCH-L1 in patients with poor prognosis

The median values of GFAP and UCH-L1 for patients of survivors and non-survivors: GFAP [0.504 (IQR 0.360–0.656) ng/ml vs. 0.744 (IQR 0.548–1.052) ng/ml, $P < .001$], UCH-L1 [6.765 (IQR 5.943–7.751) ng/ml vs. 8.349 (IQR 7.330–8.976) ng/ml, $P < .001$](Table 2).

The optimal cut-off values of GFAP to distinguish patients with Survivors from non-survivors was 0.536 ng/ml with an area under the curve of 0.773(95% CI 0.680 to 0.849), the sensitivity was 81.8 (64.5–93.0)% and the specifcity was 61.1(48.9–72.4)%, the +LR was 2.10(1.5–2.9) and -LR was 0.30(0.1–0.6).(Fig. 1b). Using ROC curve analysis, a UCH-L1 cut-off point of 8.06 ng/ml was derived yielding a sensitivity of 54.5(36.4–71.9)% and a specificity of 88.9(79.3–95.1)% to distinguish patients with Survivors from non-survivors (AUC 0.746 [95% CI 0.652 to 0.826]), the +LR was 4.91(2.4–10.1) and -LR was 0.51(0.3–0.7). (Fig. 1b).

3.4. Baseline features and biochemical indicators in in all patients and patients stratified according to the optimal cut-off values of serum GFAP and UCH-L1 levels for diagnosis of sepsis-associated encephalopathy

Table 3 show demographic, clinical, and biological data of all patients enrolled and between patients with and without elevated biomarkers according to the optimal cut-off values of serum GFAP and UCH-L1 levels for diagnosis of SAE. Patients with higher serum GFAP had higher APACHE II scores and SOFA scores, higher mortality, higher incidence of shock and Gram-negative bacteria infection, lower GCS scores, higher levels of lactic acid and IL-6, lower PaO2 and PaO2/FiO2, more patients used sedatives and analgesic. Patients with higher serum UCH-L1 levels also had higher APACHE II scores and SOFA scores, higher mortality, higher incidence of shock and lower GCS scores, higher levels of lactic acid, IL-6 and serum creatinine, more patients used sedatives. There was no significant difference in the duration of sedative and analgesic between the two groups (SAE group vs. Non-SAE group ($p = .133$), GAFP+ group vs. GFAP- group ($p = .236$), UCH-L1+ vs. UCH-L1- group ($p = .662$)).

3.5. Multiple logistic regression analyses for higher GFAP and UCH-L1 concentrations

Multivariate logistic regression analysis demonstrated that higher APACHE II scores and hyperlactacidemia were independent influence factors for higher GFAP concentration stratified according to the optimal cut-off values of serum GFAP levels for diagnosis of SAE, higher levels of Interleukin-6 were independent influence factors for higher UHC-L1 concentration (Table 4).

3.6. Association between the serum GFAP or UCH-L1 levels and the quality of life

The cutoff point for the follow-up was 180 days. 59 cases were successfully followed up. The over all quality of life of septic patients was poor, especially in usual activities and physical pain. Patients with a higher GFAP levels at ICU admission had worse usual activities than patients with a lower GFAP levels ($P = .046$). Patients with a higher UCH-L1 levels at ICU admission had more long-term pain than patients with a lower UCH-L1 levels ($P = .024$). (Table 5). In GAFP+ group, more patients used sedatives ($p = .016$) and analgesic ($p = .023$) than in the GFAP- group, whereas there was no significant difference about the sedatives ($p = .081$) and analgesic ($p = .314$) between the UCH-L1+ group and the UCH-L1- group. About the duration of sedative and analgesic between the two groups, there were no significant difference (GAFP+ group vs. GFAP- group ($p = .869$, $p = .745$), UCH-L1+ vs. UCH-L1- group ($p = .299$, $p = .145$)).

4. Discussion

This study demonstrates that serum-based neuronal and glial proteins —— glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase L1(UCH-L1), may be helpful for diagnosis of SAE, prediction the outcome and evaluating long-term quality of life of patients with sepsis. To the best of our knowledge, this is the first report, which expects to explore the role of GFAP and UCH-L1 in sepsis.

Sepsis is frequently complicated by an acute cerebral dysfunction ranging from delirium to coma, which is associated with adverse outcome and long-term poor quality of life [7,24,25]. Many studies and our work have confirmed that worse APACHE II scores and SOFA scores were presented for patients with sepsis-associated encephalopathy (SAE) than no-SAE, and the patients with SAE possessed longer length of stay ICU days and higher hospital mortality, indicating that the SAE was related to the severity of disease [20,26].

Early detection and diagnosis of SAE is beneficial to mitigate its adverse effects, and biomarkers are a better method. In sepsis, increased apoptosis in specific brain structures (ie, the amygdala, nucleus tractus solitarii and locus ceruleus) in response to stress and hypoxia, lead to excitotoxic processes, structural changes, and neurologic dysfunction [7,8]. Theses structural dysfunctions may be responsible for the neuronal and glial protein release from the brain [8]. Some studies and our previous study show serum S100B and neuron-specific enolase (NSE) can reflect severity and outcome of sepsis brain injury [18,20]. Some other studies indicated that multiple biomarkers were associated with brain injury of sepsis, such as neuronal function markers—brain-derived neurotrophic factor (BDNF) [27]; endothelial activation markers —plasminogen activator inhibitor-1 (PAI-1), *E*-selectin, vascular cellular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1

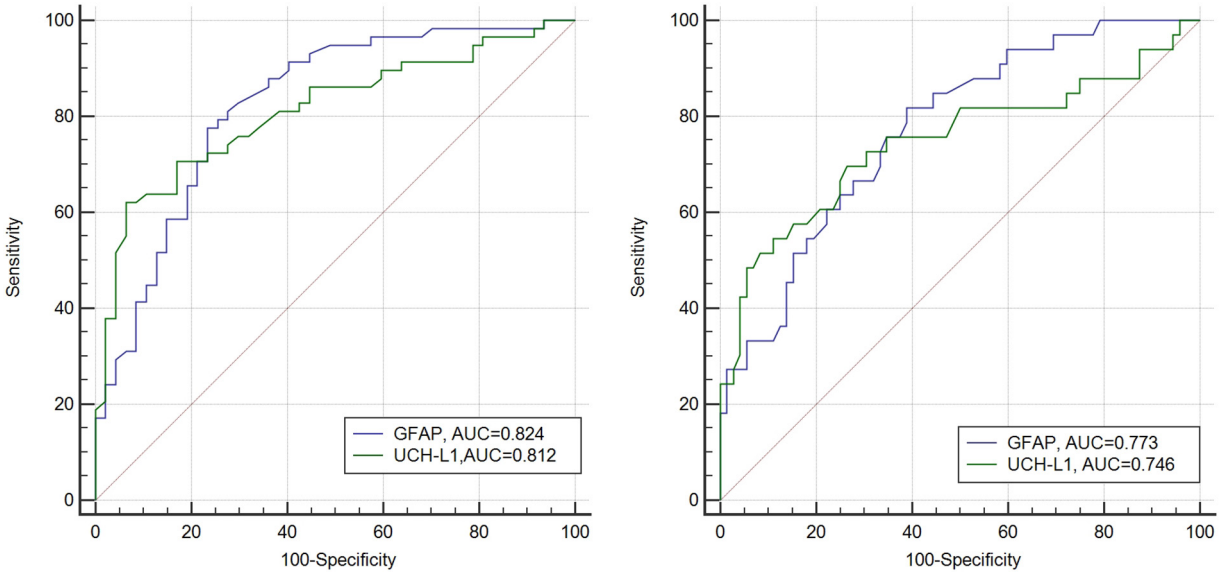

Fig. 1. ROC curves for GFAP (blue line) and UCH-L1 (purple line) in serum for distinguishing patients with SAE from no-SAE (A) or Survivors from non-survivors (B). The area under the curves is indicated.

(ICAM-1), inflammatory markers—IL-6, IL-10 and so on [10,28,29]. So far, few studies have assessed the role of GFAP and UCH-L1 in adult SAE.

GFAP is an intermediate filament protein specifically found in astrocytes in the brain [30]. Elevated levels of brain and serum GFAP have been found in CNS injuries which plays a crucial role in astrocyte activation [31]. Some studies indicated that the GFAP protein could be found in hemorrhagic stroke within 3–4 h [32], while it would be postpone to 24–48 h in ischemic stroke [22]. A autopsy study have found that human brain GFAP expression was significantly increased with sepsis. [33] UCH-L1 is one of the most abundant proteins in the brain almost exclusively in the cytoplasm of neurons and absolutely required for the maintenance of axonal integrity [34]. Several animal and clinical studies have shown that the levels of UCH-L1 were elevated in serum of patients following brain injuries, such as TBI, stroke and hypoxic-ischemic encephalopathy [22,35-37]. A recent study showed that UCHL1 was nonlinearly associated with global cognition at 3 months in critically ill patients [28].

Our results confirmed that serum GFAP and UCH-L1 concentrations from patients with SAE were signifcantly elevated compared to those with no-SAE. Sepsis may cause the permeability of blood–brain barrier (BBB) increases [11]. Neuronal and glial biomarkers may release into the blood from sepsis brain tissue through the impaired BBB. Our results indicated that serum GFAP and UCH-L1 may be able to distinguish SAE from no-SAE, but the specifcity and sensitivity were slightly hypointense. Furthermore, we found that serum GFAP and UCH-L1 concentrations had a correlation with GCS scores. Other study also showed that concentrations of GFAP and UCH-L1 reflect the magnitude of brain injury [21]. However, the correlation between GFAP, UCH-L1 and GCS scores were still not very well. An alternative explanation is that this reflects the limited ability of the GCS score to stratify SAE. On account of the influence of many factors, worse GCS scores didn't always reflect poor outcome, the imaging data may better reflect the severity of sepsis brain injury. Johannes Ehler and his colleagues demonstrated that pathological changes of Ischemic and diffuse neuroaxonal injury occur in the brain with sepsis through animal experiments, autopsy and MRI [38].In the future, it is possible to make better use of the biomarkers by exploring the relationship between the biomarkers and the imaging changes of sepsis. However, due to various constraints, we have not get enough imaging data to analyse.

Our results are in line with previous studies showing that biomarkers could predicted the hospital mortality, but their efficiency was not pleasurable. The CNS plays a crucial part in maintenance of homoeostasis during stress, mainly via the autonomic nervous system and hypothalamic-pituitary-adrenal axis [39]. Inappropriate brain responses might accelerate cardiovascular instability, metabolic disorders, and a sustained pro-inflammatory state [40,41]. Sepsis brain injury may probably facilitate early death, whereas later death was rather influenced by the immunosuppression or the subsequent infection during the ICU stay [42].

Our results indicated that the diagnostic accuracy of GFAP for SAE was only low and the accuracy of UCH-L1 was moderate in confirmation of SAE. The low specifcity and sensitivity may be explained by the fact that sepsis brain injury was evolving with the progress of the sepsis, later secondary brain insults and other complications, which could not be captured by the initial biomarker levels, potentially contributed to brain injury. Dynamic monitoring changes of serum GFAP and UCH-L1 levels may be a better reflection of brain damage. On the other hand, previous studies have also found that the diagnostic accuracy of biomarkers for SAE is weak [18,20], which may be related to the heterogeneity of delirium patients. A study has shown that rapidly reversible, sedation-related delirium does not signify the same poor prognosis as persistent delirium [43], persistence of delirium after cessation of sedatives and analgesics was associated with worse outcomes [44]. Grouping by duration of withdrawal of sedatives may be better to rule out the effects of

Table 2
Serum concentrations of GFAP and UCH-L1 in Survivors and Non-survivors.

Parameters	All Patients ($n = 105$)	Survivors group ($n = 72$)	Non-survivors group ($n = 33$)	p[a]
GFAP ng/ml	0.544(0.428–0.764)	0.504(0.360–0.656)	0.744(0.548–1.052)	<0.001
UCH-L1 ng/ml	7.042(6.317–8.079)	6.765(5.943–7.751)	8.349(7.330–8.976)	<0.001

Data are given as median (interquartile range).
[a] Mann-Whitney U test.

Table 3
Demographic, clinical, and biological parameters at admission in all patients and patients stratified according to the optimal cut-off values of serum GFAP and UCH-L1 levels for diagnosis of sepsis-associated encephalopathy.

Parameters	All Patients	GFAP +	GFAP -	p	UCH-L1+	UCH-L1-	p
	(*n* = 105)	(*n* = 56)	(*n* = 49)		(*n* = 39)	(*n* = 66)	
Age,years	56 ± 15	55 ± 15	57 ± 14	0.329	52 ± 16	58 ± 13	0.058
Gender, (Male/Female)	70/35	40/16	30/19	0.268	30/9	40/26	0.087
APACHE II scores	17 ± 7	19 ± 6	14 ± 7	<**0.001**	19 ± 6	15 ± 7	**0.003**
Max SOFA scores	10 ± 5	11 ± 4	8 ± 4	<**0.001**	12 ± 4	8 ± 4	<**0.001**
Shock, yes (%)	58(55.77)	37(66.07)	21(42.86)	**0.017**	28(71.79)	30(45.45)	**0.009**
GCS scores	15(13–15)	13(11–14)	15(14–15)	<**0.001**	13(10−13)	15(13–15)	<**0.001**
LOS ICU, days	6(3–9)	6(4–11)	5(3–9)	0.146	5(4–7)	6(3−11)	0.413
28-day mortality, *n*(%)	33(31.77)	27(48.21)	6(12.24)	<**0.001**	21(53.85)	12(18.18)	<**0.001**
Source of infection				0.120			0.909
Lung, n(%)	14(13.33)	10(17.86)	4(8.16)		6(15.38)	8(12.12)	
Abdominal cavity, n(%)	72(68.57)	40(71.43)	32(65.31)		26(66.67)	46(69.70)	
Urinary tract, n(%)	15(14.29)	5(8.93)	10(20.41)		6(15.38)	9(13.64)	
Others, n(%)	4(3.81)	1(1.79)	3(6.12)		1(2.56)	3(4.55)	
Bacteriological categories							
Gram-negative bacteria, n(%)	52(49.52)	33(58.93)	19(38.78)	**0.039**	22(56.41)	30(45.45)	0.278
Gram-positive bacteria, n(%)	30(28.57)	18(32.14)	12(24.49)	0.386	11(28.21)	19(28.79)	0.949
Fungal, n(%)	13(12.38)	6(10.71)	7(14.29)	0.579	5(12.82)	8(12.12)	0.962
Mixed infection, n(%)	22(20.95)	13(23.21)	9(18.37)	0.543	10(25.64)	12(18.18)	0.364
Blood culture positive, *n*(%)	22(20.95)	10(17.85)	12(24.49)	0.405	6(15.38)	16(24.24)	0.281
Interleukin-6, pg/L	235(77–1257)	420(110–1949)	122(60–980)	**0.016**	912(268–5000)	118(64–564)	<**0.001**
Procalcitonin, ng/ml	30(6–67)	38(8–76)	23(6–55)	0.155	38(11–78)	22(5–61)	0.077
Lactate, mmol/L	2.5(1.3–3.7)	3.0(1.8–4.7)	1.7(1.0–2.7)	<**0.001**	3.0(2.0–4.7)	2.0(1.1–2.9)	**0.001**
Creatinine, μmol/L	128.7(89.1–202.3)	132.9(90.0–192.9)	121.9(84.2–231.8)	0.523	150.3(99.8–248.8)	121.2(81.3–184.7)	**0.046**
PaO2, mmHg	110 ± 51	101 ± 54	122 ± 48	**0.041**	109 ± 55	112 ± 50	0.828
PaO2/FiO2	268 ± 135	243 ± 138	297 ± 127	**0.039**	268 ± 142	268 ± 132	0.982
Number of comorbidities ≥1, *n*(%)	46(43.81)	25(44.64)	21(42.86)	0.854	16(41.03)	30(45.45)	0.659
Sedation, *n*(%)	58(55.42)	41(73.21)	17(34.69)	<**0.001**	29(74.36)	29(43.94)	**0.002**
Sedation, days	2(1–4)	2(1–4)	1(1–3)	0.236	2(1–4)	2(1–4)	0.662
Benzodiazepines, *n*(%)	25(23.81)	18(32.14)	7(14.29)	**0.032**	11(28.21)	14(21.21)	0.370
Analgesic, *n*(%)	62(59.05)	42(75.00)	20(40.82)	<**0.001**	27(69.23)	35(53.03)	0.103
Analgesic, days	3(2–5)	3(2–5)	2(1–5)	0.343	3(1–4)	3(2–5)	0.302

GFAP+, GFAP levels >0.532 ng/ml; GFAP-, GFAP levels ≤0.532 ng/ml; UCH-L1+,UCH-L1 levels>7.72 ng/ml; UCH-L1-,UCH-L1 levels ≤7.72 ng/ml; ICU, intensive care unit; LOS, length of stay; APACHE, Acute Physiology and Chronic Health Evaluation score; Max SOFA score, maximum Sequential Organ Failure Assessment score evaluated at the fourth day of inclusion; GCS, Glasgow Coma Scale; GFAP, glial fibrillary astrocytic protein; UCH-L1, Ubiquitin Carboxyl-Terminal Esterase L1. The significance of bold is the statistical difference between the two groups ($p < 0.05$).

sedatives and improve sensitivity and specificity of GFAP and UCH-L1. A large, multicentre, prospective study [45] show that more than half of the critically ill patients with acute respiratory failure, shock, or both develop multiple clinical phenotypes of delirium with sedative-associated, hypoxic, and septic delirium being most common and cognitive impairment was different in different clinical phenotypes of delirium. To explore the differences of biomarkers in different clinical phenotype of delirium may improve the diagnostic accuracy of biomarkers for SAE.

We compared the demographic, clinical, and biological parameters to discover the cause of elevated serum GFAP and UCH-L1 levels at admission in patients stratified according to the optimal cut-off values of serum GFAP and UCH-L1 levels for diagnosis of sepsis-associated encephalopathy. We found that higher APACHE II scores and SOFA scores, higher incidence of shock, higher levels of lactic acid and Interleukin-6 were present in higher serum GFAP and UCH-L1 levels group, and lower PaO2, PaO2/FiO2 for GFAP+ group, higher serum creatinine for UCH-L1+ group. These results indicated that high serum GFAP and UCH-L1 were associated with the severity of the disease, hypoperfusion, hyoxemia and hyperinflammatory. Furthermore, multivariate logistic regression analysis demonstrated that APACHE II and lactate were independent influence factors for high serum GFAP levels and higher interleukin-6 for higher serum UCH-L1 concentration. Various causes may lead to SAE and SAE contains a variety of pathogenesis. Different biomarkers may reflect different pathogenesis caused by different causes, which may play an important role in follow-up studies on SAE. In our study, it was showed that higher lactate may be the cause of increased serum GFAP levels for SAE, but higher lactate had less effect on serum UCHL1 levels and higher levels of inflammatory factor IL-6 may be responsible for higher serum UCH-L1 levels. Exploring the related biomarkers of brain injury caused by different causes may provide information for better exploring the pathogenesis and brain protection for sepsis-associated encephalopathy.

Table 4
Logistic regression analysis of independent factors for higher GFAP or UCH-L1 levels.

Variable	GFAP levels(≤0.532 vs >0.532 ng/ml)				UCH-L1 levels (≤7.72 vs >7.72 ng/ml)			
	OR	95% CI		p	OR	95% CI		p
Age	0.980	0.948	1.013	0.229	0.971	0.938	1.005	0.092
Gender	2.112	0.800	5.575	0.131	2.340	0.801	6.836	0.120
APACHE II	1.095	1.007	1.192	**0.035**	1.071	0.978	1.174	0.138
Lactate	1.352	1.047	1.746	**0.021**	1.190	0.989	1.432	0.065
Interleukin-6	1.000	1.000	1.000	0.511	1.000	1.000	1.001	**0.027**
PaO2/FiO2	0.997	0.994	1.001	0.110	–	–	–	–
Creatinine	–	–	–	–	1.000	0.996	1.004	0.854

GFAP and UCH-L1 levels categorized according to the optimal cut-off values for SAE.
The significance of bold is the statistical difference between the two groups ($p < 0.05$).

For the clinical diagnosis of SAE, the main limitation was sedation as sedatives alter awareness and cognition, even after their discontinuation. In our study, The reasons for patients in the SAE group (GFAP+ group and UCH-L1+ group) to use more sedatives and analgesics may be as follows: 1. Patients in the SAE group had lower oxygenation and more respiratory support, which may require more sedation and analgesia for better man-machine coordinatio; 2. In the SAE group, some patients have shown delirium before sedation and analgesia. At present, there is no special treatment for delirium. When the patient shows agitation, sedatives were needed for the patient's treatment and safety. To mitigate the effects of sedation on SAE assessment, spontaneous awakening trials were performed daily for patients who were sedated. The longest evaluating time after stopping sedation in spontaneous

Table 5
Changes in EQ-5D domains and EQsum at 180 days after discharge in all patients and stratified according to the optimal cut-off values of serum GFAP and UCH-L1 levels for diagnosis of SAE.

	Total	GFAP +	GFAP -	p[a]	UCH-L1+	UCH-L1-	p[a]
	(*n* = 59)	(*n* = 26)	(*n* = 33)		(*n* = 14)	(*n* = 45)	
Mobility				0.103			0.417
No problems	54	22	32		12	42	
Moderate problems	3	3	0		2	1	
Severe problems	2	1	1		0	2	
Self-care				0.195			0.220
No problems	55	23	32		12	43	
Moderate problems	3	2	1		2	1	
Severe problems	1	1	0		0	1	
Usual activities				**0.046**			0.450
No problems	37	13	24		8	29	
Moderate problems	19	10	9		4	15	
Severe problems	3	3	0		2	1	
Pain/discomfort				0.909			**0.024**
No problems	41	18	23		6	35	
Moderate problems	16	8	8		8	8	
Severe problems	2	0	2		0	2	
Depression/anxiety				0.690			0.426
No problems	51	23	28		13	38	
Moderate problems	8	3	5		1	7	
Severe problems	0	0	0		0	0	
EQsum score	0.80(0.77–1.00)	0.80(0.74–1.00)	1.00(0.77–1.00)	0.343	0.77(0.72–1.00)	1.00(0.77–1.00)	0.055

EQ-5D, EuroQol 5-dimension questionnaire health scale; EQsum score, Summary Index of EQ-5D.
The significance of bold is the statistical difference between the two groups ($p < 0.05$).
[a] Mann-Whitney U test.

awakening trials was 24 h which was significantly longer than the half-life of sedatives and analgesics. The avoidance of benzodiazepines in ICU patients at risk for delirium received a weak recommendation in recent pain, agitation, and delirium-management guidelines [46]. In our study, midazolam was used more frequently in the SAE group. Several studies have shown that midazolam may cause delirium in comparison with other sedatives such as dexmedetomidine [47,48]. The excessive use of sedatives and the excessive depth of sedation may be the cause of delirium [49]. Stollings and his colleagues [50] found that higher lorazepam plasma concentrations were associated with delirium in critically ill patients. Midazolam has a relatively short half-life among benzodiazepines and recent studies have not found a difference between midazolam and dexmedetomidine in delirium [51]. In our study, sedation and analgesia were goal-directed, and sedation depth was assessed daily to minimize the likelihood of delirium. In addition, according to the guidelines, non-benzodiazepines are preferred for sedation, and benzodiazepines are only used when agitation is uncontrollable or not conducive to treatment. At present, there is no evidence that sedatives and analgesics cause an increase in delirium.

The long-term cognitive impairment and functional disability of patients with sepsis severely impact the quality of life of patients [52]. Multiple large-scale studies have shown that survivors of sepsis may suffer from ICU-acquired paresis and cognitive impairment, with subsequent functional disabilities and poor quality of life and which might contribute to the excess long-term mortality, especially in the elderly patients. This might be the leading cause of a declined condition with ability to live independently, thereby increasing the economic and psychological burden on patients and their families. Therefore, we should pay attention not only to the short-term survival and recovery of sepsis, but also to the long-term survival quality. A recent study which aimed to determine potentially modifiable risk factors during ICU hospitalization that play a significant role in developing persistent cognitive impairment found that some factors were modifiable for the prevention of persistent cognitive impairment, such as average duration of MAP <50 mmHg, average number of readings of SpO2 < 90%, average number of readings >39 °C [53]. It is a promising and meaningful work to explore the early biomarkers of sepsis long-term neurological sequelae. EuroQol 5-dimension questionnaire health scale is widely used global multidimensional health-related evaluation of the quality of life [54]. We assess quality of life of living sepsis patients with EQ-5D. Our results show that patients with sepsis have a long-term decline in the quality of life, especially in daily activities and physical pain. Patients with a higher GFAP levels at ICU admission had worse usual activities than patients with a lower GFAP levels, and patients with a higher UCH-L1 levels at ICU admission had more long-term pain than patients with a lower UCH-L1 levels. A lastest research found that S100B and *E*-selectin were associated with long-term cognitive impairment after critical illness [28]. In future studies, we will further explore the predictive value of biochemical markers in long-term cognitive impairment in patients with sepsis, and a timely diagnosis and efficient treatment may prevent the formation and development of brain injury in patients with sepsis, thereby improving the prognosis and reducing the economic and psychological burden.

Although there was differences about chronic pain between the UCH-L1+ group and the UCH-L1- group, there was no significant difference between the two groups in sedatives and analgesics, suggesting that chronic pain may have little relationship with sedatives and analgesics. The cause of pain difference between the two groups may be related to the pathophysiological mechanism reflected by UCH-L1. UCH-L1 is significantly correlated with neuronal integrity and may be associated with chronic pain. In an animal study [55], they demonstrated that inhibition of spinal UCH-L1 may be an effective method to alleviate cancer-induced bone pain. However, this conclusion still needs to be verified by further studies on account of the small sample size of our study and confounding factors included age, surgery, disease severity, and comorbidity and so on.

The neuro and glia biomarkers can reflect different types of neuropathological processes in sepsis and provide supplementary information for the diagnosis of SAE, but they are not sufficiently and combining with other auxiliary examination [56] [57] may be more beneficial to broadening our arsenal for detecting SAE. Multimodal brain monitoring may be a better method for brain damage in sepsis, whereas this method was complex and expensive, it is not conducive to promotion. In future studies, we expect to quickly and effectively identify brain injury with sepsis by exploring the role of different biomarkers in different brain injury mechanisms for sepsis and long-term cognitive function, so as to provide better information for brain protection.

Although the present cohort of ICU patients is a representative sample from Xiangya Hospital, there were several limitations that should be

discussed in our study. Firstly, the diagnosis of SAE was exclusive. At present, the mainstream diagnostic method of SAE is the exclusive method, usually depends on case history and clinical symptoms. For practical difficult and clinical safety, we did not obtain enough imaging data. Second, we firstly chose the Sepsis 3.0 criterion rather than the SIRS criterion for sepsis may give rise to our results different from others, future additional studies are necessary to confirm our findings. Third, although shortacting sedatives were used for sedation, 24 h may not long enough for drug elimination in someone, and auxiliary examination was performed in only part of sedation patients, we cannot exclude the effect of sedation. Fourthly, our study only evaluated the biomarkers within 24 h admission. In the future research, the dynamic changes of these biomarkers should be detected. Fifthly, this is a single-center and the relatively modest sample size may affect the reproducibility of our results, and future large multi-center studies are necessary to confirm our study findings.

5. Conclusion

In summary, we demonstrated serum GFAP and UCH-L1 early elevated and associated with sepsis-associated encephalopathy poor prognosis and quality of life. However, the diagnostic accuracy of GFAP and UCH-L1 for SAE was moderate.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.04.018.

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Conflict of interest

The authors declare that they have no conflict of interest.

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