Clinica Chimica Acta 497 (2019) 6–12

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Usefulness of serum interleukin-33 as a prognostic marker of severe traumatic brain injury

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ARTICLE INFO

Keywords:
Traumatic brain injury
Interleukin-33
Prognosis
Severity
Inflammation

ABSTRACT

Background: Interleukin-33 is recently identified as a brain injury biomarker. We determined whether serum interlerukin-33 concentrations are associated with inflammation, severity and prognosis after traumatic brain injury (TBI).

Methods: We detected serum interlerukin-33 concentrations of 102 healthy controls and 102 severe TBI patients, as well as serum concentrations of 3 inflammatory biomarkers (interleukin-6, tumor necrosis factor-alpha and C-reactive protein) and 7 cell-specific proteins (myelin basic protein, glial fibrillary astrocyte protein, S100B, neuron-specific enolase, phosphorylated axonal neurofilament subunit H, Tau and ubiquitin carboxyl-terminal hydrolase L1) in 102 severe TBI patients. The recorded poor prognosis variables included acute lung injury, acute traumatic coagulopathy, progressive hemorrhagic injury, posttraumatic cerebral infarction and six-month mortality and poor outcome (Glasgow score of 1–3).

Results: Median interlerukin-33 concentration of patients (692 pg/mL) was substantially raised, as compared to controls. Interlerukin-33 concentrations were significantly correlated with Glasgow coma scale (GCS) score and the preceding biomarkers concentrations. Interlerukin-33 concentration > 692 pg/mL emerged as an independent prognostic predictor and its discriminatory capability exceeded those of the above-mentioned inflammatory biomarkers concentrations and was in the range of GCS scores and the aforementioned cell-specific proteins concentrations.

Conclusion: Ascending serum interlerukin-33 concentrations could reflect inflammation, severity and worse prognosis following TBI.

1. Introduction

Severe traumatic brain injury (sTBI) is a devastating type of trauma with high morbidity and mortality [1]. Complications relevant to sTBI include acute lung injury (ALI), acute traumatic coagulopathy (ATC), progressive hemorrhagic injury (PHI) and posttraumatic cerebral infarction (PTCI). Their occurrences obviously increase the risk of death and poor outcome among sTBI patients [2–5]. There is substantial evidence to show that direct disruption of brain tissue, excitotoxicity, hormone pathophysiology, apoptosis, oxidative stress, as well as an aseptic central and peripheral inflammatory response participate in the development of acute brain injury following sTBI [6]. Also, there have been numerous experimental and clinical studies confirming that several neuronal or glial cell-specific proteins, such as myelin basic protein (MBP), glial fibrillary astrocyte protein (GFAP), the calcium-binding protein S100B, neuron-specific enolase (NSE), phosphorylated axonal neurofilament subunit H (pNF-H), tau protein and ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), can enter into the peripheral blood via disrupted blood-brain barrier after head trauma, and subsequently their circulating concentrations can be detected for assessing the degree of brain injury [7]. The Glasgow Coma Scale (GCS) is an integral part of clinical practice and research across the world. It is extensively utilized to estimate the traumatic severity and clinical outcome of sTBI patients [8]. In recent decades, biomarkers have attracted some clinicians'

Abbreviations: CT, computerized tomography; GCS, Glasgow coma scale; TBI, traumatic brain injury; ALI, acute lung injury; ATC, acute traumatic coagulopathy; PHI, progressive hemorrhagic injury; PTCI, posttraumatic cerebral infarction; IL-33, interleukin-33

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https://doi.org/10.1016/j.cca.2019.07.008
Received 18 June 2019; Received in revised form 29 June 2019; Accepted 2 July 2019
Available online 04 July 2019

interest for clinical assessment of severity and prognosis in sTBI.

Interleukin-33 (IL-33) is a newly found member of the interleukin-1 superfamily, and exerts dual functions via binding to its receptor ST2 [9]. IL-33 participates in inflammatory reaction in asthma, inflammatory bowel disease and acute myocardial infarction [10–13]. The accumulating data demonstrate that IL-33 can be expressed greatly in animal brain tissues after hemorrhagic or ischemic injury [14,15]. Also, it is clear that, via regulating specific microglial activities, IL-33 can alleviate brain edema, inhibit neuronal apoptosis, and improve neurological function in rats with acute brain injury [16–20]. In humans with ischemic stroke, ascending serum IL-33 concentrations were significantly correlated with large infarction volume [21]. However, another study showed that serum IL-33 concentrations were substantially decreased with rising infarction volume [22]. In aneurysmal subarachnoid hemorrhage, serum IL-33 concentrations were positively associated with the severity [23]. Thereby, the conclusions regarding relationships between serum IL-33 concentrations and severity of acute brain injury are inconsistent. Alternatively, there is a paucity of data available regarding the change of IL-33 concentrations in the peripheral blood from sTBI patients and its prognostic capability, as compared with other biochemical biomarkers, namely MBP, GFAP, S100B, NSE, pNF-H, tau protein and UCH-L1. In the current study, we intended to explore whether serum IL-33 concentrations are related to the inflammation, severity and prognosis of sTBI in humans.

2. Methods

2.1. Patients and controls

In this prospective, observational study performed at The CHC International Hospital (Cixi, China) from April 2014 to January 2018, a group of isolated sTBI patients were assessed. sTBI was defined as postresuscitation Glasgow coma scale (GCS) score of < 9. Isolated head trauma was referred to as confirmed brain injury without other major extracranial injuries, such as pelvis or femur fractures, or severe abdominal or thoracic invasive injuries, as indicated by an extracranial abbreviated injury scale score < 3 [24]. Alternatively, we required that patients must undergo ≥2 head computed tomography (CT) scans in the first 72 h and at least 4 head CT scans in the first week after injury. Moreover, some patients were removed, based on the exclusion criteria as follows: age < 18 y, admission time > 6 h since trauma, infection within recent a month, previous head trauma, existing neurological diseases such as ischemic stroke and spontaneous intracranial hemorrhage, use of antiplatelet or anticoagulant medication, and presence of other systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart or lung disease, diabetes mellitus and hypertension. Also, we enrolled healthy individuals as controls. The study protocol was approved by our institutional ethics committee for human studies as well as written informed consent was acquired from participants or their relatives.

2.2. Assessment

We recorded the following information: age, gender, admission time, time to first CT scan, blood-collection time, GCS score, unreactive pupils, CT-confirmed abnormal cisterns, midline shift > 5 mm and traumatic subarachnoid hemorrhage as well as Marshall CT classification [25]. PHI was defined as any increase in size or number of the hemorrhagic lesion, including newly developed ones [26]. PTCI was diagnosed when there was distinctly hypodense lesions within a defined cerebral vascular territory, hypodense lesions located in boundary zones between the defined cerebral vascular territories or hypodense lesions situated in the terminal zones of perforating arteries within the deep white matter [27]. ALI was considered when there were acute onset, the ratio of partial pressure of arterial oxygen to fractional inspired oxygen ≤ 300, bilateral infiltrates on chest radiograph, and no clinical evidence of left arterial hypertension [28]. The patients were followed up until death or the completion of 6 months. Poor outcome was designated as Glasgow outcome scale score of 1–3.

2.3. Determinations

The peripheral venous blood of patients was drawn at admission and that of controls was obtained at study entry. Coagulation test or blood routine test were done utilizing the conventional laboratory methods. ATC was referred to as an activated partial thromboplastic time > 40 s and/or international normalized ratio > 1.2 and/or a platelet count < 120×10^9/L [29,30]. Serum biomarker concentrations were measured following the manufactures' instructions with commercially available enzyme-linked immunosorbent assay kits below: CRP, IL-6 and TNF-α (Cusabio Biotech, China); NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 (Phoenix Pharmaceuticals, USA); IL-33 (R&D Systems, USA). All determinations were in duplicate done in batches every 3 months by the same technician inaccessible to clinical information. Two measurements were averaged for further analyses.

2.4. Statistical analysis

Statistical softwares used in this study included SPSS 19.0 and MedCalc 9.6.4.0. ualitative and quantitative data were summarized as counts (percentage) and median (interquartile range) respectively, as well as were compared by the chi-square test and Mann-Whitney *U* test respectively. Bivariate correlations were analyzed using Spearman's correlation coefficient. Two multivariate logistic regression models were established to investigate relationship between serum IL-33 concentrations and poor prognosis variables (i.e., ALI, ATC, PHI, PTCI, 6-month mortality and 6-month poor outcome). The first model included one adjusted factor, i.e., GCS scores and the second model contained the following confounding factors: age, gender, GCS scores, unreactive pupils, abnormal cisterns, midline shift > 5 mm, traumatic subarachnoid hemorrhage, Marshall CT classification, admission time, blood-collecting time and time to first CT scan. Receiver operating characteristic (ROC) curves were configured to assess the prognostic discriminatory capability. Using the Z test, differences in the prognostic predictive ability reflected by area under curve (AUC) were compared between serum IL-33 concentrations and serum CRP, IL-6, TNF-α, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 concentrations. A *P*-value < .05 was considered significant.

3. Results

3.1. Study population characteristics

Initially, a total of 148 patients were assessed. According to the exclusion criteria, 46 patients were removed (Fig. 1). Finally, 102 patients were available for further analysis. Table 1 shows age and gender percentage of the included head trauma patients. Among the excluded patients, the median age was 37 y (interquartile range, 27–52) and there were 30 males and 16 females. No differences in age and gender proportion existed between the included and excluded patients, indicating that those enrolled basically represented the total participants of sTBI. In addition, we recruited a group of healthy controls who had a median age of 34 y (interquartile range, 25–55) and 60 males (58.8%). The controls exhibited similar age and gender percentage, in comparison with the patients. Also, other components of the ultimately assessed patients, such as clinical, radiological and biochemical data, are displayed in Table 1.

3.2. Serum IL-33 concentrations and its correlation with other variables

In Fig. 2, admission serum IL-33 concentrations were profoundly

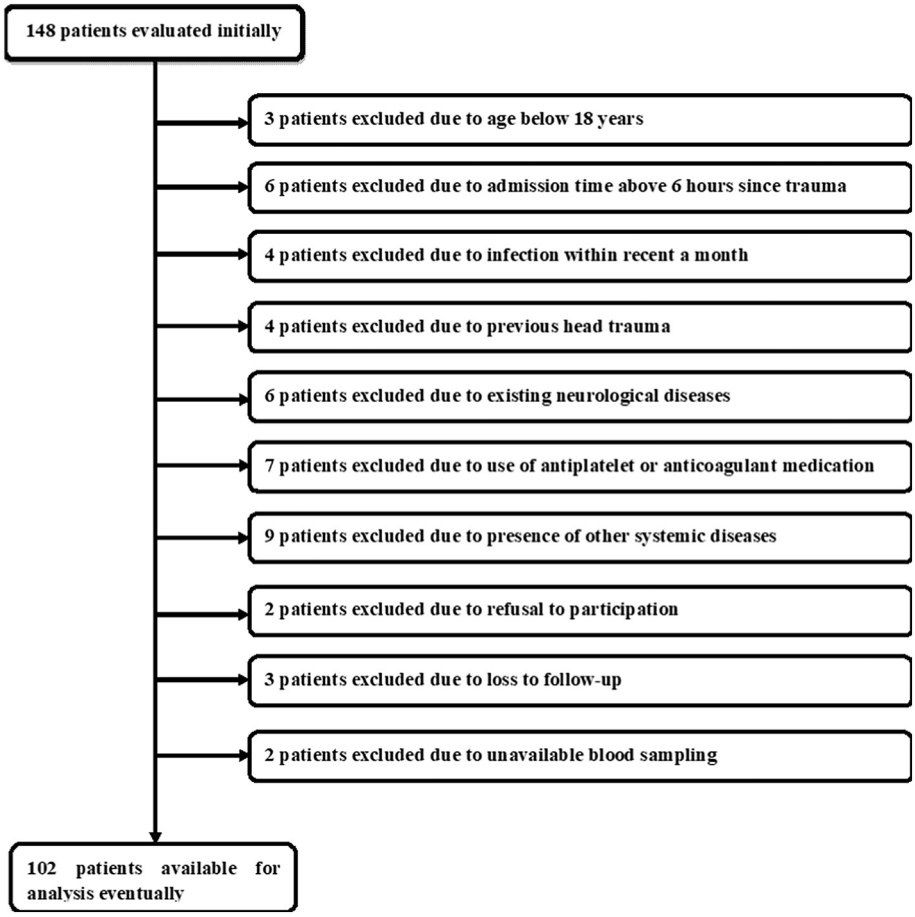


Fig. 1. Flow chart displaying selective and exclusive process of patients with severe traumatic brain injury in the current study.

raised in the TBI patients, as opposed to the controls. The TBI patients were dichotomized in accordance with the median value of serum IL-33 concentrations (> 692 pg/mL vs. < 692 pg/mL). Table 1 shows that, as compared to the remainders, those patients with serum IL-33 concentrations exceeding > 692 pg/mL tended to have a significantly lower GCS score, were more prone to have substantially elevated percentages of unreactive pupils, midline shift > 5 mm, traumatic subarachnoid hemorrhage, abnormal cisterns and Marshall CT classification 5 or 6, were more likely to exhibit remarkably rising serum CRP, IL-6, TNF-α, NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 concentrations, as well as were more possible to have markedly raised proportions of ALI, ATC, PHI, PTCI, 6-month death and six-month poor outcome. Alternatively, using Spearman's correlation coefficient, serum IL-33 concentrations were closely related to GCS score ($r = -0.490$, $P < .001$), as well as serum CRP ($r = 0.314$, $P = .001$), IL-6 ($r = 0.212$, $P = .033$), TNF-α ($r = 0.257$, $P = .009$), NSE ($r = 0.391$, $P < .001$), S100B ($r = 0.412$, $P < .001$), MBP ($r = 0.424$, $P < .001$), GFAP ($r = 0.480$, $P < .001$), tau protein ($r = 0.426$, $P < .001$), pNF-H ($r = 0.509$, $P < .001$) and UCH-L1 concentrations ($r = 0.357$, $P < .001$).

3.3. Serum IL-33 concentrations and its relation to prognosis

In Table 2, univariate logistic regression analysis demonstrated serum IL-33 concentrations > 692 pg/mL was significantly associated with ALI, ATC, PHI, PTCI, 6-month mortality and 6-month poor outcome; even if correcting for some confounding factors whether including only GCS score or other variables, i.e., age, gender, unreactive pupils, abnormal cisterns, midline shift > 5 mm, traumatic subarachnoid hemorrhage, Marshall CT classification, admission time, blood-collecting time and time to first CT scan, serum IL-33 concentrations > 692 pg/mL was still in substantial association with ALI, ATC, PHI, PTCI, 6-month mortality and 6-month poor outcome.

In Figs. 3 and 4, serum IL-33 concentrations significantly predicted patients with the development of ALI, ATC, PHI, PTCI, six-month mortality and six-month poor outcome. For each poor prognosis variable, an optimal cutoff value of serum IL-33 concentrations was selected, which yielded the medium-high sensitivity and specificity (Figs. 3 and 4). In Table 3, in terms of prognostic predictive ability assessed by AUC, there were no substantial differences between serum IL-33 concentrations and other variables, namely, serum NSE, S100B, MBP, GFAP, tau protein, pNF-H and UCH-L1 concentrations in addition to GCS score, while significant differences existed between serum IL-33 concentrations and serum CRP, IL-6 and TNF-α concentrations.

4. Discussion

IL-33, a newly found cytokine, belongs to the IL-1 superfamily and can be extensively expressed throughout the human body. Once cell damage or tissue injury, IL-33 is released into the extracellular space, wherein it produces endogenous danger signals to alert adjacent cells. This function deems IL-33 as an alarmin. IL-33 also functions as a nuclear factor regulating gene transcription in cytokine-expressing or cytokine-responsive cells [9]. Recently, IL-33 is demonstrated to play essential roles in inflammation. A great number of data have shown that IL-33 participates in inflammatory processes of numerous human diseases, such as rheumatoid arthritis, systemic sclerosis, chronic hepatitis B virus infection, asthma, inflammatory bowel disease and acute myocardial infarction [10–13]. Interestingly, astrocytes can express IL-33. Moreover, its expression can be greatly up-regulated under

Table 1
Characteristics of patients with severe traumatic brain injury and comparisons of components by median value of serum interleukin-33 levels.

	All patients	Serum interleukin-33 levels		
		> 692 pg/mL	< 692 pg/mL	*P* value
Age (years)	36 (25–53)	42 (26–53)	35 (24–52)	0.718
Gender (male/female)	64/38	30/21	34/17	0.413
Admission time (h)	2.0 (1.1–3.0)	2.3 (1.2–2.9)	1.6 (0.8–3.2)	0.188
Blood-collection time (h)	3.8 (2.0–4.8)	3.9 (2.4–4.5)	3.4 (1.8–4.9)	0.369
Time to first CT scan (h)	3.2 (2.7–4.4)	3.2 (2.9–4.2)	3.1 (2.7–4.8)	0.896
GCS score	5 (4–6)	4 (3–5)	6 (5–7)	< 0.001
Unreactive pupils	48 (47.1%)	39 (76.5%)	9 (17.7%)	< 0.001
Abnormal cisterns	46 (45.1%)	38 (74.5%)	8 (15.7%)	< 0.001
Midline shift > 5	42 (41.2%)	35 (68.6%)	7 (13.7%)	< 0.001
Traumatic SAH	61 (59.8%)	45 (88.2%)	16 (31.4%)	< 0.001
Marshall CT classification 5 or 6	54 (52.9%)	42 (82.4%)	12 (23.5%)	< 0.001
Serum CRP levels (μg/mL)	18.8 (14.7–25.6)	21.4 (16.5–26.9)	17.0 (11.2–20.9)	0.008
Serum TNF-α level s(pg/mL)	9.5 (7.2–14.0)	11.0 (7.7–16.8)	7.8 (6.6–13.2)	0.011
Serum IL-6 levels (pg/mL)	11.8 (8.8–14.4)	13.0 (9.9–16.0)	10.9 (8.4–12.9)	0.025
Serum NSE levels (ng/mL)	16.6 (13.5–21.1)	18.1 (14.3–27.4)	15.2 (11.7–19.0)	< 0.001
Serum S100B levels (pg/mL)	766.9 (508.4–1030.9)	932.1 (675.1–1397.4)	653.2 (488.6–888.6)	< 0.001
Serum MBP levels (μg/mL)	13.3 (9.6–16.7)	14.4 (11.5–23.1)	11.1 (8.9–15.3)	0.002
Serum GFAP levels (pg/mL)	16.5 (12.6–22.1)	20.6 (15.1–26.3)	14.3 (10.9–17.6)	< 0.001
Serum Tau levels (pg/mL)	275.9 (195.5–415.8)	336.0 (253.5–495.5)	258.4 (135.7–290.6)	< 0.001
Serum pNF-H levels (pg/mL)	925.6 (664.5–1440.1)	1298.8 (840.3–1782.7)	693.4 (498.3–933.4)	< 0.001
Serum UCH-L1 levels (pg/mL)	1797.7 (1463.3–2335.7)	2151.5 (1664.1–2887.2)	1650.9 (1383.7–1917.0)	< 0.001
Acute lung injury	33 (32.4%)	28 (54.9%)	5 (9.8%)	< 0.001
Acute traumatic coagulopathy	40 (39.2%)	32 (62.8%)	8 (15.7%)	< 0.001
Progressive hemorrhagic brain injury	30 (29.4%)	27 (52.9%)	3 (5.9%)	< 0.001
Post-traumatic cerebral infarction	17 (16.7%)	15 (29.4%)	2 (3.9%)	< 0.001
Death within 6 months	28 (27.5%)	24 (47.1%)	4 (7.8%)	< 0.001
Poor outcome at 6 months	50 (49.0%)	37 (72.5%)	13 (25.5%)	< 0.001

Qualitative data are reported as counts (percentage). Quantitative data are presented as median (interquartile range). For quantitative data, samples were compared by the Mann-Whitney *U* test. Qualitative data were compared by the Pearson's chi-square test. NSE indicates neuron-specific enolase; MBP, myelin basic protein; GFAP, glial fibrillary astrocyte protein; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1; IL-6, interleukin-6; TNF-a, tumor necrosis factor-alpha; CRP, C-reactive protein; GCS, Glasgow coma scale; CT, computerized tomography; SAH, subarachnoid hemorrhage.

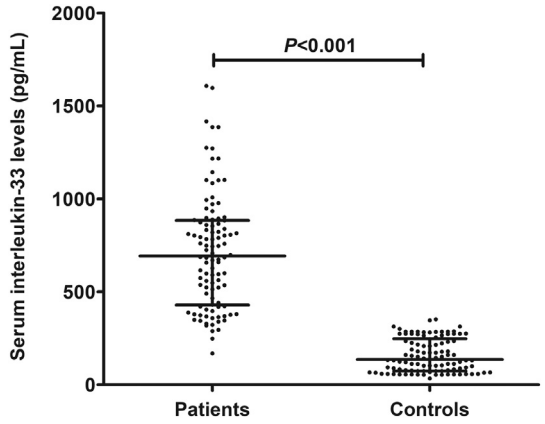


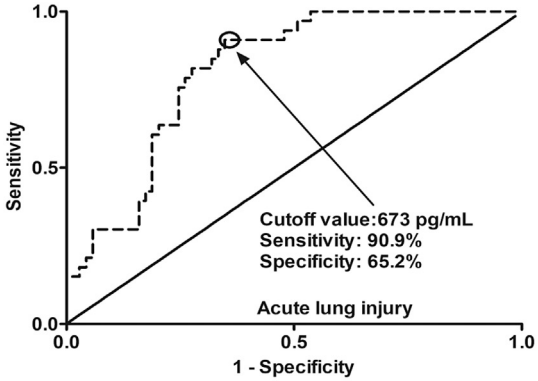
Fig. 2. Difference in serum interleukin-33 concentrations between healthy controls and patients with severe traumatic brain injury.

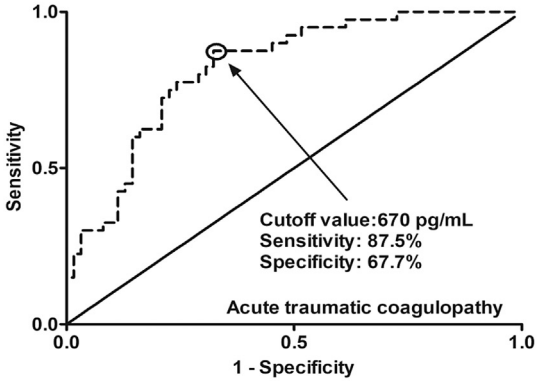
pathological conditions [14,15]. Accumulating evidence deriving from animal experiments suggests that IL-33, acting as an inflammatory cytokine, might be implicated in brain injury and moreover exerts a protective effect on neurological function. Its mechanisms are very complex and include promoting microglia M2 polarization, regulating specific microglial activities, enhancing recruitment of microglia/macrophages, improving Th2 response and suppressing Th17 response as well as increasing microglial synapse engulfment and neural circuit development [16–20]. Our data have confirmed a close correlation between serum IL-33 and CRP concentrations, between serum IL-33 and TNF-a concentrations and between serum IL-33 and IL-6 concentrations, supporting the notion that IL-33 should be involved in the inflammatory process underlying secondary brain injury following head trauma.

Table 2
Association of serum interleukin levels > 692 pg/mL with prognosis among severe traumatic brain injury patients.

	Odds ratio	95% confidence interval	*P* value
Acute lung injury			
Model 1	11.200	3.822–32.822	< 0.001
Model 2	8.261	2.274–30.015	0.001
Model 3	6.970	1.681–28.910	0.007
Acute traumatic coagulopathy			
Model 1	9.053	3.521–23.275	< 0.001
Model 2	6.703	1.981–22.645	0.002
Model 3	4.891	1.206–19.839	0.026
Progressive hemorrhage injury			
Model 1	18.000	4.957–65.359	< 0.001
Model 2	12.527	3.189–49.207	< 0.001
Model 3	11.821	2.653–52.663	0.001
Posttraumatic cerebral infarction			
Model 1	10.208	2.195–47.468	0.003
Model 2	6.104	1.243–29.982	0.026
Model 3	5.023	1.032–27.066	0.046
Six-month mortality			
Model 1	10.444	3.276–33.300	< 0.001
Model 2	7.194	1.824–28.384	0.005
Model 3	6.078	1.383–26.713	0.017
Six-month poor outcome			
Model 1	7.725	3.204–18.629	< 0.001
Model 2	5.408	1.603–18.239	0.007
Model 3	2.967	1.151–13.520	0.016

Using multivariate logistic regression analysis, model 1 was not corrected, model 2 was adjusted by Glasgow coma scale scores and model 3 was adjusted by age, gender, Glasgow coma scale scores, unreactive pupils, abnormal cisterns, midline shift > 5 mm, traumatic subarachnoid hemorrhage, Marshall computerized tomography classification, admission time, blood-collecting time and time to first computerized tomography scan.





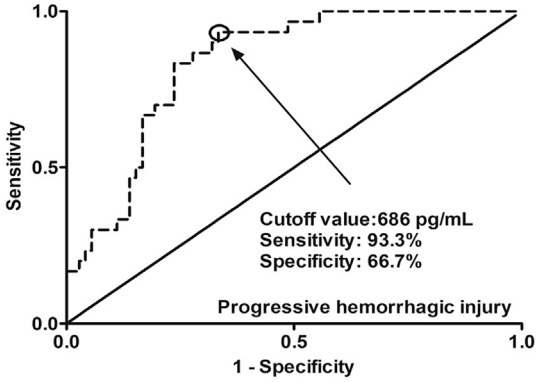
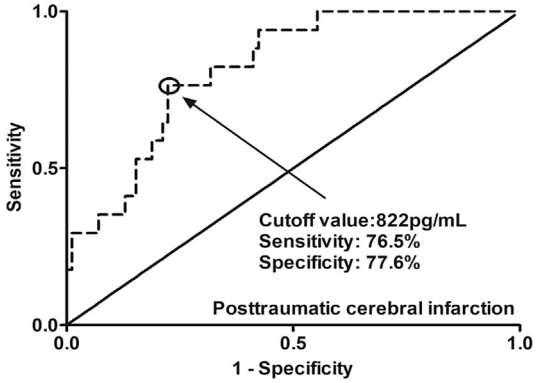
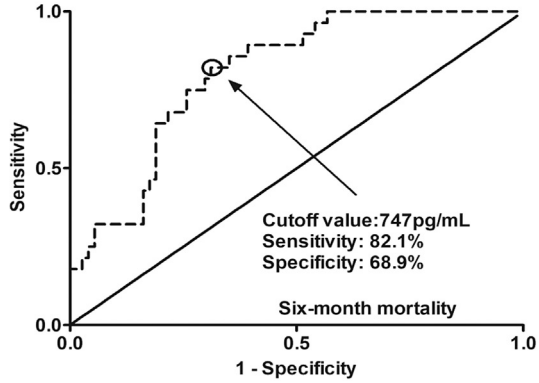


Fig. 3. Receiver operating characteristic curves displaying predictive value of serum interleukin-33 concentrations for acute lung injury, acute traumatic coagulopathy and progressive hemorrhagic injury among patients with severe traumatic brain injury.





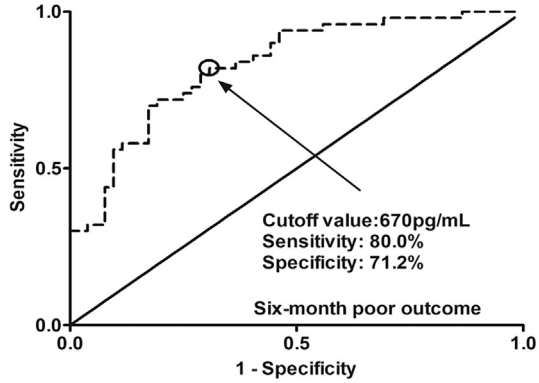


Fig. 4. Receiver operating characteristic curves depicting discriminatory ability of serum interleukin-33 concentrations for posttraumatic cerebral infarction, 6-month mortality and 6-month poor outcome among patients with severe traumatic brain injury.

There are few of previous studies regarding change of circulating IL-33 concentrations in patients with acute ischemic stroke and spontaneous subarachnoid hemorrhage as compared with healthy controls. An early study revealed a significant increase for serum IL-33 concentrations among acute ischemic stroke [21], while a recent epidemiological investigation found that serum IL-33 concentrations were substantially enhanced as opposed to healthy controls [22]. Similarly, in patients with aneurysmal subarachnoid hemorrhage, serum IL-33 concentrations actually rose statistically significantly in comparison with healthy controls [23]. Evidence from systemic sclerosis patients also showed that circulating IL-33 concentrations should be raised [31]. Our study enrolled a total of 102 patients with sTBI and 102 healthy controls and demonstrated that serum IL-33 concentrations were higher in patients than in controls. Hence, it is implied that circulating IL-33 concentrations might be increased after TBI.

Although our study, for the first time, determined the relationship between serum IL-33 concentrations and disease severity of head trauma, others have found the inverse or positive correlation of serum IL-11 concentrations with severity of ischemic stroke or spontaneous subarachnoid hemorrhage [21–23]. Therefore, this sort of relation needs to be clarified further because of its inconsistence. A study found a significantly positive correlation of serum IL-33 concentrations with cerebral infarction volume among patients with acute ischemic stroke [21], whereas another epidemiological investigation revealed that serum IL-33 concentrations were substantially negatively associated with cerebral infarction volume after acute ischemic stroke [22]. In patients with aneurysmal subarachnoid hemorrhage, serum IL-33 concentrations were in substantial correlation with hemorrhagic severity indicated by World Federation of Neurological Surgeons scale and modified Fisher grading scale [23]. Our study used clinical scale (i.e., GCS score) and laboratory severity biomarkers (i.e., NSE, GFAP, S100B, MBP, Tau, pNF-H and UCH-L1) to assess trauma severity, which are not utilized in the preceding studies [21–23]. Serum IL-33 concentrations, whether as a continuous or categorical variable, were demonstrated to

Table 3
Comparisons of the prognostic discriminatory capability among severe traumatic brain injury patients.

	Acute lung injury		Acute traumatic coagulopathy		Progressive hemorrhagic injury	
	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value
Serum IL-33	0.810 (0.7204–0.881)	Reference	0.821 (0.732–0.890)	Reference	0.835 (0.749–0.901)	Reference
Serum CRP	0.623 (0.522–0.717)	0.003	0.639 (0.538–0.732)	0.002	0.697 (0.598–0.784)	0.025
Serum TNF-a	0.631 (0.530–0.725)	0.012	0.654 (0.554–0.746)	0.013	0.652 (0.551–0.743)	0.014
Serum IL-6	0.664 (0.563–0.754)	0.036	0.596 (0.494–0.692)	< 0.001	0.685 (0.585–0.773)	0.030
Serum NSE	0.807 (0.716–0.878)	0.955	0.852 (0.768–0.914)	0.581	0.790 (0.698–0.864)	0.456
Serum S100B	0.847 (0.762–0.911)	0.510	0.853 (0.769–0.915)	0.537	0.845 (0.760–0.909)	0.862
Serum MBP	0.837 (0.751–0.903)	0.626	0.815 (0.726–0.885)	0.912	0.806 (0.716–0.878)	0.607
Serum GFAP	0.821 (0.732–0.890)	0.844	0.836 (0.750–0.902)	0.763	0.819 (0.730–0.888)	0.765
Serum Tau	0.830 (0.743–0.898)	0.706	0.862 (0.780–0.922)	0.441	0.820 (0.731–0.889)	0.777
Serum pNF-H	0.837 (0.751–0.903)	0.605	0.828 (0.741–0.896)	0.878	0.814 (0.725–0.884)	0.689
Serum UCH-L1	0.839 (0.753–0.904)	0.633	0.831 (0.744–0.898)	0.864	0.803 (0.713–0.875)	0.540
GCS score	0.866 (0.784–0.925)	0.250	0.884 (0.806–0.939)	0.179	0.850 (0.766–0.913)	0.770

	Posttraumatic cerebral infarction		Six-month mortality		Six-month poor outcome	
	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value	AUC (95% CI)	*P* value
Serum IL-33	0.819 (0.730–0.888)	Reference	0.804 (0.714–0.876)	Reference	0.830 (0.742–0.897)	Reference
Serum CRP	0.641 (0.540–0.733)	0.009	0.650 (0.549–0.742)	0.020	0.623 (0.522–0.717)	< 0.001
Serum TNF-a	0.587 (0.485–0.684)	0.010	0.594 (0.493–0.690)	0.006	0.627 (0.525–0.720)	0.002
Serum IL-6	0.627 (0.526–0.721)	0.041	0.650 (0.549–0.741)	0.033	0.587 (0.485–0.683)	< 0.001
Serum NSE	0.849 (0.765–0.912)	0.656	0.818 (0.729–0.887)	0.814	0.802 (0.711–0.874)	0.619
Serum S100B	0.864 (0.782–0.924)	0.426	0.841 (0.755–0.906)	0.510	0.880 (0.800–0.936)	0.312
Serum MBP	0.773 (0.679–0.850)	0.468	0.850 (0.766–0.913)	0.438	0.825 (0.737–0.893)	0.932
Serum GFAP	0.840 (0.755–0.905)	0.678	0.830 (0.743–0.897)	0.662	0.831 (0.744–0.898)	0.973
Serum Tau	0.828 (0.741–0.896)	0.897	0.869 (0.788–0.928)	0.215	0.855 (0.771–0.917)	0.635
Serum pNF-H	0.830 (0.743–0.897)	0.871	0.825 (0.737–0.893)	0.717	0.803 (0.713–0.875)	0.593
Serum UCH-L1	0.848 (0.763–0.912)	0.681	0.833 (0.746–0.900)	0.637	0.843 (0.758–0.908)	0.811
GCS score	0.875 (0.795–0.933)	0.421	0.872 (0.792–0.930)	0.196	0.905 (0.831–0.954)	0.085

Based on receiver operating characteristic curve, intergroup comparisons of area under curve were done using Z test. AUC means area under curve; CI, confidence interval; GCS, Glasgow coma scale; IL-33, interleukin-33; NSE, neuron-specific enolase; MBP, myelin basic protein; GFAP, glial fibrillary astrocyte protein; pNF-H, phosphorylated axonal neurofilament subunit H; UCH-L1, ubiquitin carboxyl-terminal hydrolase L1; IL-6, interleukin-6; TNF-a, tumor necrosis factor-alpha; CRP, C-reactive protein.

be intimately associated with GCS score and serum concentrations of other biochemical biomarkers listed above. Such data provide a strong powder to be supportive of the theory that increased serum IL-33 concentrations should reflect increasing severity of traumatized brain injury. However, the final conclusion warrants to be validated in a large scale study.

There are few reports assessing relationship between serum Il-33 concentrations and clinical outcome of acute brain injury. In acute ischemic stroke, the functional outcome at 3 months was determined using the Barthel index; serum IL-33 concentrations were revealed to be independently associated with 3-month functional outcome. [22] Consistently, serum IL-33 emerged as an independent predictor for 6-month mortality and poor outcome indicated by Glasgow outcome scale score of 1–3 in a group of patients with aneurysmal subarachnoid hemorrhage [23]. Obvious differences in our study were that ALI, ATC, PHI, PTCI, six-month death and 6-month poor outcome (defined as Glasgow outcome scale score of 1–3) were all recorded and regarded as poor prognosis variables. Furthermore, it was found that patients with serum IL-33 concentrations above median value had a higher percentage of ALI, ATC, PHI, PTCI, six-month death and 6-month poor outcome than other remaining ones. We configured 2 models to adjust confounding factors. And subsequently, it was demonstrated that serum IL-33 concentrations, as a categorical variable, remained to be an independent predictor for the aforementioned poor prognosis variables. Under ROC curve, this biomarker exhibited a high discriminatory capability for those poor prognoses. On the other hand, serum CRP, TNF-a and IL-6 concentrations can accurately reflect inflammatory state after acute brain injury [32–34], GCS score is a useful and conventional clinical tool for assessing prognosis of acute brain injury [8] and the common laboratory severity biomarkers for acute brain injury are NSE, GFAP, S100B, MBP, Tau, pNF-H and UCH-L1 [7]. No studied have done a comparison for prognostic values indicated by AUC between serum IL-33 concentrations and the preceding clinical or laboratory parameters. Our investigation found that AUC of serum IL-33 concentrations was obviously higher than those of serum CRP, TNF-a and IL-6 concentrations, while was equivalent to those of serum NSE, GFAP, S100B, MBP, Tau, pNF-H and UCH-L1 concentrations. Taken together, serum IL-33, emerging as an independent prognostic biomarker, exhibited a high prognostic ability in head-traumatized patients.

5. Conclusions

Our study provides evidence showing that raised serum IL-33 concentrations, in strong correlation with clinical and biochemical variables for reflecting trauma severity and degree of inflammatory response, are independently associated with some prognostic parameters, such as ALI, ATC, PHI, PTCI, six-month death and 6-month poor outcome, indicating serum IL-33 might represent an inflammatory biomarker with the potential for reflecting the severity and clinical outcome of TBI.

Acknowledgements

This study was supported financially by the Hangzhou Medical Research Fund Project (No. 2016Z10).

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