Int J Clin Exp Med 2018;11(4):3968-3973
www.ijcem.com /ISSN:1940-5901/IJCEM0067349

Original Article

Clinical significance of serum IL-18 in diagnosing and predicting severe acute pancreatitis

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Received October 16, 2017; Accepted November 22, 2017; Epub April 15, 2018; Published April 30, 2018

Abstract: Aim: To detect whether serum interleukin 18 (IL-18) serves as early predictor for diagnosis of severe acute pancreatitis (AP). Methods: AP patients were categorized into 2 groups as mild acute pancreatitis (MAP) and severe acute pancreatitis (SAP). All participants received assessment of IL-18, C-reactive protein (CRP) and chronic health evaluation (APACHE) II score. Results: IL-18 concentration in SAP participants in less than twenty-four hours subsequent to pain attack was elevated and remarkably higher than the concentration in MAP participants and healthy controls ($P<0.01$). The optimal cut off value of IL-18 was determined as 100 pg/mL in order to differentiate MAP from SAP. In terms of IL-18, specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), as well as positive and negative likelihood ratio were determined as 76.35%, 63.35%, 0.6223, 0.6598, 3.2561 and 0.5268, respectively. It was proved by area under the curve (AUC) that prognostic accuracy of IL-18 (0.722) was similar to APACHE-II (0.729), which was higher than that of CRP (0.531) in differentiation of MAP from SAP. Conclusion: IL-18 serves as an early predictor and assists diagnosis of SAP in less than twenty-four hours subsequent to pain attack or admission, which was reliable, easy, and rapid. IL-18 is insufficient to serve as a stand-alone assay to diagnose AP and additional assays are necessary to diagnosis.

Keywords: Interleukin 18, severe acute pancreatitis, C-reactive protein, APACHE II score

Introduction

Acute pancreatitis (AP) is an inflammatory response of pancreas, sometimes involving glands and tissues in the distance. AP incidence every year fluctuates from 5 to 80 per 100,000 people [1]. AP turns out to be self-limiting as well as benign inflammatory response with pancreatic oedema in three fourths of cases. The other one fourth of cases degenerates into serious necrosis, which is attributable to infection [2]. AP can bring about sepsis, systemic inflammatory reaction syndrome (SIRS), disseminated intravascular coagulation (DIC), multi-organ failure (MOFS), and less frequently diseased intestinal loop in adjacent [3]. Complications above lead to death rates of 67.5% for sepsis, 19% for necrosis after infection, 62.5% for DIC, and 50-91% for MOFS. Total death rate disregard of AP patterns fluctuates from 2.1% to 7.8% [4]. Therefore, it was essential to early diagnose and foresee severity of AP.

It has been known that acute pancreatitis can develop as an inflammatory reaction. In severe and benign AP, trypsin promotes the production of pancreatic proteolytic enzyme and activates coagulation, fibrinolytic systems and secretion of several cytokines [5]. IL-18, IL-1, tumor necrosis factor α (TNF-α) and IL-19 in combination with other secreted substances from the damaged pancreatic cells, promote the further inflammatory responses [6, 7]. For the proper treatment, there is an increasing need for accurate prognostic predictor. Although biomarkers such as C-reactive protein (CRP), amyloid A and IL-6 have been used, the results are still unsatisfactory. Thus, more suitable prognostic predictors for AP are urgent needed.

It has been shown that IL-18 can regulate the secretion of IL-2, IL-12, IL-23, IFN-γ and other interleukins [8, 9]. IL-18 was supposed to serve as an early predictor of SAP, with biomarkers auxiliary to APACHE II in terms of diagnosis of SAP. Herein, our research aimed at assessment

of the value of IL-18 in early forecast and diagnosis of SAP.

Materials and methods

Participants

A total of 82 AP participants enrolled in our pilot research were evaluated in a prospective examination lasting for one year in Dongying People's Hospital. AP diagnosis was determined according to the following criteria: (1) extended abdominal pain featured in AP; (2) promoted lipase and/or amylase concentration in blood by no less than three-folds than normal range; (3) distinctive features of AP revealed by abdominal US or CT. Participants admitted in less than the 1st twenty-four hours subsequent to pain attack were excluded from our research. Participants with other illness which could affect the results were also eliminated, for example, pancreatitis subsequent to trauma, operation, as well as ERCP. Abdominal pain resulted from other causes were eliminated.

Clinical evaluation

Our research was approved by the Ethics Committee in our hospital. Fully informed consent of every participant was acquired prior to recruitment. Population characteristics (sex, age, job, course and feature of symptom) as well as etiology of pancreatitis (gallstone, hyperlipidemia, alcohol abuse and others) were examined. Conventional clinical examination, lab assays as well as treatment were conducted. AP severity was categorized according to Atlanta Classification, Ranson as well as APACHE II score in twenty-four to forty-eight hours subsequent to admission [2]. Ultrasonography was conducted every two days in terms of every patient. Spiral contrast-enhanced CT was conducted with regard to some patients in forty-eight to seventy-two hours subsequent to admission in order to evaluate the range of inflammatory reaction and the severity of pancreatic necrosis in conformity with Balthazar's classification. Subsequent to the investigation, outcome was reviewed in order to guarantee qualification of inclusion into our research.

Clinical categories

Ranson's scores were measured during the 1st twenty-four hours as well as forty-eight hours subsequent to admission. Since Ranson and his colleagues defined eleven prognostic elements in 1974 [10], numerous studies were carried out in order to determine the optimal predictors which could evaluate severity of AP rapidly and accurately in order to cope with distinct clinical as well as regional settings. SAP was determined dependent on lab and clinical outcome according to Ranson's score. Patients in conformity to less than 3 positive criteria were determined as MAP, while those in conformity to no less than 3 criteria were defined as SAP.

Specimen acquirement and ELISA for IL-18 and CRP

In order to examine time kinetics of elevation of IL-18 as well as CRP in AP, concentrations were examined at 2 time points. The predictive value of IL-18 as well as CRP in the 1st twenty-four hours as well as forty-eight hours subsequent to pain attack or admission was explored. Blood specimens (5 mL) were acquired from eighty-five AP patients as well as fifteen healthy counterparts. Plasma was isolated with the help of the 10-minute centrifugation under circumstances of 3000 r/min and 4°C, which was reserved under -20°C before assays. IL-18 concentration as well as CRP concentration was evaluated with the help of enzyme linked immunosorbent assay kits (Sen-Xiong Technology Co., Ltd., People's Republic of China). Absorbance at 450 nm was measured.

Statistical analysis

Subsequent to assays, results of every patient were reviewed in order to guarantee the eligibility of enrollment of our research. The information of sex, etiology of AP, as well as classification variables were compared between groups with χ^2 test. ANOVA analysis was carried out in terms of age, CRP concentration, IL-18 concentration as well as other related lab assays of AP. It was regarded as statistically significant with $P \leq 0.05$. To distinguish MAP from SAP in the 1st twenty-four hours subsequent to pain attack, specificity, sensitivity, NPV, PPV, NLR, as well as PLR under circumstances of diverse concentrations of IL-18 were evaluated in comparison to APACHE II as well as CRP concentration. ROC was built to determine reference cutoff of IL-18 concentration, CRP concentration, as well as APACHE II which was able to differentiate MAP

Table 1. Characteristics of 86 patients with acute pancreatitis

	SAP, *n* = 34	MAP, *n* = 48	*P* value
Age (mean ± SE, yr)	52.5 ± 12.3	49.5 ± 11.5	>0.05
Gender (male/female)	16/18	25/23	>0.05
Length of hospital stay (d)	18.5 ± 1.3	7.5 ± 1.5	<0.001
Etiology, n (%)			
Gall stones	18 (52.9)	19 (39.6)	<0.05
Alcohol	5 (14.7)	7 (14.5)	
Idiopathic	16 (47.1)	22 (45.8)	
Test at first 24 h			
Blood amylase (U/L)	450.5 ± 165.3	369 ± 122.3	<0.05
Total bilirubin (mmol/mL)	39.50 ± 21.25	28.65 ± 24.53	>0.05
Blood glucose (mmol/mL)	9.65 ± 3.87	6.67 ± 2.32	<0.05
Blood calculus	2.35 ± 0.45	2.61 ± 2.56	>0.05
Test at 48-72 h			
Pancreatic necrosis	16	3	<0.01
Ranson's score	5.2 ± 0.5	1.5 ± 0.3	<0.001

SAP: Severe acute pancreatitis; MAP: Mild acute pancreatitis.

Table 2. Acute physiology and chronic health evaluation II score, serum interleukin-18 and C-reactive protein levels in severe acute pancreatitis and mild acute pancreatitis patients within the first 24 h after admission

	SAP, *n* = 34	MAP, *n* = 48	Control	*t*	*P* value
APACHE-II	14.27 ± 5.35	7.25 ± 1.24		7.353	<0.001
IL-18 (pg/mL)	122.15 ± 4.45	108.25 ± 5.53	85.91 ± 4.35	8.521	<0.001
CRP (mg/L)	7.5 ± 1.3	5.5 ± 1.5	1.2 ± 1.4	7.3268	<0.001

SAP: Severe acute pancreatitis; MAP: Mild acute pancreatitis; APACHE-II: Acute physiology and chronic health evaluation II; IL-18: interleukin-18; CRP: C-reactive protein.

Table 3. Changes of serum interleukin-18 and C-reactive protein levels in severe acute pancreatitis patients after admission

	Type	<24 h	48-72 h	*t*	*P* value
APACHE-II	SAP	14.27 ± 5.35	17.6 ± 2.05	3.2615	<0.05
	MAP	7.25 ± 1.24	9.25 ± 3.25	2.3615	<0.001
IL-18 (pg/mL)	SAP	122.15 ± 4.45	136.56 ± 3.65	4.2518	<0.001
	MAP	108.25 ± 5.53	112.35 ± 4.32	7.2569	<0.001
CRP (mg/L)	SAP	7.5 ± 1.3	5.6 ± 3.1	7.0254	<0.001
	MAP	5.5 ± 1.5	4.1 ± 3.5	6.3598	<0.001

SAP: Severe acute pancreatitis; MAP: Mild acute pancreatitis; APACHE-II: Acute physiology and chronic health evaluation II; IL-18: interleukin-18; CRP: C-reactive protein.

from SAP. AUC was applied to the evaluation of distinguishing capability with the perfect area at 1.0 and non-discriminating area at 0.5. SPSS v8.00 statistical analysis software (SPSS Inc., Cary, NC) was applied to every analysis.

Results

Clinical features of AP

A total of 82 AP patients (41 male, 41 female with average age at 51 years; range, 18-79 years) as well as fifteen healthy counterparts (11 male, 4 female with average age at 48.5 years; range, 23-57 years) were enrolled in our research. With the help of Ranson's criteria, 48 (58.5%) participants received diagnosis of MAP while 34 (41.5%) of SAP. Clinical features of AP patients were presented in **Table 1**. Cholelithiasis served as the most prevalent cause of MAP as well SAP (*n* = 19, 39.6% and *n* = 18, 52.9%). No distinction was discovered in gender, race as well as etiology between MAP and SAP. Average concentrations of glucose as well as amylase were noticeably elevated in SAP in comparison with MAP (*P*<0.05). No noticeable distinction in total bilirubin concentration was found between MAP and SAP in the 1st twenty-four hours subsequent to pain attack.

Average APACHE-II, CRP, and IL-18 concentration in SAP as well as MAP patients

Average APACHE-II scores of SAP in the 1st twenty-four hours subsequent to pain attack were noticeably elevated in comparison to MAP (P<0.001). Average IL-18 concentration of SAP in the 1st twenty-four hours subsequent to pain attack was noticeably elevated in comparison

Table 4. Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio of acute physiology and chronic health evaluation II, interleukin-18 and C-reactive protein in distinguishing severe acute pancreatitis from mild acute pancreatitis

	Cutoffs	Sensitivity (%)	Specificity (%)	PPV	NPV	PLR	NLR
APACHE-II	>8	76.65	56.25	0.55	0.7614	1.6356	0.2635
IL-18	100 pg/ml	63.35	76.35	0.6223	0.6598	3.2561	0.5268
CRP	6 mg/L	42.56	71.24	0.6135	0.5684	0.8625	1.1523

APACHE-II: Acute physiology and chronic health evaluation II; IL-18: interleukin-18; CRP: C-reactive protein; PPV: Positive predictive value; NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio.

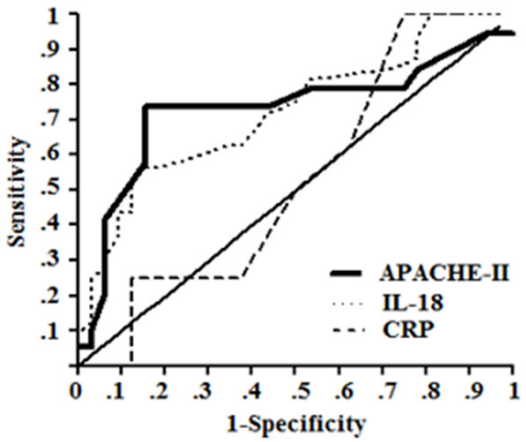

Figure 1. Cutoffs of APACHE-II score >8, CRP concentration (6 g/mL), and IL-18 concentration (100 pg/mL) that can differentiate MAP from SAP in twenty-four hours subsequent to pain attack underwent evaluation via building ROC. AUC for IL-18, APACHE-II score >8 as well as CRP in SAP prediction was 0.722, 0.729 and 0.531.

to MAP (P<0.001) as well as healthy counterparts (P<0.001). It was discovered that CRP concentration was elevated in SAP in comparison to MAP in twenty-four hours as well as healthy counterparts (P<0.001) (**Table 2**).

Average IL-18 concentration at forty-eight to seventy-two hours subsequent to admission was remarkably elevated in comparison to SAP in the 1st twenty-four hours subsequent to admission (P<0.001). CRP concentration decreased in AP during forty-eight to seventy-two hours subsequent to admission. However, it was remarkably higher in SAP but not in MAP (P<0.01). Average APACHE-II scores in both MAP and SAP during forty-eight to seventy-two hours subsequent to pain attack were mildly promoted. However, they were noticeably elevated in the 1st twenty-four hours in comparison to MAP (**Table 3**).

Sensitivity, specificity, NPV, PPV, NLR and PLR of IL-18 in differentiation of MAP from SAP

Specificity, sensitivity, NPV, PPV, NLR, as well as PLR under circumstances of diverse concentrations of IL-18 (85, 90, 95, 100, 105, 110, 115, and 120 pg/mL) were examined. Optimal cutoff of IL-18 concentration was selected with lower NLR as well as higher PLR in order to differentiate MAP from SAP in the 1st twenty-four hours subsequent to pain attack, which were 76.35%, 63.35%, 0.6598, 0.6223, 0.5268 and 3.2561. APACHE-II scores (>20, 17-20, 13-16, 9-12, 4-8, and <4) were evaluated. Those values above at optimal cutoffs of APACHE-II more than 8 were 56.25%, 76.65%, 0.7614, 0.5500, 0.2635 as well as 1.6356. Diverse CRP concentrations (3, 4, 5, 6, 7 and 8 g/mL) were evaluated applying the identical approach. Those values above at optimal cutoffs of CRP concentration at 6 g/mL were 71.24%, 42.56%, 0.5684, 0.6135, 1.1523 as well as 0.8625 (**Table 4**).

ROC curves and AUC of CRP, IL-18, as well as APACHE-II in differentiating MAP from SAP

ROC was built to conclude the optimal cutoffs of CRP concentration (6 g/mL), IL-18 concentration (100 pg/mL), as well as APACHE-II score (>8), which were used to differentiate MAP from SAP in the 1st twenty-four hours subsequent to pain attack. AUC of CRP concentration, IL-18 concentration as well as APACHE-II to foresee SAP was 0.531, 0.722, as well as 0.729 (**Figure 1**). It was proved that prognostic accuracy of IL-18 concentration resembled that of APACHE-II but was noticeably better than that of CRP. CRP concentration failed to differentiate MAP from SAP in the 1st twenty-four hours subsequent to pain attack.

Discussion

Clinical features of AP fluctuate from local inflammation to more serious pattern, related to SIRS [11]. Intensive care was necessary to

SAP patients. AP is featured as systemic stimulation of protease signaling cascades. Abnormal intracellular stimulation of digestive enzymes brings about cytokine release, necrosis, ischemia, as well as coagulation stimulation, which are essential to AP degeneration as well as the progression of related complications apart from pancreas [12]. Haemostasis is noticeably affected by the cascade; in fact, coagulation and inflammation are closely related. Therefore, failure of multiple organs resulted from SAP is frequently related to sepsis as well as DIC [13]. Some biomarkers are recognized as AP predictors [14-16]. Diverse biochemical assays, for example, CRP, IL-6, TNF and IL-2 are regarded as early predictors and to diagnose SAP [17]. Nevertheless, apart from CRP, none is able to precisely predict severity in twenty-four hours subsequent to pain attack. Few studies have been conducted on the result in triage in to ICU. Since no noticeable relationship between clinical symptoms and structural injury of pancreas, no optimal predictors or biomarkers have been discovered. The understanding of early clinical predictors of AP relapse is insufficient. The optimal predictors of SAP are supposed to be rapid, easy, secure, inexpensive, repeatable, highly specific and sensitive. An instantaneous assay with high AUC, specificity and low NLR is necessary.

IL-18 mainly arises from mononuclear cells, including macrophages, lymphocytes B, monocytes, dendritic cells, Kupffer cells, synoviocytes, Langerhans cells, keratinocytes, osteoblasts, as well as intestinal and respiratory epithelium [18]. As a cytokine with its molecular weight at 18 kD, IL-18 is triggered by the expression enhancement of 2 pro-IL-18 promoters in reaction to direct cell activation via microbial products, for example, IFN-α, β, and γ as well as LPS. Pro-IL-18, whose molecular weight is 24 kD, generates stimulated IL-18 resulting from ICE, also called caspase 1 [19, 20]. As a heterodimer, IL-18R contains 2 α as well as β subunits. IL-18Rα is linked to IL-18 as well as IL-18Rβ, which stimulates downstream pathways. Versatility of IL-18 manifests itself in counteracting inflammation, generation of IFN-γ triggered by LPS in vivo, and stimulation of the generation of other ILs [21, 22]. In our research, it was discovered that concentrations of CRP as well as IL-18 in AP from twenty-four to seventy-two hours of hospitalization was elevated, which was in conformity to previous researches demonstrating a remarkable elevation in IL-18 concentration of thirty AP patients during the 1st ten days of hospitalization.

In terms of the 82 AP participants, forty-eight received diagnosis of MAP while 34 received SAP diagnosis in conformity with Ranson's criteria. Average IL-18 concentration in SAP during the 1st twenty-four hours subsequent to pain attack was elevated in comparison to MAP as well as healthy counterparts. Average IL-18 concentration in SAP from forty-eight to seventy-two hours subsequent to admission was noticeably elevated in comparison with SAP. In consistent with previous study [23], our results demonstrated that IL-18 served as a quick, easy, and reliable approach during the 1st twenty-four hours subsequent to admission. Its sensitivity as well as specificity was elevated to early foresee and diagnose SAP. It was proved by AUC that prognostic accuracy of IL-18 resembled that of APACHE-II and was remarkably higher than that of CRP to differentiate MAP from SAP. The particular mechanism remains mysterious. Despite the fact that APACHE-II was more accurate in prognosis, the complicacy and lengthiness hinder clinical application. Nevertheless, the NPV of IL-18 is comparatively limited, preventing IL-18 from serving as stand-alone assays to diagnose AP. Other assays are necessary to diagnosis.

In a word, it was discovered that IL-18 concentration was elevated in the 1st twenty-four hours subsequent to AP attack and was able to early differentiate MAP from SAP. NPV, sensitivity, as well as specificity of IL-18 were high. It was able to serve AP screening and SAP prediction. Prognostic accuracy of IL-18 resembles that of APACHE-II and is remarkably higher than that of CRP. However, its limited NPV prevents it from serving as a stand-alone method to foresee and diagnose AP. Determination of innovative predictor of prognosis and severity of AP is necessary to promote accuracy of prediction.

Disclosure of conflict of interest

None.

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