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RESEARCH ARTICLE

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Longitudinal change of serum inter-alpha-trypsin inhibitor heavy chain H4, and its correlation with inflammation, multiorgan injury, and death risk in sepsis

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Abstract

Background: Inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) inhibits infection-induced inflammation and multiorgan injury through several methods. The present study aimed to estimate the association of serum ITIH4 with inflammatory cytokines, multiorgan injury, and death risk in sepsis patients.

Methods: Serum samples were collected to detect ITIH4 by enzyme-linked immunosorbent assay in 127 sepsis patients at admission (baseline), day (D)1, D3, and D7 after admission, as well as in 30 healthy controls (HCs). Additionally, 28-day mortality was recorded in sepsis patients.

Results: ITIH4 was reduced in sepsis patients versus HCs (median [interquartile range]: 147.9 [78.2–208.8] vs. 318.8 [237.2–511.4] ng/ml) ($p < 0.001$). In sepsis patients, ITIH4 was associated with the absence of cardiovascular and cerebrovascular disease history ($p = 0.021$). Additionally, ITIH4 was negatively correlated with tumor necrosis factor-α ($p < 0.001$), interleukin (IL)-1β ($p < 0.001$), IL-6 ($p = 0.019$), IL-17A ($p = 0.002$), and C-reactive protein ($p = 0.001$), but positively related to IL-10 ($p = 0.007$). Moreover, ITIH4 was also inversely associated with Acute Physiology and Chronic Health Evaluation II score ($p = 0.002$), Sequential Organ Failure Assessment (SOFA) score ($p < 0.001$), SOFA-respiratory system score ($p = 0.023$), and SOFA-renal system score ($p = 0.007$). Interestingly, ITIH4 gradually increased from baseline to D7 ($p < 0.001$); besides, ITIH4 at baseline ($p = 0.009$), D1 ($p = 0.002$), D3 ($p < 0.001$), and D7 ($p = 0.015$) were all decreased in sepsis deaths versus sepsis survivors.

Conclusion: Serum ITIH4 is raised from baseline to D7 after disease onset, and it reflects the reduction of systemic inflammation, disease severity, and 28-day mortality for sepsis. However, further verification is required.

KEYWORDS
inflammatory cytokines, inter-alpha-trypsin inhibitor heavy chain H4, longitudinal change, multiorgan injury, sepsis

Xiangwang Zhao and Yong Guo contributed equally to this work.

1 | INTRODUCTION

Sepsis is a life-threatening infectious disease, which affects 49 million people with 11 million deaths in 2017, representing nearly 20% of all global deaths.[1] Common symptoms of sepsis include inflammation, fever, elevated heart rate, low blood pressure, low urine output, etc.[2] Basically, treatments such as antibiotics, intravenous fluids, and vasopressors for sepsis patients should be provided timely after diagnosis.[3–6] However, the optimal pharmacological treatments for sepsis patients are still lacking, and severe multiorgan injuries (such as injuries of renal, liver, cardiomyopathy, etc.) frequently occur even after receiving the treatments, which are crucial factors contributing to unfavorable clinical outcomes of sepsis patients.[7–11] As a result, it is imperative to find new biomarkers to better realize the stratified management of sepsis patients.

Inter-alpha-trypsin inhibitor heavy chain H4 (ITIH4) is primarily secreted by the liver, which belongs to the family of inter-alpha inhibitor proteins.[12] Some previous studies have illustrated that ITIH4 plays a fundamental role in infection-induced inflammation and organ injury.[13–16] For instance, ITIH4 inhibits the secretion of inflammatory cytokines by inactivating nuclear factor kappa B (NF-κB) and extracellular signal-regulated kinase (ERK) pathways in sepsis mice.[14] Meanwhile, ITIH4 interacts with vitronectin to promote epithelial adhesion and migration, thereby repairing lung injury.[16] In addition, the clinical role of ITIH4 in infectious and inflammation-related diseases has also been revealed by several studies.[17–20] For example, serum ITIH4 is decreased in hepatitis C patients compared to healthy subjects.[21] At the same time, serum ITIH4 is strongly associated with interleukin (IL)-2 and IL-10 in acute ischemic stroke patients.[17] However, the clinical role of ITIH4 in sepsis patients should be further explored.

Accordingly, the present research intended to investigate the relationship of serum ITIH4 with inflammation and disease severity, as well as the implication of serum ITIH4 from baseline to day (D)7 after admission for predicting death risk in sepsis patients.

2 | METHODS

2.1 | Subjects

From February 2019 to January 2022, a total of 127 sepsis patients were included serially in this research. The inclusion criteria were: (i) diagnosed as sepsis in accordance with the sepsis-3 criteria[22]; (ii) above 18 years old; (iii); were immediately admitted to our department within 24 h of onset. The exclusion criteria were: (i) with solid tumor or hematological malignancy; (ii) females who were under pregnancy or lactating. In the same period, 30 age- and gender-matched healthy subjects were recruited as healthy controls (HCs), who received physical examination recently and showed healthy. This research gained approval from the Ethics Committee of Shanghai East Hospital. The written informed consents were also gained from all subjects or their guardians.

2.2 | Data collection and sample detection

Clinical features from sepsis patients were assembled, which included demographics, medical history, primary infection site, primary organism, CRP, acute physiology and chronic health evaluation (APACHE) II score, and sequential organ failure assessment (SOFA) score. Peripheral blood (PB) samples were collected immediately after patients were diagnosed with sepsis (baseline), and serum samples were separated subsequently. ITIH4 levels and common inflammatory cytokines were measured by the enzyme-linked immunosorbent assay (ELISA) method. The corresponding reagent kits were as follows: (i) Human ITIH4 ELISA Kit (Cat. ml037314) for ITIH4 levels detecting; (ii) Human tumor necrosis factor (TNF)-α ELISA Kit (Cat. ml077385) for TNF-α detecting; (iii) Human IL-1β ELISA Kit (Cat. ml058059) for IL-1β detecting; (iv) Human IL-6 ELISA Kit (Cat. ml058097) for IL-6 detecting; (v) Human IL-10 ELISA Kit (Cat. ml064299) for IL-10 detecting; (vi) Human IL-17A ELISA Kit (Cat. ml058052) for IL-17A detecting. All testing steps were carried out in strict accordance with the instructions of each kit. Then, on D1 (1 day after admission), D3 (3 days after admission), and D7 (7 days after admission), serum samples from sepsis patients were obtained for detecting ITIH4 levels using the same ELISA Kit as the baseline.

The serum samples from HCs were obtained immediately after enrollment. ITIH4 levels of HCs were detected by ELISA and using the same kits as sepsis patients used.

2.3 | Follow-up and evaluation

Sepsis patients were closely followed up for 28 days. During the follow-up, the survival status of sepsis patients was documented. Notably, some patients died during follow-up; therefore, the analysis for these patients was only focused on their existing data, and the lost data was omitted.

2.4 | Statistics

SPSS v26.0 and GraphPad Prism 7.01 were used for data processing and figure plotting. Receiver operating characteristic (ROC) curves were applied to show the differentiation efficiency of the ITIH4 levels for different subjects. The Kruskal–Wallis test was utilized to compare the ITIH4 levels in multigroups. The Wilcoxon rank sum test was utilized to compare the ITIH4 levels in two groups. The Spearman rank correlation analysis was applied to observe the correlation between two variables. Friedman test was used to compare the changes of ITIH4 levels at different time points. Independent predictors for death were screened by backward stepwise

multivariate logistic regression analysis. $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Clinical features

The included sepsis patients had a mean age of 60.4 ± 11.6 years with 82 (64.6%) males and 45 (35.4%) females. In terms of the inflammatory indexes, the median (interquartile range [IQR]) value of TNF-α was 156.0 (120.6–239.7) pg/ml; the median (IQR) value of IL-1β was 6.6 (4.6–8.8) pg/ml; the median (IQR) value of IL-6 was 37.8 (29.4–48.2) pg/ml; the median (IQR) value of IL-10 was 56.7 (45.2–78.6) pg/ml; the median (IQR) value of IL-17A was 132.3 (97.6–186.1) pg/ml; the median (IQR) value of CRP was 59.9 (42.3–82.8) mg/L. Regarding disease assessment scales, the mean values of the APACHE II score, SOFA score, SOFA-respiratory system score, SOFA-nervous system score, SOFA-cardio vascular system score, SOFA-liver system score, SOFA-coagulation system score, and SOFA-renal system score were 11.3 ± 5.5, 4.7 ± 2.1, 1.1 ± 0.8, 0.8 ± 0.7, 0.6 ± 0.7, 0.7 ± 0.7, 0.9 ± 0.8, and 0.7 ± 0.7, respectively. The specific information is listed in Table 1.

3.2 | ITIH4 levels

ITIH4 was reduced in sepsis patients (median [IQR]: 147.9 [78.2–208.8] ng/ml) compared with HCs (median [IQR]: 318.8 [237.2–511.4] ng/ml) ($p < 0.001$) (Figure 1A). Meanwhile, ITIH4 had a good potency to discriminate sepsis patients from HCs (area under the curve [AUC; 95% confidence interval [CI]]: 0.892 [0.820–0.956]); besides, the value of ITIH4 at the best cut-off point was 235.6 ng/ml (sensitivity: 80.0%, specificity: 85.8%) (Figure 1B).

3.3 | Association of ITIH4 with clinical features, disease severity, and inflammatory cytokines

ITIH4 was linked with the absence of cardiovascular and cerebrovascular disease history ($p = 0.021$); whereas it was not linked to other medical histories, primary infection site, or primary organism (all $p > 0.05$) (Table 2).

ITIH4 was inversely related to APACHE II ($r = -0.270$, $p = 0.002$), SOFA ($r = -0.339$, $p < 0.001$), SOFA-respiratory system ($r = -0.202$, $p = 0.023$), and SOFA-renal system ($r = -0.238$, $p = 0.007$). Nevertheless, ITIH4 was not associated with the SOFA-nervous system, SOFA-cardiovascular system, SOFA-liver system, or SOFA-coagulation system in sepsis patients (all $p > 0.05$) (Table 3).

ITIH4 was inversely linked to TNF-α ($r = -0.313$, $p < 0.001$) (Figure 2A), IL-1β ($r = -0.305$, $p < 0.001$) (Figure 2B), IL-6 ($r = -0.208$, $p = 0.019$) (Figure 2C). However, ITIH4 was positively linked to IL-10 ($r = 0.238$, $p = 0.007$) (Figure 2D), but negatively associated with IL-17A ($r = -0.279$, $p = 0.002$) (Figure 2E) and CRP ($r = -0.294$, $p = 0.001$) (Figure 2F) in sepsis patients.

TABLE 1 Clinical characteristics of sepsis patients.

Items	Sepsis patients ($N = 127$)
Demographics	
Age (years), mean ± SD	60.4 ± 11.6
Gender, No. (%)	
Male	82 (64.6)
Female	45 (35.4)
BMI (kg/m^2), mean ± SD	24.0 ± 3.7
History of smoke, No. (%)	35 (27.6)
History of drink, No. (%)	31 (24.4)
Medical history	
History of hypertension, No. (%)	50 (39.4)
History of hyperlipidemia, No. (%)	19 (15.0)
History of diabetes, No. (%)	12 (9.4)
History of CKD, No. (%)	7 (5.5)
History of cardiovascular and cerebrovascular diseases, No. (%)	23 (18.1)
Primary infection site	
Abdominal infection, No. (%)	47 (37.0)
Respiratory infection, No. (%)	37 (29.2)
Skin and soft tissue infection, No. (%)	28 (22.0)
Other infections, No. (%)	15 (11.8)
Primary organism	
G^- bacteria, No. (%)	66 (52.0)
G^+ bacteria, No. (%)	36 (28.3)
Fungus, No. (%)	13 (10.2)
Others, No. (%)	23 (18.1)
Culture negative, No. (%)	22 (17.3)
Inflammatory indexes	
TNF-α (pg/ml), median (IQR)	156.0 (120.6–239.7)
IL-1β (pg/ml), median (IQR)	6.6 (4.6–8.8)
IL-6 (pg/ml), median (IQR)	37.8 (29.4–48.2)
IL-10 (pg/ml), median (IQR)	56.7 (45.2–78.6)
IL-17A (pg/ml), median (IQR)	132.3 (97.6–186.1)
CRP (mg/L), median (IQR)	59.9 (42.3–82.8)
Disease assessment scales	
APACHE II score, mean ± SD	11.3 ± 5.5
SOFA, mean ± SD	4.7 ± 2.1
SOFA-respiratory system, mean ± SD	1.1 ± 0.8
SOFA-nervous system, mean ± SD	0.8 ± 0.7
SOFA-cardiovascular system, mean ± SD	0.6 ± 0.7
SOFA-liver system, mean ± SD	0.7 ± 0.7
SOFA-coagulation system, mean ± SD	0.9 ± 0.8
SOFA-renal system, mean ± SD	0.7 ± 0.7

Abbreviations: APACHE, acute physiology and chronic health evaluation; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; G^-, gram-negative; G^+, gram-positive; IL, interleukin; IQR, interquartile range; SD, standard deviation; SOFA, sequential organ failure assessment; TNF-α, tumor necrosis factor-α.

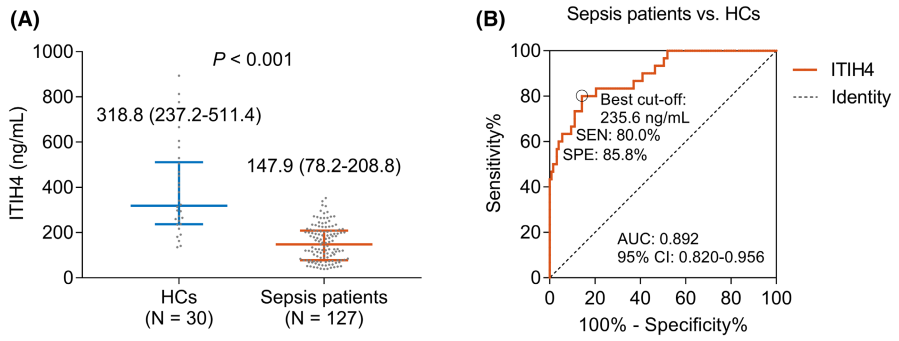


FIGURE 1 Comparison of ITIH4 between sepsis patients and healthy controls (HCs). ITIH4 was lower in sepsis patients compared to HCs (A); ROC curve of ITIH4 for discriminating sepsis patients from HCs (B).

TABLE 2 Correlation of ITIH4 with medical history, primary infection site, and primary organism in sepsis patients.

Items	ITIH4 (ng/ml), median (IQR)	*p* Value
Medical history		
History of hypertension		
No	147.9 (82.1–220.0)	0.591
Yes	147.6 (76.6–202.9)	
History of hyperlipidemia		
No	157.4 (80.3–215.0)	0.120
Yes	134.4 (58.9–183.5)	
History of diabetes		
No	155.7 (78.2–213.0)	0.331
Yes	131.9 (78.7–176.0)	
History of CKD		
No	154.8 (80.3–210.1)	0.157
Yes	90.5 (57.9–194.8)	
History of cardiovascular and cerebrovascular diseases		
No	162.6 (85.8–216.1)	0.021
Yes	123.3 (63.4–176.3)	
Primary infection site		
Abdominal infection	197.7 (108.3–227.5)	0.076
Respiratory infection	126.0 (81.2–183.8)	
Skin and soft tissue infection	122.9 (75.3–184.5)	
Other infections	103.7 (77.4–243.4)	
Primary organism		
G^- bacteria		
No	169.2 (77.5–218.4)	0.748
Yes	144.6 (83.4–204.9)	
G^+ bacteria		
No	134.4 (78.1–197.7)	0.076
Yes	199.9 (90.6–249.5)	
Fungus		
No	150.9 (83.4–208.1)	0.706
Yes	95.8 (73.2–222.2)	
Others		
No	142.7 (78.1–212.9)	0.766
Yes	159.1 (89.0–195.3)	
Culture negative		
No	153.9 (78.8–212.9)	0.485
Yes	130.9 (73.1–198.8)	

Abbreviations: CKD, chronic kidney disease; G^-, gram-negative; G^+, gram-positive; ITIH4, inter-alpha-trypsin inhibitor heavy chain H4.

3.4 | Longitudinal change of ITIH4

The median (IQR) values of ITIH4 at baseline, D1, D3, and D7 after admission were 147.9 (78.2–208.8) ng/ml, 146.8 (90.1–210.3) ng/ml, 180.0 (103.6–273.5) ng/ml, and 214.7 (136.6–302.0) ng/ml, respectively. Further analysis revealed that ITIH4 gradually increased from baseline to D7 after admission in sepsis patients ($p < 0.001$). The post-hoc comparison disclosed that ITIH4 at D3 ($p < 0.001$) and D7 ($p < 0.001$) had a higher median value compared to ITIH4 at baseline. In addition, the median value of ITIH4 at D3 ($p < 0.001$) and D7 ($p < 0.001$) was also increased compared to ITIH4 at D1. Moreover, ITIH4 at D7 also had a higher median value compared with ITIH4 at D3 ($p < 0.001$). However, the median value of ITIH4 at D1 and baseline was not changed ($p = 0.099$) (Figure 3).

3.5 | Comparison of ITIH4 at different time points between deaths and survivors

ITIH4 at baseline ($p = 0.009$), D1 ($p = 0.002$), D3 ($p < 0.001$), and D7 ($p = 0.015$) after admission were decreased in sepsis deaths compared with sepsis survivors (Figure 4A). At the same time, the ROC curves exhibited that ITIH4 at baseline only had an acceptable ability to distinguish sepsis deaths from survivors (AUC [95% CI]: 0.664 [0.550–0.778]); the best cut-off point of ITIH4 at baseline was 136.0 ng/ml (sensitivity: 70.4%, specificity: 58.0%) (Figure 4B). However, ITIH4 at D1 (AUC [95% CI]: 0.701 [0.580–0.823]) (Figure 4C), D3 (AUC [95% CI]: 0.778 [0.672–0.885]) (Figure 4D), and D7 (AUC [95% CI]: 0.759 [0.577–0.942]) (Figure 4E) possessed a good capacity to discriminate sepsis deaths from survivors. Furthermore, the best cut-off points of ITIH4 at D1, D3, and D7 were 61.4 ng/ml (sensitivity:

40.0%, specificity: 96.0%), 183.4 ng/ml (sensitivity: 89.5%, specificity: 53.0%), and 113.5 ng/ml (sensitivity: 62.5%, specificity: 85.0%), respectively (Figure 4C–E).

3.6 | Independent factors for death

The multivariate logistic regression analysis suggested that higher ITIH4 showed a slight independent correlation with a lower possibility of death but did not achieve statistical significance (OR = 0.989, $p = 0.056$). Only a higher APACHE II score was independently associated with an increased possibility of death in sepsis patients (OR = 1.160, $p = 0.034$) (Table 4).

TABLE 3 Correlation of ITIH4 with APACHE II and SOFA in sepsis patients.

Items	*p* Value	*r*
APACHE II	0.002	−0.270
SOFA	<0.001	−0.339
SOFA-respiratory system	0.023	−0.202
SOFA-nervous system	0.066	−0.164
SOFA-cardiovascular system	0.225	−0.108
SOFA-liver system	0.050	−0.175
SOFA-coagulation system	0.240	−0.105
SOFA-renal system	0.007	−0.238

Abbreviations: APACHE, acute physiology and chronic health evaluation; ITIH4, inter-alpha-trypsin inhibitor heavy chain H4; SOFA, sequential organ failure assessment.

4 | DISCUSSION

As a novel anti-inflammatory factor, the dysregulation of ITIH4 has been revealed in various diseases, such as autoimmune, cardiovascular, and cerebrovascular diseases.[17,23–26] For instance, serum ITIH4 is reduced in inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) patients compared to HCs.[23,24] Meanwhile, a previous study claims that serum ITIH4 may be a potential biomarker for coronary heart disease (CHD) patients since it is decreased in patients with acute cardiovascular events compared to patients without those events.[25] In addition, serum ITIH4 is also reduced in acute ischemic stroke patients compared to HCs.[17] In terms of sepsis, the dysregulation of serum ITIH4 in this type of patient still needs exploration. The current study discovered that serum ITIH4 was reduced in sepsis patients in contrast to HCs. The potential reason would be that the infection-induced inflammation was aggravated in sepsis patients, which further inhibited the level of ITIH4.[14,15] As a result, serum ITIH4 was decreased in sepsis patients versus HCs. Additionally, the current study also disclosed that serum ITIH4 had a good capacity to discriminate sepsis patients from HCs. Considering that the diagnosis of sepsis is still a huge challenge,[27] the finding of this study might be helpful for improving the diagnosis of sepsis. Notably, the reason why ITIH4 had a good ability to reflect sepsis risk might be due to its correlation with inflammation. Therefore, the specificity of ITIH4 would be poor for discriminating sepsis from other severe inflammatory diseases (such as rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, etc.). This aspect could be further explored by subsequent studies.

Regarding the association between ITIH4 with clinical characteristics and inflammatory cytokines, several studies have explored

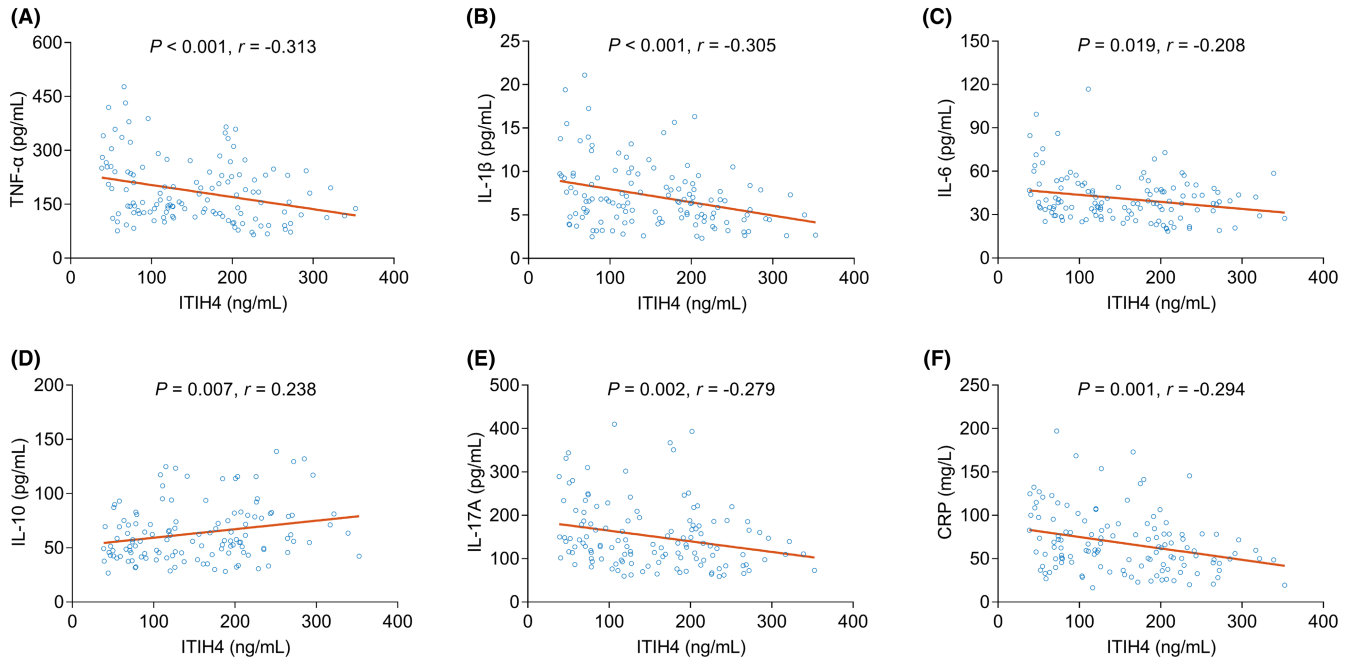
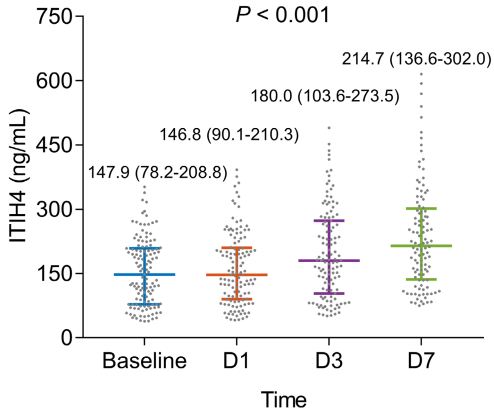


FIGURE 2 Association of ITIH4 with inflammatory cytokines in sepsis patients. ITIH4 was negatively correlated with TNF-α (A), IL-1β (B), and IL-6 (C); ITIH4 was positively correlated with IL-10 (D); ITIH4 was negatively correlated with IL-17A (E) and CRP (F) in sepsis patients.



Post-hoc comparison	*P* value
Baseline vs. D1	0.099
Baseline vs. D3	<0.001
Baseline vs. D7	<0.001
D1 vs. D3	<0.001
D1 vs. D7	<0.001
D3 vs. D7	<0.001

FIGURE 3 Longitudinal change of ITIH4 in sepsis patients.

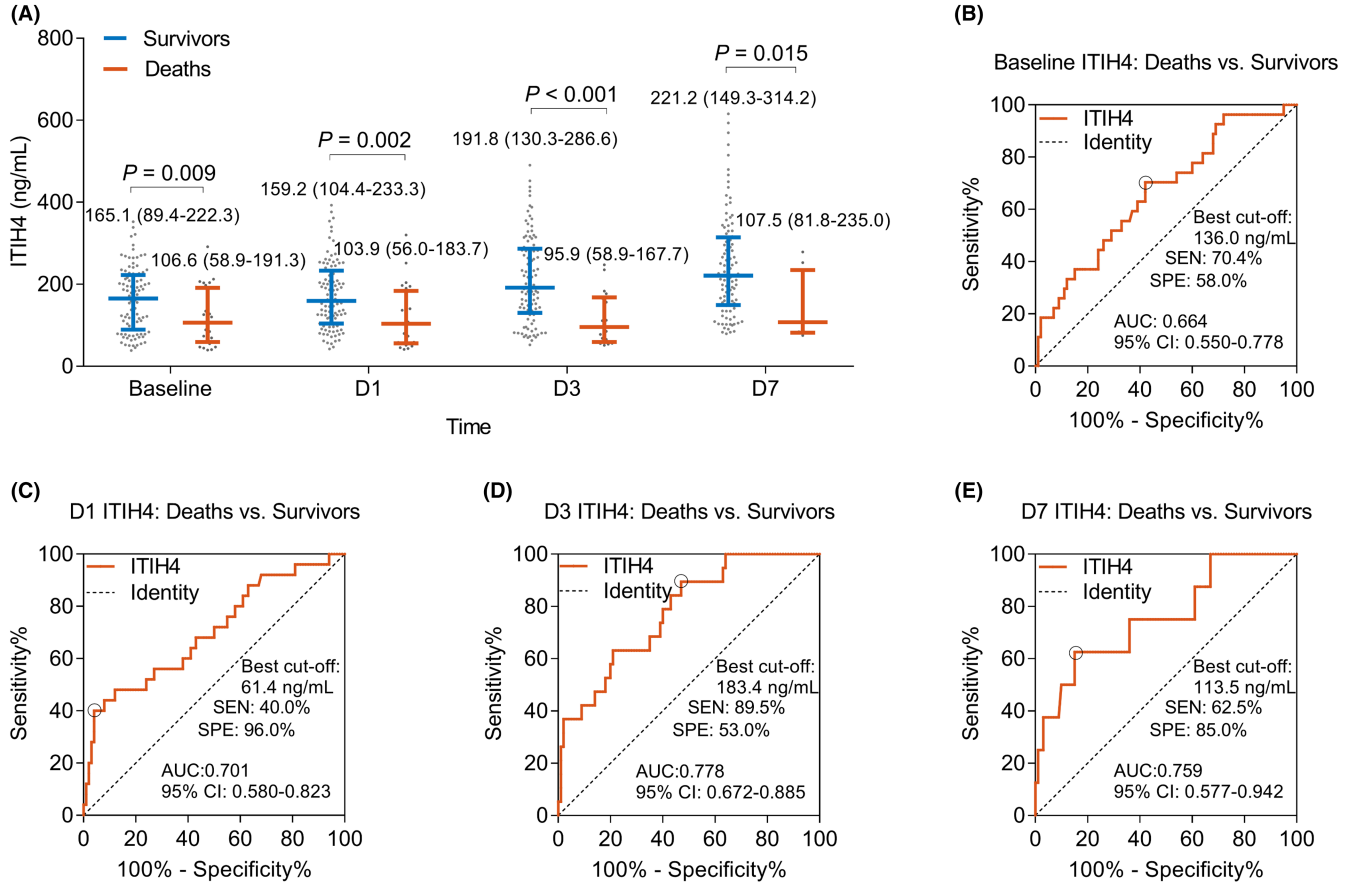


FIGURE 4 Difference of ITIH4 between sepsis deaths and survivors. ITIH4 at baseline, D1, D3, and D7 after admission was reduced in sepsis deaths compared to sepsis survivors (A); ROC curve of ITIH4 at baseline (B), D1 (C), D3 (D), and D7 (E) for discriminating sepsis deaths from sepsis survivors.

this aspect in patients with autoimmune diseases.[23,24] Whereas the correlation between ITIH4 with clinical properties and inflammation in sepsis patients still should be investigated. Firstly, it was discovered that serum ITIH4 was related to the absence of cardiovascular and cerebrovascular disease history in sepsis patients. The possible argument would be that: ITIH4 could reflect no occurrence of atherosclerosis and a high level of high-density lipoprotein (HDL), while atherosclerosis and decreased HDL were crucial risk factors for cardiovascular and cerebrovascular diseases.[28–30] As a result, serum ITIH4 could also reflect no history of cardiovascular and cerebrovascular diseases in sepsis patients. Secondly, the present study also discovered that ITIH4 was reversely linked to inflammation in sepsis patients. The probable arguments would be that: (1) the production of ITIH4 would be regulated under the stimulation of inflammatory cytokines (such as IL-1β and IL-6)[15,31,32]; (2) ITIH4 could also modulate the secretion of inflammatory cytokines through various pathways, such as NF-κB, ERK, and early growth response-1, thereby attenuating the inflammation.[13,14] As a result, serum ITIH4 was inversely associated with CRP, TNF-α, IL-1β, IL-6, and IL-17A but positively correlated with IL-10 in sepsis patients.

TABLE 4 Backward stepwise multivariate logistic regression analysis for death.

Items	*p* Value	OR	95% CI	
			Lower	Upper
Higher ITIH4 at D7	0.056	0.989	0.978	1.000
Higher APACHE II score	0.034	1.160	1.011	1.331

Abbreviations: APACHE, acute physiology and chronic health evaluation; CI, confidence interval; D7, day 7 after admission; ITIH4, inter-alpha-trypsin inhibitor heavy chain H4; OR, odds ratio.

Apart from clinical characteristics and inflammation, this study also evaluated the association of serum ITIH4 with multiorgan injury and disease severity in sepsis patients. It was discovered that serum ITIH4 was inversely related to lung injury, renal injury, and disease severity. The potential explanations would be that: (1) ITIH4 could inhibit alveolar epithelial cell apoptosis and senescence, thus reducing respiratory injury[33,34]; (2) ITIH4 might also suppress the mesangial cell proliferation to relieve renal injury[35]; (3) as discussed above, ITIH4 could reflect favorable clinical features, attenuated inflammation, and relieved organ injury; therefore, it might also represent decreased disease severity to a certain extent. Taken together, serum ITIH4 was negatively correlated with lung and renal injury, along with disease severity in sepsis patients.

Moreover, this study also estimated the longitudinal change of serum ITIH4 and its relationship with mortality in sepsis patients. It was disclosed that serum ITIH4 was increased from baseline to D7 after admission in sepsis patients. It could be argued that as discussed above, ITIH4 could represent low inflammatory status to some extent, while the inflammation would be reduced after receiving treatments.[13,14,36] Meanwhile, the current study also disclosed that serum ITIH4 at any time point declined in sepsis deaths compared to survivors. The potential reasons would be that: (1) ITIH4 exerted an anti-inflammatory effect; thus, its decrease could reflect aggravated inflammation[13,14]; (2) ITIH4 involved in the pathology of multiorgan function and its reduction might represent anabatic lung and kidney injury.[33–35] Notably, inflammation and multiorgan injuries were worse in sepsis deaths compared with survivors[37]; thus, serum ITIH4 at any time point was reduced in deaths in contrast to survivors.

Notably, it was speculated that the source of ITIH4 might be derived from various cells and organs. The most possible source might be lymphocytes in the blood due to infection of sepsis leading to the inflammation flare, then, the lymphocytes would be increased, which further inhibited the production of ITIH4. In addition, ITIH4 might also come from several organs, such as the liver and kidney. Moreover, due to the close correlation of ITIH4 with cerebral vascular, ITIH4 may also derive from the vascular endothelial cells. However, these speculations should be further verified.

Several limitations should be noticed in this study: (1) the specific mechanism of ITIH4 in the progression of sepsis was not explored, which could be a research objective for further studies; (2) the sample size was not large enough; further studies could consider enrolling more patients to draw a clearer conclusion; (3) disease controls were not enrolled in this study; however, this might be meaningful to estimate the diagnostic effect of ITIH4 for sepsis; (4) the mean age of enrolled sepsis patients was 60.4 ± 11.6 years in the present study; further study could explore the clinical implication of ITIH4 in younger sepsis patients; (5) the prognostic role of ITIH4 would be affected by the treatment options; further studies should take this into account and investigate this aspect.

In summary, serum ITIH4 is gradually increased from baseline to D7 after disease onset, and it correlates with the decrease of inflammation, disease severity, and 28-day death risk in sepsis patients. These findings indicate that serum ITIH4 may serve as an anti-inflammatory marker, then contributes to its association with sepsis symptoms and mortality. However, the clinical implications of ITIH4 for sepsis still need more solid evidence to verify.

CONFLICT OF INTEREST

The authors have no relevant financial or nonfinancial interests to disclose.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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