The correlation of JKAP with risk, severity, inflammation and in-hospital mortality of severe acute pancreatitis

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Abstract

Background This study aimed to investigate the predictive value of JNK pathway-associated phosphatase (JKAP) level for severe acute pancreatitis (SAP) risk, and its association with disease severity, inflammation and in-hospital mortality in SAP patients. **Methods** Our study recruited 50 SAP patients, 50 moderate-severe acute pancreatitis (MSAP) patients, 50 mild acute pancreatitis (MAP) patients and 50 healthy controls. And the serum samples were obtained from all acute pancreatitis patients within 24 hours after admission and from health controls at their enrollment to detect JKAP level by enzyme-linked immunosorbent assay. **Results** JKAP level was decreased in SAP patients compared with healthy controls, MSAP and MAP patients. And receiver operating characteristics (ROC) curve analysis revealed that JKAP could not only distinguish SAP patients from healthy controls (AUC: 0.914, 95%CI: 0.857-0.971), but also differentiate SAP patients from MAP patients (AUC: 0.869, 95%CI: 0.802-0.937) and MSAP patients (AUC: 0.712, 95%CI: 0.610-0.813). In SAP patients, JKAP was negatively correlated with Ranson score, acute physiology and chronic health care evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score and C-reactive protein (CRP). And lower JKAP level, higher CRP level, Ranson score, APACHE II score and SOFA score were associated with increased in-hospital mortality in SAP patients. Additionally, ROC curve analysis showed that JKAP could predict decreased in-hospital mortality in SAP patients (AUC: 0.720, 95%CI: 0.526-0.914). **Conclusions** JKAP might serve as a biomarker for disease risk and management for SAP.

Background

Acute pancreatitis (AP), a sudden inflammatory of the pancreas, is frequently caused by pancreatic ductal obstruction secondary to gallstones and alcohol misuses, which affects 34 per 100,000 person-years worldwide [1, 2]. Most of the AP patients experience mild AP (MAP), while approximately 20% of AP patients develops severe AP (SAP) with a mortality rate approximately 30% [3]. SAP is characterized by multiple organ failure as well as necrosis of the pancreas and the surrounding tissues [4]. Due to the facet of rapid deterioration and high mortality of SAP, early identification of disease severity becomes essential for the evaluation of clinical treatment and the management of SAP [5]. Many multi-factoring scoring systems such as acute physiology and chronic health evaluation II (APACHE II) score and Ranson score have been widely applied for assessing SAP severity and predicting prognosis in clinical practice [3, 6]. However, under some circumstances such as at the time of initial presentation of SAP, the use of APACHE II score and Ranson score may be complex and with low sensitivity [3, 7]. Therefore, it is essential to explore novel sensitive biomarkers with the potential for assisting disease monitoring and improving prognosis in SAP patients.

JNK pathway-associated phosphatase (JKAP, also referred as dual-specificity phosphates (DUSP) 22) specifically activates the kinase JNK and functions as a tyrosine phosphate to dephosphorylate as well as inactivate focal adhesion kinase [8]. JKAP is abundantly expressed in various types of mammalian cells such as T cells, B cells and natural killer cells, which participates in important biological processes such as inflammatory and immune responses in human autoimmune and inflammatory disorders [9]. A

few studies have displayed that the downregulation of JKAP is negatively correlated with disease severity and inflammation in inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE) and sepsis [9–11]. Based on the role of JKAP in the regulation of inflammation and immune response and its association with the etiology of several inflammatory disorders, we hypothesized that JKAP might be involved in the development and progression of SAP as well. However, no studies have been done in evaluating the role of JKAP in SAP until now. Therefore, this study aimed to investigate the predictive value of JKAP level for SAP risk, and its association with disease severity, inflammation and in-hospital mortality in SAP patients.

Methods

Subjects

Between January 2016 and March 2019, 50 SAP patients, 50 MSAP patients and 50 MAP patients were recruited from our hospital in this study. All patients were older than 18 years and had a diagnosis of AP according to the Atlanta classification and definitions of acute pancreatitis [12]. While the patients were excluded if they were diagnosed as biliary duct-related or pancreatic-related carcinomas presenting with AP, concomitant with autoimmune diseases, complicated with malignancies, pregnant or breast feeding. The severity of AP was identified in accordance with the Atlanta classification and definitions [12]: (i) SAP was characterized by persistent organ failure (persisted for >48 h); (ii) MSAP was characterized by the presence of transient organ failure (presented for <48 h) or local complications (including peripancreatic fluid collections and acute necrotic collections) or systemic complications (exacerbations of underlying co-morbidities related to the acute pancreatitis) in the absence of persistent organ failure; (iii) MAP was characterized by the absence of organ failure and the absence of local or systemic complications. In addition, the current study also enrolled 50 healthy controls whose age and gender were matched with recruited AP patients, between April 2019 and May 2019. The general healthy status of healthy controls was confirmed by the physical examination, and all of them had no history of pancreatic-related diseases. The present study was approved by the Ethics Committee of our hospital, and all subjects provided the written informed consents.

Data collection

Demographic information including age and gender of all AP patients were documented on their recruitment. Also, the etiology, the C-reaction protein (CRP) served as inflammatory level markers, the Ranson score evaluated within 48 hours, the APACHE II score assessed within 24 hours, and the sequential organ failure assessment (SOFA) score assessed within 24 hours were recorded after patients were admitted to the hospital. And the etiology-based treatment and conventional treatment were administered to AP patients according to the IAP/APA evidence-based guidelines of for the management of acute pancreatitis [13]. Moreover, all AP patients were followed up closely until they died in the hospital or were discharged from the hospital, during which, there were 10 deaths among SAP patients, 3 deaths

among MSAP patients, and no one died among MAP patients. Accordingly, SAP patients were further analyzed by being categorized as SAP survivors and SAP deaths. Besides, demographic characteristics (age and gender) of healthy controls were also collected on their enrollment.

Blood sample collection and measurement

Venous blood samples of AP patients were collected into vacuum tubes within 24 hours after admission to the hospital. After collection, the serum was isolated from the blood samples through centrifugation at 3000 rpm for 5 min, subsequently, the serum JKAP level was measured by the enzyme-linked immunosorbent assay (ELISA) using the Human JKAP ELISA Kit (Shanghai Enzyme-linked Biotechnology Co., Ltd, Shanghai, China), and all experiments were performed according to the protocols provided by the manufacturers. In addition, the blood samples of healthy controls were also collected on their enrolment, and the process of serum isolation and JKAP measurement were performed as same as that in AP patients.

Statistical analysis

Normality was checked for all continuous variables using Shapiro-Wilk test, and the continuous variables were described as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) if non-normally distributed. Categorical variables were displayed as count (percentage). For the normally distributed continuous variables, comparison among groups was determined by the one-way analysis of variance (ANOVA) or Student's t test; as for non-normally distributed continuous variables, comparison among groups was determined by Kruskal-Wallis H rank sum test or Wilcoxon rank sum test. With respect to the multiple comparison of continuous variables, it was determined by the Dunn's multiple comparisons test. Comparison of categorical variables among groups was determined by the Chi-square test. Correlation between continuous variables was analyzed by the Spearman's rank correlation test. The performance of continuous variables in identifying different subjects was analyzed by the receiver-operating characteristic (ROC) curve and the area under the ROC curve (AUC) with 95% confidence interval (CI). P value <0.05 was considered statistically significant. All statistical analyses were performed in SPSS software version 20.0 (IBM Corporation, Armonk, NY, USA), and all graphics were plotted by the GraphPad Prism software version 7.02 (GraphPad Software Inc., San Diego, CA, USA).

Results

Baseline characteristics

There were 50 healthy controls, 50 MAP patients, 50 MSAP patients and 50 SAP patients enrolled in our study (*Table 1*). The mean age was 58.9 ± 13.4 years in health controls, 59.5 ± 12.6 years in MAP patients, 58.4 ± 12.5 years in MSAP patients and 59.6 ± 13.2 years in SAP patients. Regarding gender, there were 27

(54.0%) males and 23 (46.0%) females in health controls, 29 (58.0%) males and 21 (42.0%) females in MAP patients, 34 (68.0%) males and 16 (32.0%) females in MSAP patients, 33 (66.0%) males and 17 (34.0%) females in SAP patients. No difference of age ($P = 0.963$) or gender ($P = 0.429$) was observed among healthy controls, MAP, MSAP and SAP patients. Among all AP patients, three-group comparison analysis showed that median CRP level ($P < 0.001$), median Ranson score ($P < 0.001$), median APACHE II score ($P < 0.001$) and median SOFA score ($P < 0.001$) were different, which were all highest in SAP patients, followed by MSAP patients, and then MAP patients. While etiology ($P = 0.171$) was of no difference among MAP, MSAP and SAP patients. The detailed characteristics of all participants were shown in *Table 1*.

Comparison of JKAP level among healthy controls, MAP, MSAP and SAP patients

The median level of JKAP was lower in SAP patients (7.523 (4.584–11.570) pg/mL) than that in MSAP patients (13.606 (7.849–18.900) pg/mL) ($P = 0.012$), MAP patients (18.724 (13.060–24.374) pg/mL) ($P < 0.001$), and healthy controls (46.323 (21.246–66.725) pg/mL) ($P < 0.001$) (*Figure 1*). These suggested that the downregulation of JKAP was associated with increased SAP risk.

Predictive value of JKAP for SAP risk

ROC curve analysis exhibited that JKAP was with an acceptable value in distinguishing SAP patients from MSAP patients (AUC: 0.712, 95%CI: 0.610–0.813) (*Figure 2A*). More notably, JKAP was of a good value in differentiating SAP patients from MAP patients (AUC: 0.869, 95%CI: 0.802–0.937) (*Figure 2B*) and healthy controls (AUC: 0.914, 95%CI: 0.857–0.971) (*Figure 2C*). Additionally, JKAP could differentiate MSAP patients from MAP patients (*Figure 2D*), MSAP patients from healthy controls (*Figure 2E*), MAP patients from healthy controls (*Figure 2F*) as well. These data implied that JKAP could not only differentiate SAP patients from health controls, but also distinguish SAP patients from MAP and MSAP patients.

Correlation of JKAP with Ranson score, APACHE II score, SOFA score and CRP in SAP patients

In SAP patients, the level of JKAP was negatively associated with Ranson score ($P < 0.001$, $r = -0.549$) (*Figure 3A*), APACHE II score ($P = 0.007$, $r = -0.376$) (*Figure 3B*), SOFA score ($P < 0.001$, $r = -0.594$) (*Figure 3C*) and CRP ($P < 0.001$, $r = -0.527$) (*Figure 3D*), which suggested that JKAP was negatively correlated with disease severity and inflammation in SAP patients.

Comparison of patients' characteristics between survivors and deaths in SAP patients

SAP patients were further divided into SAP survivors (N = 40) and SAP deaths (N = 10) based on the in-hospital medical records. SAP deaths exhibited lower median JKAP ($P = 0.032$), higher median CRP ($P = 0.032$), median Ranson score ($P < 0.001$), median APACHE II score ($P = 0.005$) and median SOFA score ($P = 0.010$) compared with SAP survivors (*Table 2*). Furthermore, there was no difference of mean age ($P = 0.589$), gender ($P = 0.756$) or etiology ($P = 0.171$) between SAP survivors and SAP deaths. These disclosed that lower median JKAP, higher inflammation and disease severity scores were associated with increased in-hospital mortality in SAP patients.

Predictive value of JKAP for in-hospital mortality in SAP patients

ROC curve analysis displayed that JKAP was of an acceptable value in differentiating SAP survivors from SAP deaths (AUC: 0.720, 95%CI: 0.526–0.914) (*Figure 4*). Regarding commonly used assessing score systems and inflammation marker, Ranson score was of a good value in distinguishing SAP survivors from SAP deaths (AUC: 0.886, 95%CI: 0.756–1.000). And APACHE II score (AUC: 0.783, 95%CI: 0.607–0.914), SOFA score (AUC: 0.761, 95%CI: 0.600–0.923) and CRP (AUC: 0.720, 95%CI: 0.522–0.920) were with a fair value in differentiating SAP survivors from SAP deaths. By comparison, the predictive value of JKAP for in-hospital mortality was similar with that of APACHE II score, SOFA score and CRP numerically, while was inferior to that of Ranson score. These data suggested that JKAP level was of an acceptable value for predicting decreased in-hospital mortality in SAP patients.

Discussion

In this study, we discovered that: (1) JKAP could not only differentiate SAP patients from health controls, but also distinguish SAP patients from MAP and MSAP patients. (2) JKAP level was negatively correlated with disease severity and inflammation in SAP patients. (3) JKAP was with an acceptable value in predicting decreased in-hospital mortality in SAP patients.

SAP is a serious and often lethal disorder with complex pathophysiology, in which autoimmune responses and inflammation are the major contributors [14]. The deterioration of SAP occurs rapidly within a few hours or days after the onset of symptoms [5]. It starts with systemic inflammatory response through mediating the release of proinflammatory mediators, resulting in pulmonary, cardiovascular and renal insufficiency [15–17]. And the late deterioration of organ dysfunction or failure mainly results from secondary infection of pancreatic or peripancreatic necrosis [18]. Thus, it is important to investigate new biomarkers for determining the SAP risk and severity as well as forecasting the mortality of SAP patients.

JKAP is a member of the DUSPs family, which specifically mediates the JNK pathway and subsequent cytokine-induced JNK activation [19]. Besides, JKAP also inhibits T-cell receptor signaling through inactivating Lck, resulting in suppression of T-cell-mediated immunity and autoimmunity [8, 9]. Previous studies have revealed that the downregulation of JKAP is involved in the development and progression of

several autoimmune and inflammatory diseases such as SLE and sepsis [10, 11]. For instance, JKAP expression in peripheral blood T cells is lower in SLE patients than that in health volunteers, and the downregulation of JKAP expression in T cells is associated with higher daily urinary protein amounts and poor renal outcomes in SLE patients [10]. Another study illuminates that the serum JKAP is downregulated in sepsis patients compared with healthy volunteers, and the downregulation of JKAP is correlated with advanced disease severity (APACHE II score and SOFA score) and systemic inflammation (CRP, PCT, TNF- α , IL-1 β , IL-6 and IL-17) in sepsis patients [11]. Considering that SAP is an extremely severe immune and inflammatory disease, we hypothesized that JKAP might be dysregulated and play an important role in the pathogenesis of SAP. Our study displayed that JKAP could well distinguish SAP patients from healthy controls (AUC: 0.914, 95%CI: 0.857–0.971). Besides, JKAP could to some extent tell SAP patients from MAP patients (AUC: 0.869, 95%CI: 0.802–0.937) and MSAP patients (AUC: 0.712, 95%CI: 0.610–0.813). This provided evidence for JKAP as a unique predicting factor for SAP risk. The possible reasons were as follow: (1) The downregulation of JKAP promoted the expression of pro-inflammatory cytokines and activated inflammation, thus, contributed to the development of SAP. (2) The downregulation of JKAP facilitated the T-cell receptor immunity and autoimmunity through the activation of T-cell receptor signaling, thus, resulted in the elevate SAP risk. (3) The downregulation of JKAP might cause organ injuries and accelerate multiple organ dysfunction or failure, thus, led to higher SAP risk. However, the mechanism of JKAP in causing and accelerating organ injury needed further exploration. Furthermore, our study revealed that JKAP level was negatively associated with disease severity (Ranson score, APACHE II score and SOFA score) and inflammation (CRP level) in SAP patients. The results might be explained by: (1) Decreased JKAP level promoted immune and inflammatory responses via mediating the activation of T-cell receptor signaling and the release of inflammatory cytokines, resulting in higher inflammation and advanced disease severity in SAP patients. (2) Lower JKAP level might result in the necrosis of several organs and subsequent multiple organ dysfunction via its downstream pathway, thus, contributing to higher disease severity in SAP patients.

Previous studies have elucidated that downregulation of JKAP is associated with poor prognosis in IBD and sepsis [9, 11]. For example, low JKAP level predicts active status of Crohn's disease and ulcerative colitis [9]. Another study reports that JKAP presents a good value in differentiating deaths from survivors in sepsis patients [11]. However, no study reports the association of JKAP level with prognosis in SAP patients. Our study exhibited that JKAP level was of an acceptable value in predicting decreased in-hospital mortality (AUC: 0.720, 95%CI: 0.526–0.914) in SAP patients. These results might be explained by that: (1) JKAP inhibited immune and autoimmune response, subsequently suppressed inflammatory responses and decreased SAP severity, thus, led to lower in-hospital mortality in SAP patients. (2) Higher JKAP level was correlated with lower SOFA score (decreased severity of organ dysfunction) and CRP level (decreased inflammation, immune response and disease severity), thus, contributed to lower in-hospital mortality in SAP patients. Additionally, we also observed that the predictive value of JKAP for in-hospital mortality was similar compared with APACHE II score, SOFA score and CRP, while inferior compared with Ranson score. These suggested that JKAP might serve as an additional biomarker to assist commonly applied multi-factorial scoring systems for predicting prognosis in SAP patients.

There were some limitations in our study: (1) The sample size was relatively small, which might reduce the statistical power. (2) The mortality of all SAP patients was only measured during their hospitalization, thus, the long-term predictive value of JKAP for prognosis needed to be further studied. (3) The detailed mechanism of JKAP in regulating the development and progression of SAP was not explored, thus, further experiments in investigating the detailed mechanism of JKAP in SAP should be carried out in the future.

Conclusions

In conclusion, the downregulation of JKAP level is correlated with increased risk, disease severity, inflammation and in-hospital mortality of SAP, which implies that JKAP exhibits the potential as a biomarker for disease monitoring and prognosis in SAP patients.

Abbreviations

AP: Acute pancreatitis; MAP: mild AP; SAP: severe AP; APACHE II: acute physiology and chronic health evaluation II; DUSP: dual-specificity phosphates; IBD: inflammatory bowel disease; SLE: systemic lupus erythematosus; CRP: C-reaction protein; SOFA: sequential organ failure assessment; ELISA: enzyme-linked immunosorbent assay; SD: standard deviation; IQR: interquartile range; ANOVA: one-way analysis of variance; ROC: receiver-operating characteristic; AUC: Area Under The Curve; CI: confidence interval.

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Ethics approval and consent to participate

The present study was approved by the Ethics Committee of our hospital, and all subjects provided the written informed consents.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JL and MM designed and coordinated the study, made substantial contributions to the analysis, and drafted the manuscript. YH performed statistical analysis. JL and MM participated in data collection and interpretation. JL and MM helped to draft the manuscript. YH reviewed the manuscript and exerted a major impact on the interpretation of data and critical appraisal of the manuscript. All authors have read and approved the final manuscript.

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References

- 1.Lee PJ, Papachristou GI. New insights into acute pancreatitis. *Nat Rev Gastroenterol Hepatol*. 2019.
- 2.Wang D, Tang M, Zong P, Liu H, Zhang T, Liu Y *et al*. MiRNA-155 Regulates the Th17/Treg Ratio by Targeting SOCS1 in Severe Acute Pancreatitis. *Front Physiol*. 2018; 9:686.
- 3.Lupia E, Pigozzi L, Pivetta E, Bosco O, Vizio B, Loiacono M *et al*. Thrombopoietin as Early Biomarker of Disease Severity in Patients With Acute Pancreatitis. *Pancreas*. 2017; 46:164–9.
- 4.Brisinda G, Vanella S, Crocco A, Mazzari A, Tomaiuolo P, Santullo F *et al*. Severe acute pancreatitis: advances and insights in assessment of severity and management. *Eur J Gastroenterol Hepatol*. 2011; 23:541–51.
- 5.Werner J, Feuerbach S, Uhl W, Buchler MW. Management of acute pancreatitis: from surgery to interventional intensive care. *Gut*. 2005; 54:426–36.
- 6.Cho JH, Kim TN, Chung HH, Kim KH. Comparison of scoring systems in predicting the severity of acute pancreatitis. *World J Gastroenterol*. 2015; 21:2387–94.
- 7.Harshit Kumar A, Singh Griwan M. A comparison of APACHE II, BISAP, Ranson's score and modified CTSI in predicting the severity of acute pancreatitis based on the 2012 revised Atlanta Classification. *Gastroenterol Rep (Oxf)*. 2018; 6:127–31.
- 8.Li JP, Yang CY, Chuang HC, Lan JL, Chen DY, Chen YM *et al*. The phosphatase JKAP/DUSP22 inhibits T-cell receptor signalling and autoimmunity by inactivating Lck. *Nat Commun*. 2014; 5:3618.

- 9.Zhou R, Chang Y, Liu J, Chen M, Wang H, Huang M *et al*. JNK Pathway-Associated Phosphatase/DUSP22 Suppresses CD4(+) T-Cell Activation and Th1/Th17-Cell Differentiation and Negatively Correlates with Clinical Activity in Inflammatory Bowel Disease. *Front Immunol*. 2017; 8:781.
- 10.Chuang HC, Chen YM, Hung WT, Li JP, Chen DY, Lan JL *et al*. Downregulation of the phosphatase JKAP/DUSP22 in T cells as a potential new biomarker of systemic lupus erythematosus nephritis. *Oncotarget*. 2016; 7:57593–605.
- 11.Zhao M, Huang X. Downregulation of JKAP is correlated with elevated disease risk, advanced disease severity, higher inflammation, and poor survival in sepsis. *J Clin Lab Anal*. 2019:e22945.
- 12.Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG *et al*. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013; 62:102–11.
- 13.Working Group IAPAAPAG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology*. 2013; 13:e1–15.
- 14.Dai SR, Li Z, Zhang JB. Serum interleukin 17 as an early prognostic biomarker of severe acute pancreatitis receiving continuous blood purification. *Int J Artif Organs*. 2015; 38:192–8.
- 15.Johnson CD, Kingsnorth AN, Imrie CW, McMahon MJ, Neoptolemos JP, McKay C *et al*. Double blind, randomised, placebo controlled study of a platelet activating factor antagonist, lexipafant, in the treatment and prevention of organ failure in predicted severe acute pancreatitis. *Gut*. 2001; 48:62–9.
- 16.Norman J. The role of cytokines in the pathogenesis of acute pancreatitis. *Am J Surg*. 1998; 175:76–83.
- 17.Werner J, Z'Graggen K, Fernandez-del Castillo C, Lewandrowski KB, Compton CC, Warshaw AL. Specific therapy for local and systemic complications of acute pancreatitis with monoclonal antibodies against ICAM–1. *Ann Surg*. 1999; 229:834–40; discussion 41–2.
- 18.Beger HG, Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis. A prospective clinical study. *Gastroenterology*. 1986; 91:433–8.
- 19.Chen AJ, Zhou G, Juan T, Colicos SM, Cannon JP, Cabrera-Hansen M *et al*. The dual specificity JKAP specifically activates the c-Jun N-terminal kinase pathway. *J Biol Chem*. 2002; 277:36592–601.

Tables

Table 1. Characteristics of subjects

Characteristics	Healthy controls	MAP patients	MSAP patients	SAP patients	<i>P</i> value
No. of subjects	50	50	50	50	
Age (years), mean±SD	58.9±13.4	59.5±12.6	58.4±12.5	59.6±13.2	0.963
Gender, No. (%)					0.429
Male	27 (54.0)	29 (58.0)	34 (68.0)	33 (66.0)	
Female	23 (46.0)	21 (42.0)	16 (32.0)	17 (34.0)	
Etiology, No. (%)					0.171
BAP	-	20 (40.0)	24 (48.0)	30 (60.0)	
AAP	-	2 (4.0)	4 (8.0)	5 (10.0)	
HTGAP	-	21 (42.0)	19 (38.0)	10 (20.0)	
Others	-	7 (14.0)	3 (6.0)	5 (10.0)	
CRP (mg/L), median (IQR)	-	33.7 (23.8-51.5)	95.3 (68.7-122.3)	129.8 (94.8-164.9)	<0.001
Ranson score, median (IQR)	-	1.0 (1.0-1.0)	2.0 (1.0-2.0)	3.0 (3.0-4.0)	<0.001
APACHE II score, median (IQR)	-	4.0 (3.0-5.0)	7.0 (4.0-9.3)	13.5 (8.0-18.0)	<0.001
SOFA score, median (IQR)	-	2.0 (2.0-2.0)	4.0 (3.0-5.3)	7.0 (5.0-8.0)	<0.001

Comparison was determined by one-way analysis of variance (ANOVA), Chi-square test or Kruskal-Wallis H rank sum test. SAP, severe acute pancreatitis; MSAP, moderate-severe acute pancreatitis; MAP, mild acute pancreatitis; SD, standard deviation; BAP, biliary acute pancreatitis; AAP, alcohol-induced acute pancreatitis, HTGAP, hypertriglycemic acute pancreatitis; CRP, C-reaction protein; IQR, interquartile range; APACHE II, Acute Physiology and Chronic Health Care Evaluation II; SOFA, sequential organ failure assessment.

Table 2. Comparison of characteristics between SAP survivors and SAP deaths

Characteristics	SAP survivors	SAP deaths	<i>P</i> value
No. of subjects	40	10	
JKAP (pg/mL), median (IQR)	8.1 (5.0-11.6)	4.6 (2.1-9.5)	0.032
Age (years), mean±SD	60.2±12.8	57.6±15.2	0.589
Gender, No. (%)			0.756
Male	26 (65.0)	7 (70.0)	
Female	14 (35.0)	3 (30.0)	
Etiology, No. (%)			0.171
BAP	22 (55.0)	8 (80.0)	
AAP	5 (12.5)	0 (0.0)	
HTGAP	10 (25.0)	0 (0.0)	
Others	3 (7.5)	2 (20.0)	
CRP (mg/L), median (IQR)	128.6 (89.2-161.0)	216.4 (105.2-305.9)	0.032
Ranson score, median (IQR)	3.0 (3.0-3.8)	5.0 (4.0-5.3)	<0.001
APACHE II score, median (IQR)	11.0 (8.0-15.8)	17.0 (13.7-20.7)	0.005
SOFA score, median (IQR)	6.0 (4.0-7.0)	7.5 (6.7-9.2)	0.010

Comparison was determined by Wilcoxon rank sum test, Student's *t* test, or Chi-square test.

SAP = severe acute pancreatitis, MSAP, moderate-severe acute pancreatitis; MAP, mild acute pancreatitis; IQR, interquartile range; SD, standard deviation; BAP, biliary acute pancreatitis; AAP, alcohol-induced acute pancreatitis; HTGAP, hypertriglycemic acute pancreatitis; CRP, C-reaction protein; APACHE II, Acute Physiology and Chronic Health Care Evaluation II; SOFA, sequential organ failure assessment.

Figures

Figure 1

The level of JKAP in healthy controls, MAP, MSAP and SAP patients. The level of JKAP in healthy controls, MAP, MSAP and SAP patients. Comparison of JKAP level was assessed by Dunn's multiple comparisons test. $P < 0.05$ was considered significant. JKAP, JNK pathway-associated phosphatase; MAP, mild acute pancreatitis; MSAP, moderate-severe acute pancreatitis; SAP, severe acute pancreatitis.

Figure 2

ROC curve analysis of JKAP for predicting SAP risk. The ability of JKAP in differentiating SAP patients from MSAP patients (A), SAP patients from MAP patients (B), SAP patients from healthy controls (C), MSAP patients from MAP patients (D), MSAP patients from healthy controls (E) and MAP patients from healthy controls (F). The performance of JKAP in identifying different subjects was analyzed by ROC curve and AUC with 95% CI. ROC, receiver operating characteristic; JKAP, JNK pathway-associated phosphatase; SAP, severe acute pancreatitis; MSAP, moderate-severe acute pancreatitis; MAP, mild acute pancreatitis; AUC, area under the curve; CI, confidence interval.

Figure 3

Negative association of JKAP level with disease severity and inflammation in SAP patients. The association of JKAP level with Ranson score (A), APACHE II score (B), SOFA score (C) and CRP (D) in SAP patients. The association of JKAP level with Ranson score, APACHE II score, SOFA score and CRP was analyzed by the Spearman's rank correlation test. $P < 0.05$ was considered significant. JKAP, JNK pathway-associated phosphatase; SAP, severe acute pancreatitis; APACHE II score, acute physiology and chronic health evaluation II score; SOFA score, sequential organ failure assessment score; CRP, C-reactive protein.

Figure 4

ROC curve analysis of JKAP, Ranson score, APACHE II score, SOFA score and CRP for predicting in-hospital mortality. The ability of JKAP, Ranson score, APACHE II score, SOFA score and CRP in differentiating survivors from deaths in SAP patients. The performance of JKAP, Ranson score, APACHE II score, SOFA score and CRP in predicting in-hospital mortality was evaluated by ROC curve and AUC with 95% CI. ROC, receiver operating characteristic; JKAP, JNK pathway-associated phosphatase; APACHE II score, acute physiology and chronic health evaluation II score; SOFA score, sequential organ failure

assessment score; CRP, C-reactive protein; SAP, severe acute pancreatitis; AUC, area under the curve; CI, confidence interval.