Received: 8 April 2020 | Revised: 6 June 2020 | Accepted: 23 June 2020

DOI: 10.1111/eci.13346

ORIGINAL ARTICLE

WILEY

Predictive value of serum soluble B7-H4 in acute pancreatitis

Zhixiang Cheng[1] | **Zhengfang Liu**[2] | **Yufeng Yuan**[1] | **Zhisu Liu**[1] | **Yueming He**[1] | **Ping Jiang**[1]

[1]Department Hepatobiliary & Pancreat Surgery, Zhongnan Hospital, Wuhan University, Wuhan, China

[2]Department Neurology, Wuhan Fourth Hospital, Puai Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Correspondence
Ping Jiang, Wuhan University, Zhongnan Hospital, Department Hepatobiliary & Pancreat Surgery, Donghu Road 169, Wuhan 430071, Hubei, China.
Email: ping_jiang18@163.com

Abstract

Background: Studies reported that soluble B7-H4 (sB7-H4) was significantly related to the progression and prognosis of inflammatory diseases, and whether sB7-H4 is related to the severity and prognosis of acute pancreatitis (AP) timely has not been reported.

Materials and methods: Clinical database data of 446 AP patients were retrospectively collected, and the correlation between the expression serum levels of sB7-H4 with inflammatory factors and prognostic scores was analysed in AP patients.

Results: Soluble B7-H4 was significantly correlated with IL-6, IL-8, TNF-α, PCT, CRP levels and WBC count ($P < .01$), with correlation coefficients of $R = .61$, .53, .46, .60, .57 and .47, respectively, and AUCs were 0.905, 0.837, 0.797, 0.858, 0.890, 0.841 and 0.855, respectively. In addition, sB7-H4 was significantly correlated with the Ranson score, APACHE II score and BISAP score ($P < .001$), with correlation coefficients of $R = .58$, .63 and .59, respectively. The AUCs of assessing local complications of AP were 0.908, 0.863, 0.785 and 0.844, respectively; assessing organ failure were 0.872, 0.790, 0.796 and 0.857, respectively; and assessing in-hospital mortality were 0.839, 0.821, 0.796 and 0.823, respectively.

Conclusions: Soluble B7-H4 could be used as a marker for the diagnosis, severity assessment and poor prognosis assessment of AP patients, which may have potential clinical applications.

KEYWORDS

acute pancreatitis, B7-H4, diagnosis, inflammatory factors, prognostic scores

1 | INTRODUCTION

In recent years, the incidence of acute pancreatitis (AP) has been increasing, and AP consumes a large amount of medical resources and has a high treatment cost.[1] According to the revised Atlanta classification diagnostic criteria for AP in 2012,[2] the prognoses of different types of AP are significantly different. Mild acute pancreatitis (MAP) is a self-limiting disease with a good prognosis; moderately severe acute pancreatitis (MSAP) has transient organ failure but is easy to correct and has a very low mortality rate; severe acute pancreatitis (SAP) can cause death due to persistent organ failure.[3,4] MSAP and SAP are sometimes associated with pancreatic parenchyma and/or peripancreatic tissue necrosis, that is necrotizing pancreatitis. If necrotic tissue becomes infected, the patient's condition can rapidly deteriorate to a life-threatening status.[5,6] Early assessment of the severity of AP and its prognosis, as well as the indications and timing of surgical treatment for complications, are hot topics in current research.[7]

The costimulatory molecule B7-H4 was discovered by Gabriel L in 2004. B7-H4 is one of the important members of the B7 family and plays an important role in the antigen-specific immune response.[8,9] B7-H4 is widely present in various human tissues at the mRNA level, but its protein expression is limited.[10] However, if there is an inflammatory response, a spontaneous immune response or a viral infection, B7-H4 protein can be expressed at abnormally high levels in $CD31^+$ vascular endothelial cells, $CD34^+$ neovascular endothelial cells, macrophages, T cells, B cells and dendritic cells(DCs).[9,11-13] In addition, B7-H4 expressing cells can secrete soluble B7-H4(sB7-H4),[14] and sB7-H4 is found at high levels in the peripheral blood of patients with rheumatoid arthritis (RA)[15] and type 1 diabetes (T1D).[16] Increases of sB7-H4 are significantly associated with increases of CRP levels in RA patients,[15] and it can be used as a biomarker for the diagnosis and assessment of disease progression in RA and T1D.

Acute pancreatitis causes excessive release of inflammatory factors from inflammatory cells, leading to local or systemic inflammatory reactions. The inflammatory factors cause a waterfall-like cascade of multiple inflammatory factors through trigger-like effects, leading to systemic inflammatory response syndrome (SIRS) and multiple organ failure syndrome (MODs).[17] Whether sB7-H4 is highly expressed in the peripheral blood of patients with AP and whether it has any value for the diagnosis, assessment of disease and prognostication of AP are unknown.

In this article, we reviewed clinical database data and retrospectively analysed the correlation between the expression levels of serum sB7-H4 of AP patients and laboratory results, including IL-6, IL-8, TNF-α, procalcitonin levels (PCT), C-reactive protein (CRP) and white blood cell (WBC) count. In addition, we evaluated the correlation between the expression level of sB7-H4 and the prognostic factors of AP, including the Ranson score, APACHE II score and BISAP score. The objective of this study was to determine the value of the sB7-H4 expression level for assessing patient condition and prognosis in the early stage of AP.

2 | PATIENTS AND METHODS

This study was a retrospective study. All of the patient data included in the study were from Zhongnan Hospital of Wuhan University, collected from 2015.1.1 to 2019.6.30. This study was approved and supported by the Ethics Committee of Zhongnan Hospital of Wuhan University. A total of 446 cases of AP were included in this study. The inclusion criteria were based on the revised Atlanta classification for AP in 2012. All patients were directly admitted to our hospital for treatment without self-administration of oral drugs or receiving other treatments. All patients had blood samples taken within 24 hours of admission before taken any treatment. The exclusion criteria were as follows: 1, younger than 18 years old; 2, acute pregnancy pancreatitis, traumatic pancreatitis or iatrogenic pancreatitis; or 3, recurrent pancreatitis within one month. Healthy volunteers were recruited from 2018.6.1 to 2019.12.31 as a control group. The inclusion criteria for healthy volunteers as follows: (a) age: 18~60 years old; (b) gender: half male and half female; (c) body weight: The body weight of normal subjects should generally not be less than 50 kg. Body mass index (BMI) is generally within the range of standard body mass index (19-24). The subjects in the same batch shall not vary too much in body weight; (d) the subjects are qualified in comprehensive physical examination, and the blood cytology, blood biochemistry, urine and stool routine, coagulation function, ECG, chest X-ray and B ultrasound examination indicators shall be within the normal range. Exclusion criteria were as follows: history of chronic disease and history of chronic drug use. All of the study subjects provided written informed consent. Reporting of the study conforms to broad EQUATOR guidelines (Simera et al January 2010 issue of EJCI).

2.1 | Collection of clinical data

(a) Patient data collection included sex, age, weight, time of onset, time from onset to admission, timing and results of biochemical examinations from onset to admission, aetiology and treatment of acute pancreatitis; (b) severity and prognosis of AP: based on laboratory test results including IL-6, IL-8, PCT and CRP levels and WBC count results, as well as the 48-hour Ranson score, 24-hour APACHE II score and 24-hour BISAP score. Contrast-enhanced computed tomography (CE-CT) was conducted 72-96 hours after the onset of symptoms to assess the local complications of AP, and the modified Marshall scoring system was used to assess organ failure associated with AP.

2.2 | Data collection

As soon as patients were admitted to the hospital, blood samples were taken and stored before administering any medication. The APACHE II score and BISAP score were calculated within 24 hours of admission, and the Ranson score was calculated within 48 hours. The results of routine laboratory tests, including IL-6, IL-8, PCT and CRP levels and WBC count, were obtained from patients' electronic medical records and clinical databases. Blood samples used to detect sB7-H4 and TNF-α were collected and allowed to stand at room temperature for 30 minutes and then

centrifuged at 1000 *g* at −4℃ to separate serum, which was stored at −70℃ until use. The expression levels of sB7-H4 and TNF-α were measured with a B7-H4 ELISA kit (R & D System) and a TNF-α ELISA kit (R & D System) according to the manufacturer's instructions.

2.3 | Data analysis

SPSS software version 25.0 (SPSS, Chicago, IL, USA) was used for routine data analysis. Mann-Whitney *U* test and *t* test were performed to identify significant differences between MAP, MSAP and SAP. Pearson's chi-square and post hoc ANOVA test was used to analyse the correlations among the clinical factors. Receiver operating characteristic (ROC) curves were used to assess the diagnostic value of sB7-H4 in discriminating among health, MAP, MSAP and SAP. ROC curves were also performed to assess the prognostic value of sB7-H4 in AP. Logistic multivariate regression analysis was used to analyse the relationship between sB7-H4 and the prognosis of AP. *P* values < .05 were considered statistically significant.

3 | RESULTS

3.1 | Expression of serum sB7-H4 in MAP, MSAP and SAP

A B7-H4 ELISA kit was used to detect the expression level of sB7-H4 in serum samples, including those from healthy volunteers (100) and MAP (187), MSAP (142) and SAP (117) cases. The basic clinical parameters of the AP patients are shown in Table 1. There were no significant differences in age, sex, BMI index, time to admission, time to sample collection or aetiology among the three groups of patients. However, there were significant differences among the three groups in terms of laboratory tests, including the IL-6, IL-8, TNF-α, PCT and CRP levels and the WBC count. There were also differences among the prognostic score indicators, including the Ranson scores, APACHE II scores and BISAP scores ($P < .001$).

The expression levels of sB7-H4 in the health, MAP, MSAP and SAP groups are shown in Figure 1. The mean concentration in health was 4.27 ng/mL (a range of 0.56-11.62 ng/mL), MAP 13.03 ng/mL (a range of 1.63-34.93 ng/mL), MSAP 22.64 ng/

TABLE 1 Patients characteristics

Characteristics	MAP	MSAP	SAP	*P* value
Number	187	142	117	NS
Age (y)	47.03 ± 11.49	46.01 ± 15.23	45.71 ± 14.53	NS
Sex (Male/Female)	99/88	80/62	63/54	NS
BMI (kg/m^2)	25.36 ± 2.50	26.02 ± 3.08	25.92 ± 3.43	NS
Admission time (h)	10.21 ± 3.41	10.09 ± 3.39	9.95 ± 3.84	NS
Sample-collecting time (h)	10.69 ± 3.4	10.56 ± 3.39	10.39 ± 3.78	NS
Ranson scores	1.83 ± 1.17	3.66 ± 1.24	5.42 ± 1.72	< .001
APACHE II scores	6.35 ± 3.84	9.12 ± 4.18	15.68 ± 5.59	< .001
BISAP scores	1.25 ± 0.66	2.18 ± 0.747	3.07 ± 1.04	< .001
IL-6 (pg/mL)	166.12 ± 41.81	257.75 ± 74.88	385.72 ± 83.84	< .001
IL-8 (pg/mL)	11.77 ± 7.79	18.37 ± 10.85	37.65 ± 14.29	< .001
TNF-α (pg/mL)	60.62 ± 14.17	70.42 ± 18.68	101.55 ± 22.14	< .001
PCT (ng/mL)	1.84 ± 0.47	2.15 ± 0.62	4.98 ± 1.08	< .001
CRP (mg/L)	41.21 ± 6.54	65.07 ± 12.00	112.33 ± 21.25	< .001
WBC (10^9/L)	14.79 ± 4.25	25.72 ± 5.63	40.45 ± 7.93	< .001
Aetiology				
Alcoholic	55	37	35	NS
Biliary	61	43	32	
Hypertriglyceremic	58	44	40	
Others	13	18	10	

Abbreviations: APCHCE II, acute physiology and chronic health care evaluation II; BISAP, bedside index for severity in acute pancreatitis; BMI, body mass index; CRP, C-reactive protein; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; NS, no significant; PCT, procalcitonin; SAP, severe acute pancreatitis; TNF-α, tumour necrosis factor α; WBC, white blood cell.

Values are displayed as a mean ± SD.

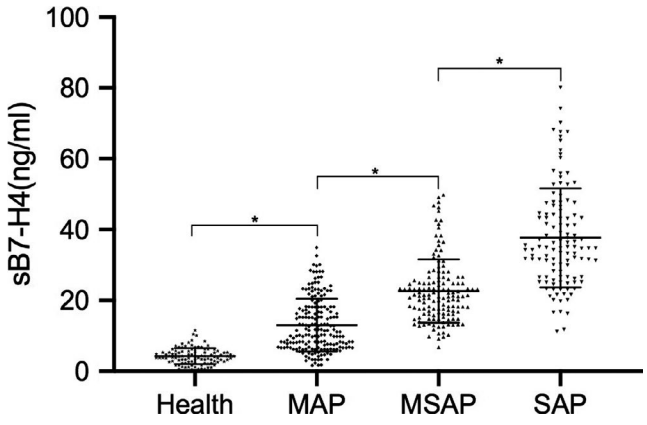

FIGURE 1 The sB7-H4 expression level in serum was detected by ELISA. The results showed that the expression level of sB7-H4 was gradually increased in healthy people (4.27 ± 2.26 ng/mL), MAP(13.03 ± 7.41 ng/mL), MSAP(22.64 ± 8.92 ng/mL) and SAP(37.68 ± 13.94 ng/mL), and there were significant differences among the four groups of samples (*$P < .01$)

mL (a range of 6.76-49.76 ng/mL) and SAP 37.68 ng/mL (a range of 11.24-80.13 ng/mL). With exacerbation of the disease, the expression level of sB7-H4 gradually increased, with significant differences among the groups ($P < .001$).

ROC curve analyses were used to assess the value of sB7-H4 in differentiating between the health and AP, health and MAP, MAP and MSAP, and MSAP and SAP groups. As shown in Figure 2, the areas under the ROC curves were 0.958, 0.899, 0.811 and 0.826, respectively. When the sB7-H4 cut-off values of these four sets of data were set at 8.124, 7.405, 15.283 and 28.859 ng/mL, respectively, the sensitivity and specificity were 86.5% and 96%, 73.3% and 93%, 81.8% and 67.9%, and 71.8% and 83.3%, respectively. These results indicate that serum sB7-H4 showed good performance for AP diagnosis relative to the traditional diagnostic method based on inflammatory markers.

3.2 | Correlative analysis between serum sB7-H4 and clinical evaluation indicators

We used SPSS 25.0 to analyse the correlation between the serum sB7-H4 expression level and the inflammatory response in AP patients. As shown in Figure 3, there were significant correlations between the serum sB7-H4 expression level and the levels of IL-6, IL-8, TNF-α, PCT and CRP and the WBC count ($P < .001$). The correlation coefficients were $R = .61$, .53, .46, .60, .57 and .47, respectively. Using the clinical diagnosis of SAP as the reference standard, we evaluated the utility of the various markers to diagnosis the severity of the disease. As shown in Figure 4, the areas under the ROC curve (AUCs) of sB7-H4, IL-6, IL-8, TNF-α, PCT, CRP and WBC were 0.905, 0.837, 0.797, 0.858, 0.890, 0.841 and 0.855, respectively. It can be seen that sB7-H4 is better than the other indicators in assessing the severity of AP inflammation. The above results show that sB7-H4 can be used as an indicator of the severity of AP.

3.3 | Predictive value of serum sB7-H4 for a poor clinical outcome of AP patients

We used SPSS 25.0 to analyse the correlation between the serum sB7-H4 expression level and the prognosis of AP patients. It was found that sB7-H4 was significantly correlated with the Ranson score, APACHE II score and BISAP score (Figure 5, $P < .001$). The correlation coefficients were $R = .58$, .63 and .59, respectively. Then, ROC curve analysis was performed. As shown in Figure 6 and Table 2, for the ability to predict AP local complications (acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and walled-off necrosis), the AUCs of sB7-H4, the Ranson score, the APACHE II score and the BISAP score were 0.908, 0.863, 0.785 and 0.844, respectively. For predicting organ failure, the AUCs of sB7-H4, the Ranson score, the APACHE II score and the BISAP score were 0.872, 0.790, 0.796 and 0.857, respectively. To predict in-hospital mortality, the AUCs of sB7-H4, the Ranson score, the APACHE II score and the BISAP score were 0.839, 0.821, 0.796 and 0.823, respectively. It can be seen that sB7-H4 has the best predictive value for local complications, organ failure and in-hospital mortality.

In addition, the levels of sB7-H4 in AP patients tended to increase as their condition worsened. We chose the median value of sB7-H4 (25.12 ng/mL) as the cut-off value and divided the AP patients into two groups: a high group (n = 152) and a low group (n = 294). Next, we explored the correlations between the expression level of sB7-H4 and the clinical characteristics of the two groups of patients. As shown in Table 3, the levels of inflammatory factors, the prognostic scores and poor prognosis of AP patients in the sB7-H4 high expression group were significantly higher than those in the sB7-H4 low expression group, both of which had significant differences.

In addition, logistic multivariate regression analysis showed an association between the serum sB7-H4 level and prognosis after adjusting for sex, age and pancreatitis aetiology. As shown in Table 4, a higher serum sB7-H4 level was independently associated with AP prognosis, including local complications (OR = 4.21, $P < .001$), organ failure (OR = 3.36, $P < .001$) and in-hospital mortality (OR = 3.12, $P < .001$).

4 | DISCUSSION

Acute pancreatitis is a common acute disease of the digestive system. Although there has been progress in its

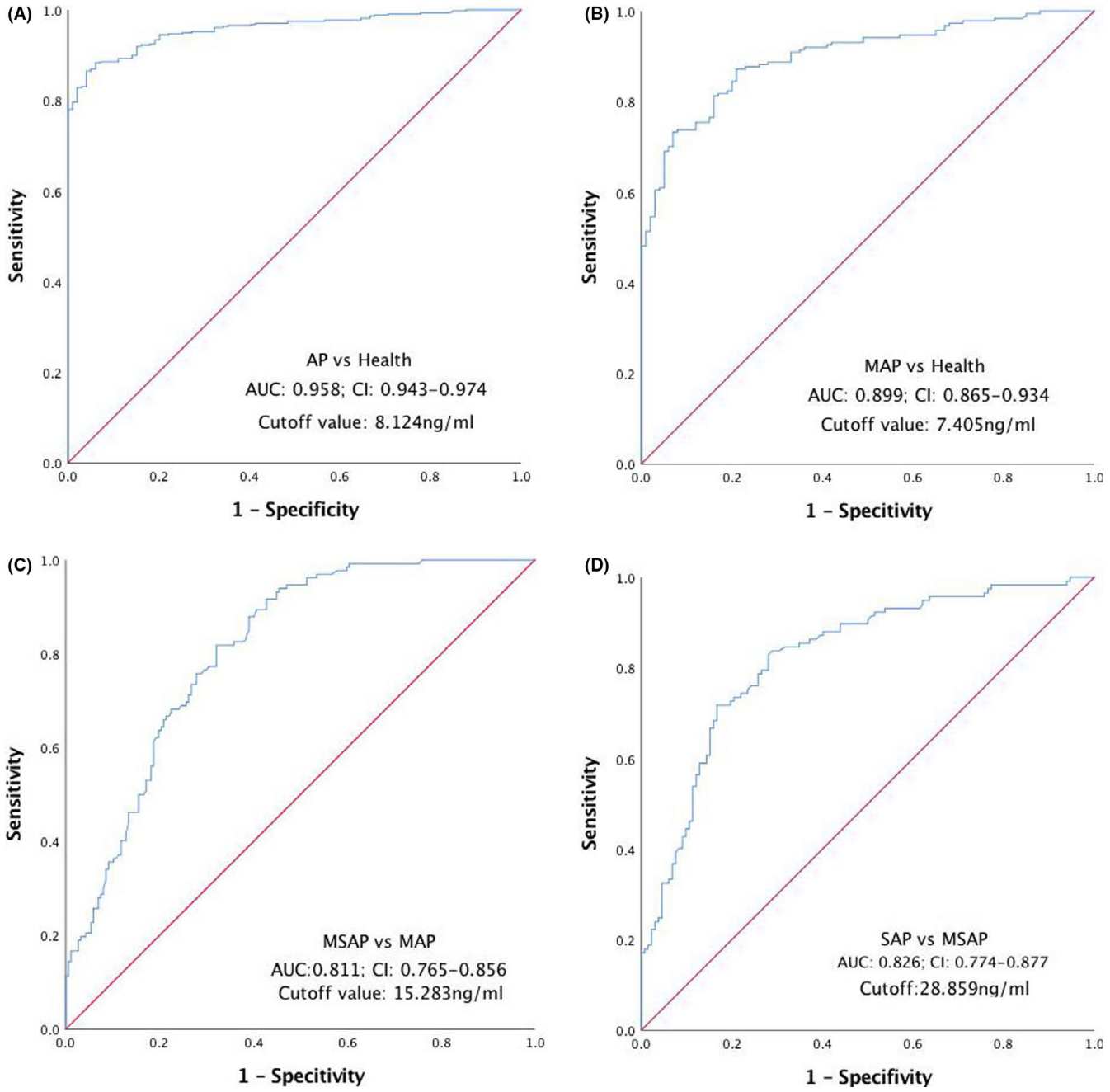

FIGURE 2 Diagnostic value of sB7-H4 in AP. ROC curve analyses were used to assess the value of sB7-H4 in differentiating between the A, Health and AP; B, Health and MAP; C, MAP and MSAP and D, MSAP and SAP groups. The AUCs, 95% confidence intervals and cutoff values are marked in the figure

diagnosis and treatment over the past 10 years, 20%-30% of patients develop a serious clinical condition, which has an overall mortality rate of 5%-10%.[18,19] AP, in particular SAP, often causes organ failure and severe local or systemic complications, and its mortality rate is as high as 10%-30%.[20] To accurately assess the condition and provide timely interventions to improve the patient's prognosis, clinicians rely on the patient's symptoms and signs, laboratory indicators and scoring systems to estimate the severity and prognosis of the disease.

At present, the main inflammatory indicators for detecting the inflammatory response of AP include the IL-6, IL-8, TNF-α, PCT, CRP levels and the WBC count.[21,22] However, there are complex interactions among the multiple inflammation indicators, and their expression levels are also affected by multiple factors. For example, IL-6 can participate in acute inflammatory phase reactions, such as fever, enhanced vascular permeability, increased WBC count and complement activation[23]; TNF-α can activate lymphocytes and neutrophils at the site of the inflammation

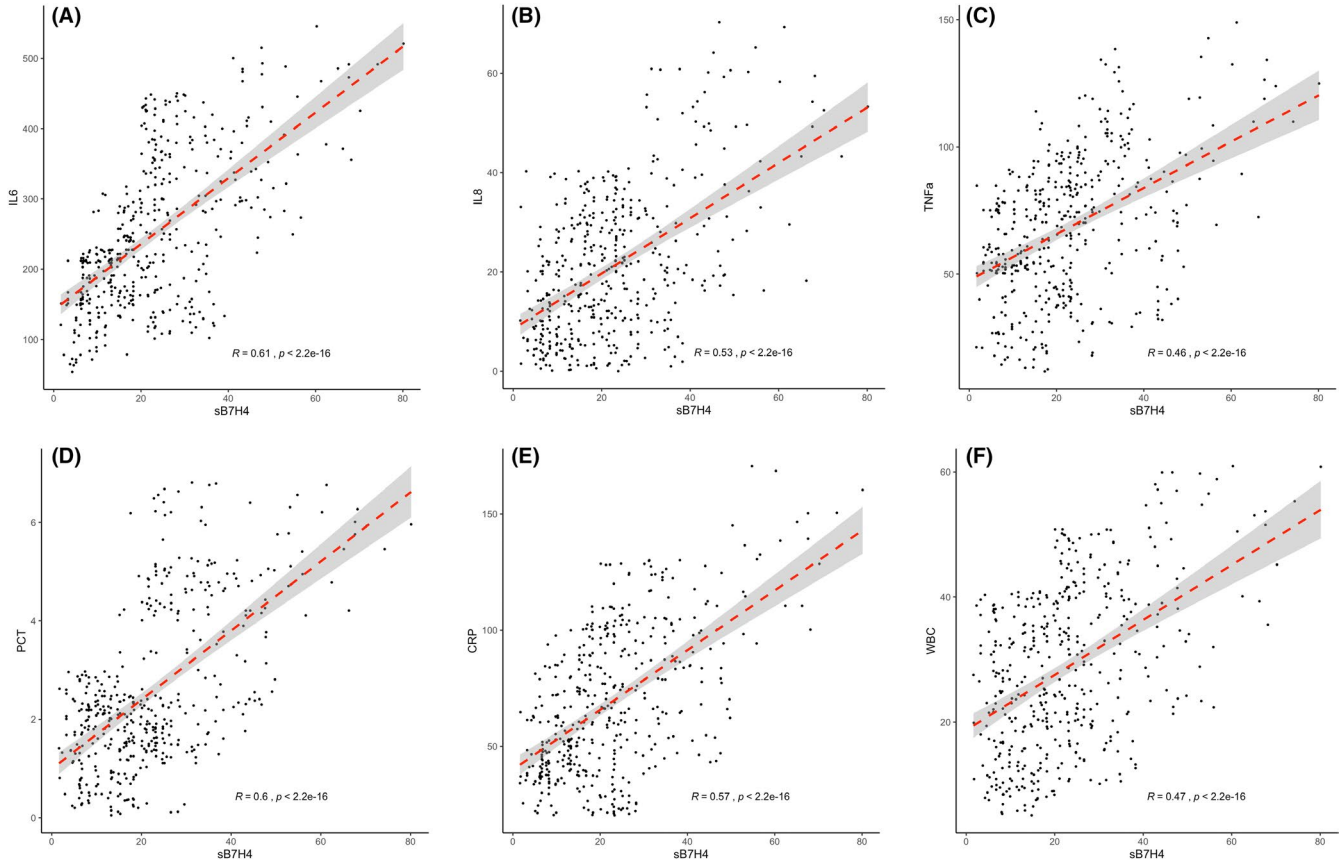

FIGURE 3 Correlation analysis between sB7-H4 and AP inflammatory factors. A, Correlation analysis between sB7-H4 and IL-6, $R = .61$, ($P < .001$); B, Correlation analysis between sB7-H4 and IL-8, $R = .53$, ($P < .001$); C, Correlation analysis between sB7-H4 and TNF-α, $R = .46$, ($P < .001$); D, Correlation analysis between sB7-H4 and PCT, $R = .61$, ($P < .001$); E, Correlation analysis between sB7-H4 and CRP, $R = .57$, ($P < .001$); and F, Correlation analysis between sB7-H4 and WBC count, $R = .47$ ($P < .001$)

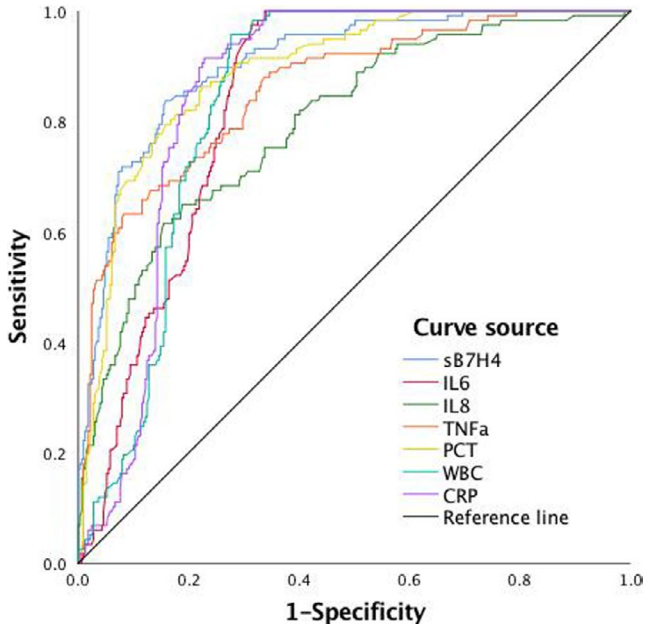

FIGURE 4 Predictive values of sB7-H4 and inflammatory factors for the severity of AP. The severity of the disease was evaluated with AUC values of 0.905, 0.837, 0.797, 0.858, 0.890, 0.841 and 0.855, respectively, for sB7- H4, IL-6, IL-8, TNF-α, PCT, CRP and WBC count

and increase capillary endothelial cell permeability.[24] In addition, TNF-α can promote the synthesis and release of proinflammatory cytokines, such as IL-6 and IL-8, causing a 'waterfall' effect, which can lead to serious consequences, such as SIRS and MODs.[25] The aforementioned inflammatory factors can also increase CRP levels, PCT and WBC count.[26]

For the evaluation of the prognosis of acute pancreatitis, the Ranson, APACHE II and BISAP score systems are recognized as the ideal scoring systems. However, these scoring systems are designed for comprehensive populations, and it is difficult to accurately assess the risk of individual patients.[27] Different patients have different degrees of development of their condition, and their sensitivity to treatment may also differ. The required parameters to complete the score or calculate the mortality rate cannot be achieved in a short time, and some calculation procedures are more complicated.[28] Some scoring systems require more parameters, and dynamic scoring every day results in higher medical costs, which is difficult for patients and their families to understand and accept.[29] To be simple and easy to use, each scoring system is applied independently, inevitably leading to the omission of information other than that used in

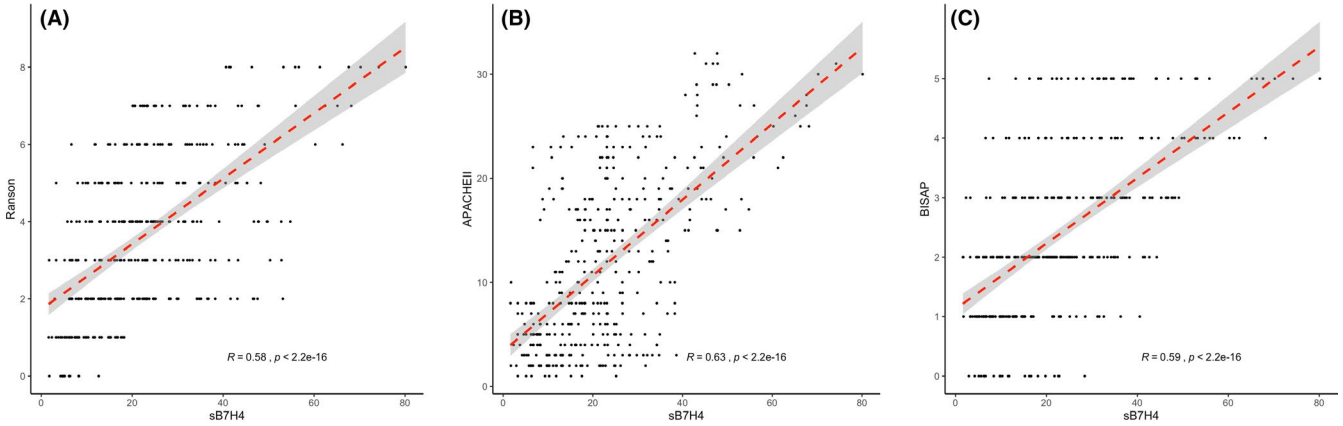

FIGURE 5 Correlation analysis between sB7-H4 and the AP prognostic score. A, Correlation analysis between sB7-H4 and the Ranson score, $R = .58$, ($P < .001$); B, Correlation analysis between sB7-H4 and the APACHE II score, $R = .63$, ($P < .001$); C, Correlation analysis between sB7-H4 and the BISAP score, $R = .59$, ($P < .001$)

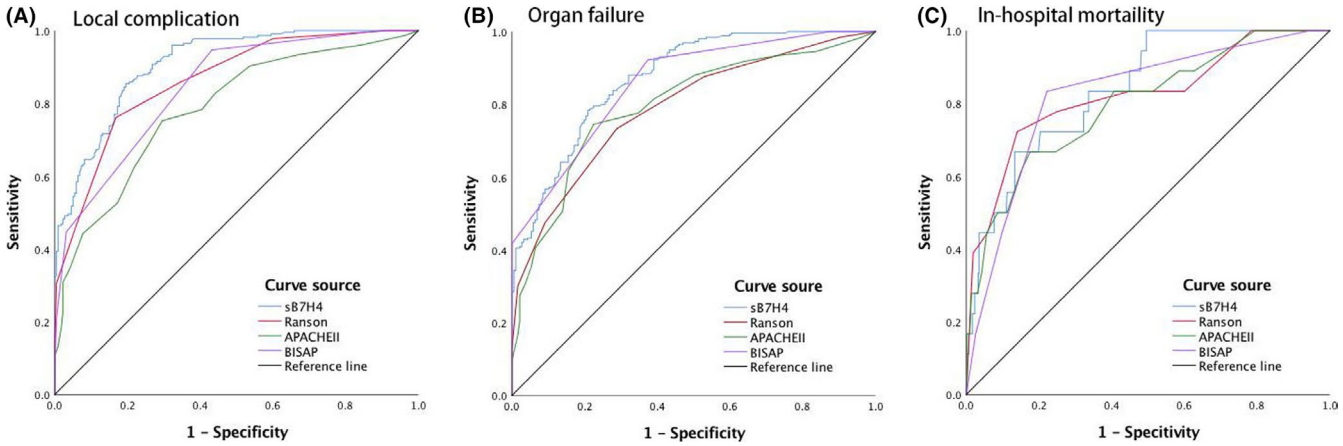

FIGURE 6 Predictive value of sB7-H4 and the prognostic scores of AP. A, For predicting local complications of AP with sB7-H4, the Ranson score, the APACHE II score, and the BISAP score, their AUCs were 0.908, 0.863, 0.785 and 0.844, respectively; B, for organ failure, their AUCs were 0.872, 0.790, 0.796 and 0.857, respectively; C, for death in the hospital their AUCs were 0.839, 0.821, 0.796 and 0.823, respectively

TABLE 2 Factors associated with poor prognosis after acute pancreatitis

	Local complication			Organ failure			In-hospital mortality		
Factors	**AUC**	**95%CI**	***P* value**	**AUC**	**95%CI**	***P* value**	**AUC**	**95%CI**	***P* value**
sB7-H4 level	0.908	0.883-0.934	< .001	0.872	0.840-0.904	< .001	0.839	0.758-0.921	< .001
Ranson scores	0.863	0.830-0.896	< .001	0.790	0.748-0.831	< .001	0.821	0.706-0.936	.003
APACHEII scores	0.785	0.743-0.827	< .001	0.796	0.754-0.838	< .001	0.796	0.685-0.907	< .001
BISAP scores	0.844	0.809-0.879	< .001	0.857	0.823-0.891	< .001	0.823	0.726-0.920	< .001

Abbreviations: APCHCE II, acute physiology and chronic health care evaluation II; AUC, area under the curve; BISAP, bedside index for severity in acute pancreatitis.

the evaluation, which cannot fully and accurately reflect the changing trend of the patient's overall pathophysiology parameters and reduces the accuracy of the prediction.[30]

A single inflammatory factor or scoring system may not completely reflect the criticality of pancreatitis. Multiple indicators need to be combined to effectively improve the assessment of the severity and the prognosis of AP. In the immune response, T cell activation requires the stimulation of two signals: the first signal is transduced by T cell receptors and enhanced by adhesion molecules; and the second

TABLE 3 Correlations between sB7-H4 level and clinical characteristics of AP

Characteristics	B7-H4 level		*P* value
	High (152)	Low (294)	
Age (y)	46.75 ± 13.64	46.12 ± 12.87	NS
Sex (male/ female, N)	152(83/69)	294(161/133)	NS
BMI (kg/m^2)	24.67 ± 2.73	27.76 ± 2.24	NS
Ranson scores	5.01 ± 1.72	2.51 ± 1.54	< .001
APACHE II scores	14.17 ± 5.54	7.39 ± 4.51	< .001
BISAP scores	2.90 ± 1.11	1.58 ± 0.76	< .001
IL-6 (pg/mL)	345.58 ± 87.27	206.03 ± 65.28	< .001
IL-8 (pg/mL)	32.14 ± 16.30	14.83 ± 10.27	< .001
TNF-α (pg/mL)	92.37 ± 25.57	65.41 ± 18.08	< .001
PCT (ng/mL)	4.16 ± 1.63	2.04 ± 0.77	< .001
CRP (mg/L)	97.77 ± 31.25	52.08 ± 17.45	< .001
WBC count (10^9/L)	36.31 ± 10.96	19.27 ± 7.22	< .001
Poor prognosis			
Local complication	142	110	.034
Organ failure	135	91	
In-hospital mortality	15	2	

Abbreviations: N, number; NS, no significant.

Values are displayed as a mean ± SD.

TABLE 4 Multivariate analysis showing association of serum sB7-H4 level with poor prognosis after adjusting for pancreatitis aetiology, age and sex

Poor prognosis	Regression coefficient	OR	*P* value
Local complication	1.38	4.21	< .001
Organ failure	1.23	3.36	< .001
In-hospital mortality	1.22	3.12	< .001

signal is a nonspecific costimulatory signal provided by antigen presenting cells. The CD28/ B7 family is considered to be the most basic family of costimulatory molecules, and B7-H4 is an important part of it. In the innate immune and adaptive immune response, the B7-H4 protein is highly expressed on a variety of major immune cells, including activated NK cells, B cells, T cells, monocytes/macrophages, DCs and regulatory T cells (Tregs).[9,31,32] B7-H4 is currently the only known source of sB7-H4, and no inflammatory factor that directly affects sB7-H4 expression has been found in the inflammatory response, which indicates that sB7-H4 may indirectly reflect the activities of the above-mentioned various immune cells. This characteristic is an important prerequisite for using sB7-H4 as an assessment of AP inflammation status and poor prognosis in this study.

In this article, by examining the expression level of sB7-H4 in the peripheral blood of healthy volunteers and patients with AP, we found that sB7-H4 was highly expressed in AP patients, with an AUC of 0.958 and a sensitivity of 0.865. The level of sB7-H4 gradually increases with the severity of AP and has a significant correlation with other inflammation markers, including IL-6, IL-8, TNF-α, PCT and CRP levels and the WBC count. For assessing the severity of AP, the AUC of sB7-H4 is 0.905, which is better than that the other markers of inflammation. This result shows that sB7-H4 could be used as a good biological indicator for the diagnosis of and the assessment of the severity of AP.

In addition, this study further explored the value of sB7-H4 in predicting a poor prognosis of patients with AP. We found that sB7-H4 had a significant correlation with the Ranson, APACHE II and BISAP scores. For predicting local complications, organ failure and in-hospital mortality, the AUC of sB7-H4 was better than that of the Ranson, APACHE II and BISAP scores.

Logistic multivariate regression analysis showed that the sB7-H4 level was independently associated with early prediction of AP outcomes, including local complications, organ failure and in-hospital mortality. After dividing AP into two groups according to the median value of sB7-H4, the high expression group was significantly higher than the low expression group in terms of inflammatory factor expression levels and prognostic scores.

The above results show that early detection of peripheral blood sB7-H4 levels in AP patients could be helpful for predicting clinical progress and a poor prognosis. AP patients with high expression levels of sB7-H4 in the peripheral blood will have a stronger inflammatory response. These patients are more likely to need ICU monitoring for organ function maintenance and to have poor outcomes. The use of this new marker will allow clinicians to apply more effective interventions early to improve prognosis and save lives, while patients with low expression of sB7-H4 may be given the appropriate conventional treatment.

However, it should be noted that this study has certain deficiencies. Although multiple researchers have confirmed that sB7-H4 is derived from overexpressed B7-H4 in activated immune cells, in this study, we did not confirm that B7-H4 was overexpressed in immune cells in the peripheral blood of AP patients. In addition, the use of sB7-H4 for the diagnosis, prediction of severity of disease and prognostication of AP needs to be further confirmed by multi-centre prospective studies.

5 | CONCLUSIONS

In general, sB7-H4 can be considered an index for the diagnosis and severity assessment of AP. Moreover, sB7-H4 can be used as a biomarker to predict a poor prognosis. sB7-H4 is an independent risk factor for a poor clinical outcome, including local complications, organ failure and in-hospital mortality. sB7-H4 has certain advantages in the diagnosis and prognostication of AP and has potential clinical value.

ACKNOWLEDGEMENT

The authors acknowledge Yang Gu from Wuhan University, Zhongnan Hospital, Department Hepatobiliary & Pancreat Surgery, Donghu Road 169, Wuhan 430071, Hubei, Peoples Republic of China, for help with statistical analysis and critical reading of the manuscript.

CONFLICT OF INTERESTS

No conflict of interests for all authors.

AUTHOR CONTRIBUTIONS

This paper was written by Zhixiang Cheng and Zhengfang Liu, Yufeng Yuan and Zhisu Liu have participated in data analysis and experimental research. Yueming He and Ping Jiang have completed the design and proofreading of this article.

ORCID

Zhixiang Cheng https://orcid.org/0000-0003-0060-945X
Ping Jiang https://orcid.org/0000-0002-2715-6860

REFERENCES

1. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143(5):1179-1187.e1173.
2. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111.
3. Garg PK, Singh VP. Organ failure due to systemic injury in acute pancreatitis. *Gastroenterology*. 2019;156(7):2008-2023.
4. Leppäniemi A, Tolonen M, Tarasconi A, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. *World J Emerg Surg*. 2019;14:27.
5. Habtezion A, Gukovskaya AS, Pandol SJ. Acute pancreatitis: a multifaceted set of organelle and cellular interactions. *Gastroenterology*. 2019;156(7):1941-1950.
6. Brown LA, Hore TA, Phillips AR, Windsor JA, Petrov MS. A systematic review of the extra-pancreatic infectious complications in acute pancreatitis. *Pancreatology*. 2014;14(6):436-443.
7. James TW, Crockett SD. Management of acute pancreatitis in the first 72 hours. *Curr Opin Gastroenterol*. 2018;34(5):330-335.
8. Prasad DV, Richards S, Mai XM, Dong C. B7S1, a novel B7 family member that negatively regulates T cell activation. *Immunity*. 2003;18(6):863-873.
9. Sica GL, Choi IH, Zhu G, et al. B7–H4, a molecule of the B7 family, negatively regulates T cell immunity. *Immunity*. 2003;18(6):849-861.
10. Choi IH, Zhu G, Sica GL, et al. Genomic organization and expression analysis of B7–H4, an immune inhibitory molecule of the B7 family. *J Immunol*. 2003;171(9):4650-4654.
11. Chen L, Lu Y, Wang F, et al. Expression of co-stimulatory molecule B7–H4 in patients suffering from rheumatoid arthritis. *Immunol Lett*. 2013;154(1–2):25-30.
12. Hofmeyer KA, Scandiuzzi L, Ghosh K, Pirofski LA, Zang X. Tissue-expressed B7x affects the immune response to and outcome of lethal pulmonary infection. *J Immunol*. 2012;189(6):3054-3063.
13. Cao Q, Wang Y, Zheng D, et al. IL-10/TGF-beta-modified macrophages induce regulatory T cells and protect against adriamycin nephrosis. *J Am Soc Nephrol*. 2010;21(6):933-942.
14. Kamimura Y, Kobori H, Piao J, et al. Possible involvement of soluble B7–H4 in T cell-mediated inflammatory immune responses. *Biochem Biophys Res Commun*. 2009;389(2):349-353.
15. Azuma T, Zhu G, Xu H, et al. Potential role of decoy B7–H4 in the pathogenesis of rheumatoid arthritis: a mouse model informed by clinical data. *PLoS Med*. 2009;6(10):e1000166.
16. Radichev IA, Maneva-Radicheva LV, Amatya C, et al. Nardilysin-dependent proteolysis of cell-associated VTCN1 (B7–H4) marks type 1 diabetes development. *Diabetes*. 2014;63(10):3470-3482.
17. Lee PJ, Papachristou GI. New insights into acute pancreatitis. *Nat Rev Gastroenterol Hepatol*. 2019;16(8):479-496.
18. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*. 2011;141(4):1254-1263.
19. Forsmark CE, Baillie J. AGA Institute technical review on acute pancreatitis. *Gastroenterology*. 2007;132(5):2022-2044.
20. Agarwal S, George J, Padhan RK, et al. Reduction in mortality in severe acute pancreatitis: a time trend analysis over 16 years. *Pancreatology*. 2016;16(2):194-199.
21. Mo XJ, Ye XZ, Li YP. Effects of euphorbia kansui on the serum levels of IL-6, TNF-alpha, NF-kappaB, sTNFR and IL-8 in patients with severe acute pancreatitis. *J Biol Regul Homeost Agents*. 2019;33(2):469-475.
22. Aoun E, Chen J, Reighard D, Gleeson FC, Whitcomb DC, Papachristou GI. Diagnostic accuracy of interleukin-6 and interleukin-8 in predicting severe acute pancreatitis: a meta-analysis. *Pancreatology*. 2009;9(6):777-785.
23. Dambrauskas Z, Giese N, Gulbinas A, et al. Different profiles of cytokine expression during mild and severe acute pancreatitis. *World J Gastroenterol*. 2010;16(15):1845-1853.
24. Sternby H, Hartman H, Johansen D, Thorlacius H, Regner S. Predictive capacity of biomarkers for severe acute pancreatitis. *Eur Surg Res*. 2016;56(3–4):154-163.
25. Malmstrom ML, Hansen MB, Andersen AM, et al. Cytokines and organ failure in acute pancreatitis: inflammatory response in acute pancreatitis. *Pancreas*. 2012;41(2):271-277.
26. Gao N, Yan C, Zhang G. Changes of serum procalcitonin (PCT), C-reactive protein (CRP), interleukin-17 (IL-17), interleukin-6 (IL-6), high mobility group protein-B1 (HMGB1) and D-Dimer in patients with severe acute pancreatitis treated with continuous renal replacement therapy (CRRT) and its clinical significance. *Med Sci Monit*. 2018;24:5881-5886.
27. Valverde-Lopez F, Matas-Cobos AM, Alegria-Motte C, Jimenez-Rosales R, Ubeda-Munoz M, Redondo-Cerezo E. BISAP, RANSON, lactate and others biomarkers in prediction of severe

acute pancreatitis in a European cohort. *J Gastroenterol Hepatol*. 2017;32(9):1649-1656.
28. Yang L, Liu J, Xing Y, et al. Comparison of BISAP, Ranson, MCTSI, and APACHE II in predicting severity and prognoses of hyperlipidemic acute pancreatitis in chinese patients. *Gastroenterol Res Pract*. 2016;2016:1834256.
29. Mounzer R, Langmead CJ, Wu BU, et al. Comparison of existing clinical scoring systems to predict persistent organ failure in patients with acute pancreatitis. *Gastroenterology*. 2012;142(7):1476-1482.
30. Hagjer S, Kumar N. Evaluation of the BISAP scoring system in prognostication of acute pancreatitis - A prospective observational study. *Int J Surg*. 2018;54(Pt A):76-81.
31. Kryczek I, Zou L, Rodriguez P, et al. B7–H4 expression identifies a novel suppressive macrophage population in human ovarian carcinoma. *J Exp Med*. 2006;203(4):871-881.
32. Galazka K, Wicherek L, Pitynski K, et al. Changes in the subpopulation of CD25+ CD4+ and FOXP3+ regulatory T cells in decidua with respect to the progression of labor at term and the lack of analogical changes in the subpopulation of suppressive B7–H4 macrophages–a preliminary report. *Am J Reprod Immunol*. 2009;61(2):136-146.

How to cite this article: Cheng Z, Liu Z, Yuan Y, Liu Z, He Y, Jiang P. Predictive value of serum soluble B7-H4 in acute pancreatitis. *Eur J Clin Invest*. 2020;50:e13346. https://doi.org/10.1111/eci.13346