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CLINICAL TRIAL REPORT

Circulating Protectin D1 and Neutrophils Extracellular Traps in the Diagnosis and Progression of Acute Pancreatitis

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Purpose: Protectin D1 (PD1), a biologically active molecule derived from docosahexaenoic acid (DHA), plays a major role in the body's endogenous lipid-mediated inflammatory response. The study aims to explore the relationship between PD1, inflammatory response and the severity of acute pancreatitis (AP).

Patients and Methods: Sixty consecutive AP patients within 72h of disease onset were enrolled as the study group, a further thirty healthy people were enrolled as the control group. General demographics collected at the time of enrollment. Serum PD1, Citrullinated Histone 3 (CitH3), myeloperoxidase-Deoxyribonucleic acid (MPO-DNA), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) level were measured in AP patients on enrollment day 0, day 1, day 3 and day 7. Meanwhile, the Acute Physiology and Chronic Health evaluation II (APACHE II) scores, Sequential Organ Failure Assessment (SOFA) scores were also evaluated on day 0, day 1, day 3 and day 7.

Results: AP was severe in 29 patients (48.3%), moderately severe acute pancreatitis (MSAP) was found in 9 patients (15%), and mild acute pancreatitis (MAP) was found in 22 patients (36.7%). The level of PD1, CitH3 and MPO-DNA were statistically significantly higher in AP patients than in the healthy population. Serum PD1, CitH3 and MPO-DNA concentration increased with AP severity. In AP patients, PD1 has a strong linear association with TNF-α, CitH3 and MPO-DNA. The AUC for SAP predicted by PD1 was 0.938. The calculated cut-off point for prognosis SAP is 7.94 pg/mL. The AUC for infected pancreatic necrosis (IPN) predicted by PD1 was 0.836 and the cut-off point was 8.65 pg/mL. The AUC for organ failure (OF) predicted by PD1 was 0.719 and the cut-off point was 7.94 pg/mL.

Conclusion: PD1 is associated with both the presence of AP and the severity of pancreatitis.

Keywords: PD1, acute pancreatitis, CitH3, MPO-DNA, infected pancreatic necrosis, organ failure

Introduction

Acute pancreatitis (AP) is an inflammatory disease of the pancreas, the leading cause of hospitalization for gastrointestinal disorders.[1] It is characterized by the activation of digestive enzymes within the acinar cells, leading to a subsequent inflammatory response. The course of AP is variable and complex, and is often unpredictable in the early stages of the disease. Approximately 80% of patients develop mild to moderately severe disease (organ failure not exceeding 48 hours) which runs a self-limiting course.[2] Nevertheless, one in five patients are severely ill, with a mortality rate of approximately 20%.[2] Despite improvements in access to care, imaging and interventional techniques, AP

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continues to be associated with significant morbidity and mortality.[3] The search for early prediction and diagnosis of AP severity, infected pancreatic necrosis (IPN) and organ failure (OF) through the exploration of bioindicators is of paramount importance in determining further treatment and prognosis.[4]

Protective protectin D1 (PD1) is a biologically active product derived from docosahexaenoic acid,[5] which has been demonstrated to exert anti-inflammatory effects in a range of diseases, including acute kidney injury and neurodegenerative disorders.[6,7] It modulates the innate immune response and stimulates resolution. Our previous study on animals also demonstrated that exogenous supplementation PD1 ameliorated AP by reducing the early infiltration of neutrophils into the pancreas and the formation of neutrophil extracellular traps (NETs).[8]

The aim of this study was to examine the potential correlation between PD1, circulating indicators of NETs formation and disease severity in the acute phase of AP. Furthermore, we also attempted to see whether PD1 can predict the severity of AP and the occurrence of IPN and OF.

Materials and Methods

Study Population

A total of 60 adult patients diagnosed with SAP were admitted to Qilu Hospital, Qingdao, China. The study population consisted of individuals who experienced abdominal pain between November 2023 and March 2024 and were enrolled within 72 hours of the onset of symptoms. The study was approved by the Ethics Committee of the Qilu Hospital and registered with Chictr.cn (identifier ChiCTR2400085321) and adhered to ethical principles outlined in the Helsinki Declaration. Informed consent was obtained from the patients or their next of kin before enrollment. The diagnostic criteria for AP were defined in accordance with the Atlantic criteria.[9] Patients with one or more of the following conditions were excluded from the study: (1) chronic pancreatitis, (2) pre-existing OF, (3) prior surgical intervention, (4) malignant tumor. All patients received standard treatment for AP.[10]

Definitions

The diagnosis of AP[9] requires the presence of two or more of the following three features: (1) abdominal pain consistent with AP (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of AP on contrast-enhanced computer tomography and in less common cases, magnetic resonance imaging or transabdominal ultrasonography may be employed.[11] Infection may be suspected if percutaneous image-guided fine-needle aspiration, gram stains and cultures are positive for bacteria and/or fungi. IPN may be associated with variable amounts of septicemia (pus), which increases with liquefaction over time.[11] IPN includes acute necrotic collection and walled-off necrosis. Acute necrotic collection occurs early in the course of the disease and is characterized by an accumulation of mixed fluid and necrotic tissue. Walled-off necrosis is a solid cystic structure containing pancreatic and/or peripancreatic necrotic tissue with a well-defined inflammatory envelope.[3] OF was defined using the modified Marshall scoring system, and OF was defined as a score of 2 or more for any of these three organ systems.[12]

Mild acute pancreatitis (MAP) is defined by the absence of OF and the absence of local or systemic complications.[13] Moderately severe acute pancreatitis (MSAP) is defined by the presence of transient OF (within 48h) or local or systemic complications.[14] Severe acute pancreatitis (SAP) is defined by the persistence of OF for a period exceeding 48h.[15]

Laboratory Assessments

Blood samples were obtained on admission, day 1, day 3 and day 7. Levels of amylase were uniformly measured by department of clinical laboratory in the hospital. Blood samples were immediately centrifuged and stored at −80° Celsius. Serum PD1, citrullinated Histone 3 (CitH3), myeloperoxidase-Deoxyribonucleic acid (MPO-DNA), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) levels were measured by using commercially available Human ELISA Kits. The sensitivity by the kit is 0.1ng/mL and variation range less than 15%. All ELISA kits were purchased from FANKEW (Shanghai, China).

Clinical Data Collection

Demographic information and clinical relevant data of the patients were duly recorded. The Acute Physiology and Chronic Health evaluation II (APACHE II) scores and Sequential Organ Failure Assessment (SOFA) scores were collected at admission, day 1, day 3 and day 7. Systemic inflammatory response syndrome (SIRS) scores and computed tomography (CT) scores were assessed only at admission.

Statistical Analysis

Data were presented with a description of the median and interquartile range (25^{th} to 75^{th} percentiles). Descriptive data was presented as an absolute number or a percentage number. Continuous variables were tested for normality or lognormality, and the S-*W* test results were viewed and the normal QQ plot was drawn to determine whether the distribution was normal. Differences between groups were analyzed by one-way ANOVA for normally distributed, variance-aligned, independent data. The Kruskal–Wallis rank sum test was used for non-normally distributed data. Serum parameters over time in different subgroups were compared using repeated measures ANOVA. Correlation analyses between PD1 and other indicators employed either Pearson or Spearman tests, depending on the characteristics of the data. The comparison of the efficacy of the prediction of AP severity, IPN and OF was calculated by the area under the receiver operating characteristic curve (ROC). A p value beneath 0.05 was deemed to be statistically significant. All data were analyzed with SPSS version 27.0 and GraphPad Prism version 8.0.

Results

Characteristics of Patients

A total of 60 patients with AP were included in the study. AP was mild in 22 patients (36.7%); moderate in 9 patients (15%) and severe in 29 patients (48.3%). The etiology of pancreatitis was biliary in 24 patients (40%), hyperlipidemic in 22 patients (36.7%), alcoholic in 2 patients (3.3%) and due to other causes in 12 patients (20%). Of 60 enrolled patients, 5 patients (8.3%) developed IPN, 4 patients (6.7%) developed OF (Table 1).

PD1, CitH3 and MPO-DNA Level in Prediction of AP Incidence

On admission, the levels of PD1, CitH3 and MPO-DNA in the AP group were significantly higher than non-AP group ($p<0.0001$). The median PD1, CitH3, MPO-DNA level was 8.38 pg/mL, 12.73 pg/mL, 65.31 pg/mL in AP patients and 0.99 pg/mL, 0.77 pg/mL, 6.01 pg/mL in non-AP patients (Figure 1).

PD1, CitH3 and MPO-DNA Level in Prediction of AP Severity

Serum PD1 concentration values on admission were compared between MAP, MSAP and SAP, with concentrations of PD1 4.01 ± 0.9 pg/mL, 7.83 ± 2.25 pg/mL, and 11.83 ± 3.74 pg/mL. These differences were statistically significant ($p<0.01$). Concentrations of CitH3 on admission of MAP, MSAP and SAP were 6.81 ± 1.38 pg/mL, 11.53 ± 1.88 pg/mL and 17.59 ± 7.95 pg/mL ($p<0.01$). MPO-DNA values of these three subgroups on admission were 27.26 ± 8.14 pg/mL, 74.43 ± 25.95 pg/mL and 91.35 ± 29.34 pg/mL ($p<0.01$) (Figure 2). Overall, serum PD1, CitH3 and MPO-DNA values increased with AP severity.

Predictive Value of PD1 in SAP, IPN and OF

The optimal PD1 concentration threshold to distinguish SAP from MAP and MSAP was determined by creating a ROC curve. PD1 had a higher value in the prediction of SAP compared to APACHE II score and SOFA score. The cut-off value, sensitivity and specificity were shown in Table 2.

We further evaluated the ability of serum PD1 levels to predict IPN. Serum PD1 had the higher AUC of 0.836 compared with APACHE II score and SOFA score in the setting of IPN and non-IPN. For prediction of OF, the AUC was 0.719 for serum PD1, 0.824 for APACHE II score and 0.868 for SOFA score as shown in Figure 3c. PD1 is less valuable than APAPCHE II score in predicting OF.

Table 1 Characteristics of Patients with AP Included in the Study

Variable	All Patients N=60
Age (median age: IQR)	54.5 (37–67.75)
Gender (Male/female)	32/28
Body mass index, kg/m^2	26.8
MAP (n, %)	22 (36.7%)
MSAP (n, %)	9 (15%)
SAP (n, %)	29 (48.3%)
Etiology (% of total)	
Gallstones	24 (40%)
Hyperlipidemia	22 (36.7%)
Alcohol	2 (3.3%)
Other causes	12 (20%)
WBC (×10^9/L)	12.1 (9.31–14.7)
Amylase (U/L)	631.1
SOFA score	2 (0–3)
APACHE II score	7 (4–9)
IPN	5 (8.3%)
OF	4 (6.7%)
CT score	4 (2–4)
Length of hospital stay	11 (7–64)
Mortality	1 (0.02%)

Abbreviations: AP, acute pancreatitis; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; WBC, white blood cell; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; IPN, infected pancreatic necrosis; OF, organ failure; CT, computed tomography.

Change of PD1, CitH3 and MPO-DNA Within the First Week of Hospital Admission

Serum concentrations of PD1, CitH3 and MPO-DNA changes over time (Table 3). All these indexes were markedly elevated in SAP patients relative to non-SAP patients at various time points. There was a decline in serum PD1 levels in both non-SAP and SAP patients when compared to those at the time of admission. A statistically significant difference

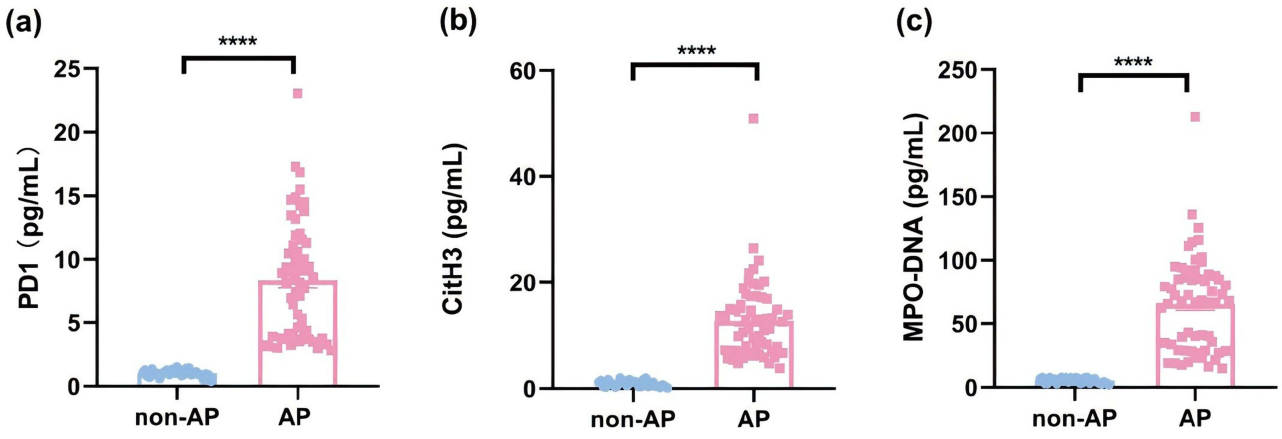

Figure 1 Comparison of serum PD1, CitH3, MPO-DNA levels in non-AP and AP patients. (**a**) Serum PD1 levels. (**b**) Serum CitH3 levels. (**c**) Serum MPO-DNA levels. AP, Acute pancreatitis. ****p<0.0001.

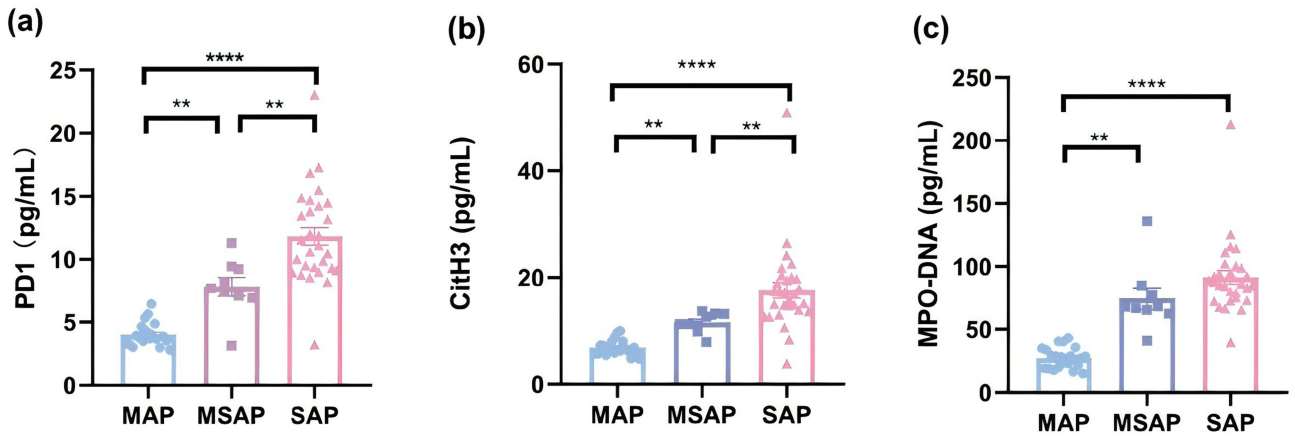

Figure 2 Comparison of serum PD1, CitH3, MPO-DNA levels in patients with different AP severities at admission. (**a**) Serum PD1 levels in different groups. (**b**) Serum CitH3 levels in different groups. (**c**) Serum MPO-DNA levels in different groups. MAP, mild acute pancreatitis, MSAP, moderate severe acute pancreatitis, SAP, severe acute pancreatitis. ****$p<0.0001$, **$p<0.01$.

was observed in serum PD1 levels between day 7 and day 0 ($p<0.01$). Serum levels of PD-1, CitH3 and MPO-DNA remained consistently high in patients with OF.

Correlation Analysis Between PD1 and Inflammation/Disease Severity-Related Parameters

The correlation results showed that on the first after admission, there were positive relativity the levels of PD1 and CitH3 (r = 0.7818, $p<0.0001$), MPO-DNA (r = 0.7655, $p<0.0001$), TNF-α (r = 0.8222, $p<0.0001$) and IL-6 (r = 0.7851, $p<0.0001$). Therefore, there is a strong correlation between PD1 and the indexes of NETS formation and the level of inflammatory factors.

The correlation results also showed positive relativity the levels of PD1 and APACHE II scores (r = 0.3518, $p<0.01$), SOFA scores (r = 0.3520, $p<0.01$), CT scores (r = 0.4029, $p<0.01$) and SIRS scores (r = 0.3280, $p<0.05$) (Figure 4).

Table 2 Values of PD1, APACHE II Score and SOFA Score in the Prediction of SAP, IPN and OF

SAP	**Cut-off value**	**Sensitivity (%)**	**Specificity (%)**
PD1	7.94 pg/mL	96.6	87.1
APACHE II	5.5	72.4	48.4
SOFA	1.5	86.2	61.3
IPN	**Cut-off value**	**Sensitivity (%)**	**Specificity (%)**
PD1	8.65 pg/mL	100	56.4
APACHE II	8.5	80	67.3
SOFA	4.5	40	90.9
OF	**Cut-off value**	**Sensitivity (%)**	**Specificity (%)**
PD1	7.94 pg/mL	100	50
APACHE II	8.5	100	67.9
SOFA	2.5	100	66.1

Abbreviations: PD1, protectin D1; SAP, severe acute pancreatitis; SOFA, sequential organ failure assessment; APACHE II, acute physiology and chronic health evaluation II; IPN, infected pancreatic necrosis; OF, organ failure.

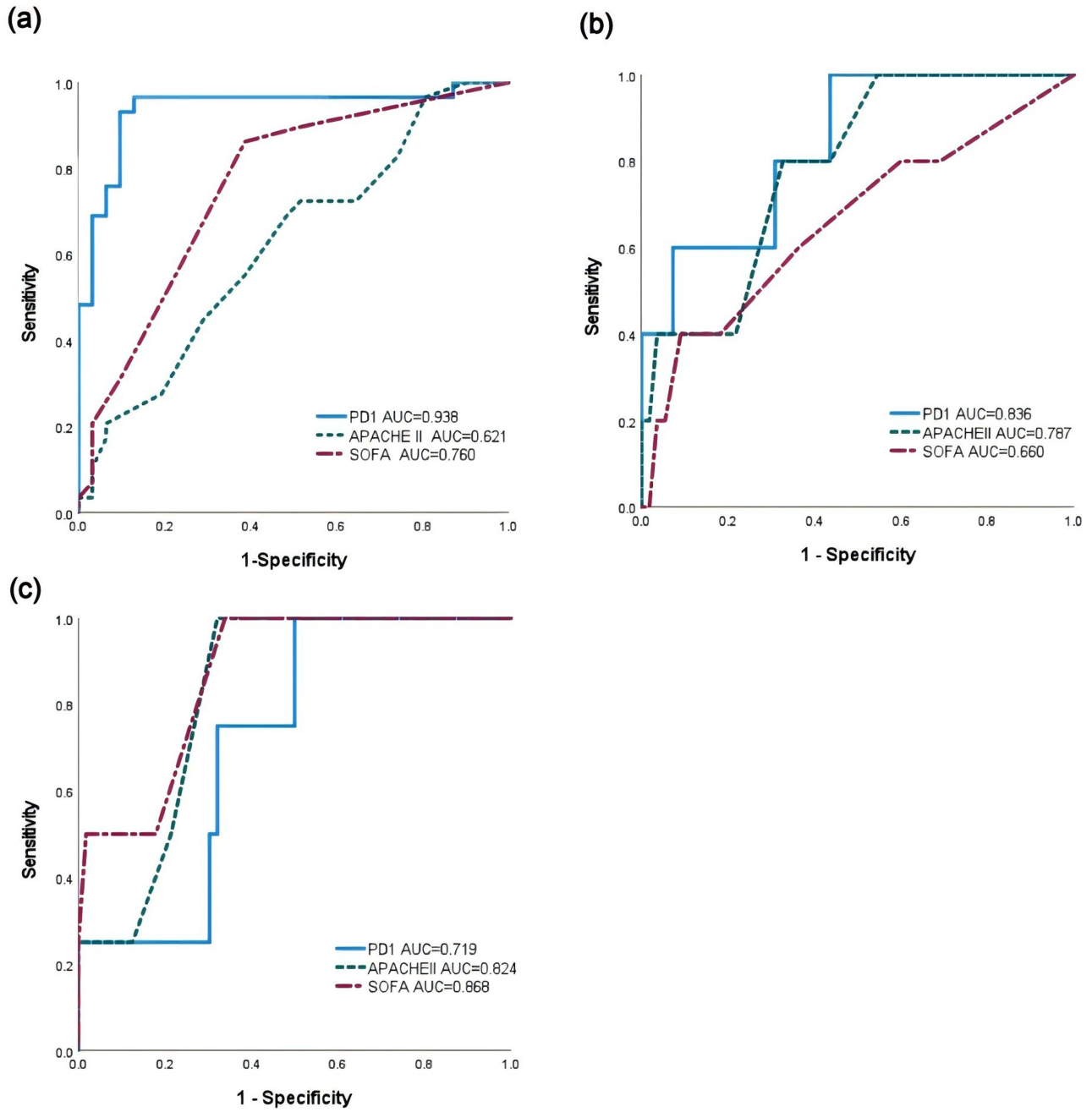

Figure 3 Prediction of AP severity, IPN and OF by serum PD1 level, APACHE II score and SOFA score. (**a**) ROC curve of AP severity. (**b**) ROC curve of IPN. (**c**) ROC curve of OF.
Abbreviations: AP, acute pancreatitis, IPN, infected pancreatic necrosis, OF, organ failure.

Discussion

The main findings of the present study were as follows. (1) Serum PD1, CitH3 and MPO-DNA were significantly higher in AP patients than in non-AP patients. (2) Serum PD1, CitH3 and MPO-DNA demonstrated a statistically significant increase with increasing AP severity. (3) There is a high correlation between serum PD1 and TNF-α; a significant correlation between PD1 and CitH3, and MPO-DNA; and significant correlation between APACHE II scores, SOFA scores, CT scores and SIRS scores. (4) Serum PD1 has high value in predicting AP severity and IPN.

AP is defined as an inflammatory disease of self-digestion of pancreatic tissue. After the initial injury, infiltration of neutrophils in pancreas is observed.[16] On the one hand, activated neutrophils have the capability to capture microbes and to

Table 3 Serum Concentration of PD1 of Patients in Different Subgroups

	Non-SAP	SAP	*p*
PD1 (mean ± SD, pg/mL)			
Day 0	5.12 ± 2.24	11.83 ± 3.74	<0.01
Day 1	5.47 ± 1.85	11.30 ± 3.32	<0.01
Day 3	4.92 ± 1.83	10.62 ± 3.19*	<0.01
Day 7	4.20 ± 1.75*	9.61 ± 3.16*	<0.01
CitH3 (mean ± SD, pg/mL)			
Day 0	8.18 ± 2.65	17.59 ± 7.95	<0.01
Day 1	9.01 ± 1.68	17.22 ± 7.40	<0.01
Day 3	7.99 ± 1.99	16.01 ± 7.45*	<0.01
Day 7	6.97 ± 2.74	14.79 ± 8.02*	<0.01
MPO-DNA (mean ± SD, pg/mL)			
Day 0	40.96 ± 26.45	91.35 ± 29.34	<0.01
Day 1	47.55 ± 21.85	85.71 ± 24.35	<0.01
Day 3	41.29 ± 17.91	78.14 ± 26.83*	<0.01
Day 7	35.00 ± 16.60	74.51 ± 24.73*	<0.01
	Non-IPN	**IPN**	***p***
PD1 (mean ± SD, pg/mL)			
Day 0	7.80 ± 4.01	14.62 ± 5.88	<0.01
Day 1	7.80 ± 3.50	13.62 ± 5.10	0.01
Day 3	7.31 ± 3.54	11.65 ± 5.23*	<0.05
Day 7	6.37 ± 3.19*	11.77 ± 5.59*	0.01
CitH3 (mean ± SD, pg/mL)			
Day 0	11.87 ± 5.67	22.12 ± 16.52	<0.05
Day 1	12.23 ± 4.86	21.23 ± 16.65	<0.05
Day 3	11.16 ± 4.75	19.59 ± 16.50	0.06
Day 7	9.91 ± 4.68*	20.04 ± 17.43	0.01
MPO-DNA (mean ± SD, pg/mL)			
Day 0	60.70 ± 32.20	116.12 ± 57.10	0.01
Day 1	62.22 ± 25.67	107.50 ± 44.04	<0.01
Day 3	54.90 ± 23.24	105.33 ± 48.25	<0.01
Day 7	50.30 ± 23.41*	95.87 ± 49.14	<0.01
	Non-OF	**OF**	***p***
PD1 (mean ± SD, pg/mL)			
Day 0	8.05 ± 4.25	12.70 ± 6.93	<0.05
Day 1	8.02 ± 3.74	11.20 ± 5.54	0.051
Day 3	7.43 ± 3.60	11.10 ± 6.04	0.064
Day 7	6.52 ± 3.38*	10.90 ± 6.08	<0.05
CitH3 (mean ± SD, pg/mL)			
Day 0	11.70 ± 5.48	27.11 ± 16.00	<0.01
Day 1	12.04 ± 4.71	26.16 ± 14.89	<0.01
Day 3	10.88 ± 4.56	25.63 ± 15.08	<0.01
Day 7	9.80 ± 4.60*	23.98 ± 17.85	<0.01
MPO-DNA (mean ± SD, pg/mL)			
Day 0	61.75 ± 32.95	115.27 ± 65.17	0.05
Day 1	63.22 ± 26.64	104.85 ± 49.09	0.06
Day 3	56.19 ± 24.35	99.86 ± 58.90	<0.05
Day 7	51.03 ± 24.13*	97.02 ± 54.31	0.01

Notes: Repeated measures ANOVA was analyzed using the Greenhouse-Geisser correction due to the assumption of Mauchly's test of sphericity not being met. *p<0.01, compare with day 0.
Abbreviations: PD1, protectin D1; CitH3, citrullinated histone 3; MPO-DNA, myeloperoxidase-deoxyribonucleic acid; SAP, severe acute pancreatitis; IPN, infected pancreatic necrosis; OF, organ failure.

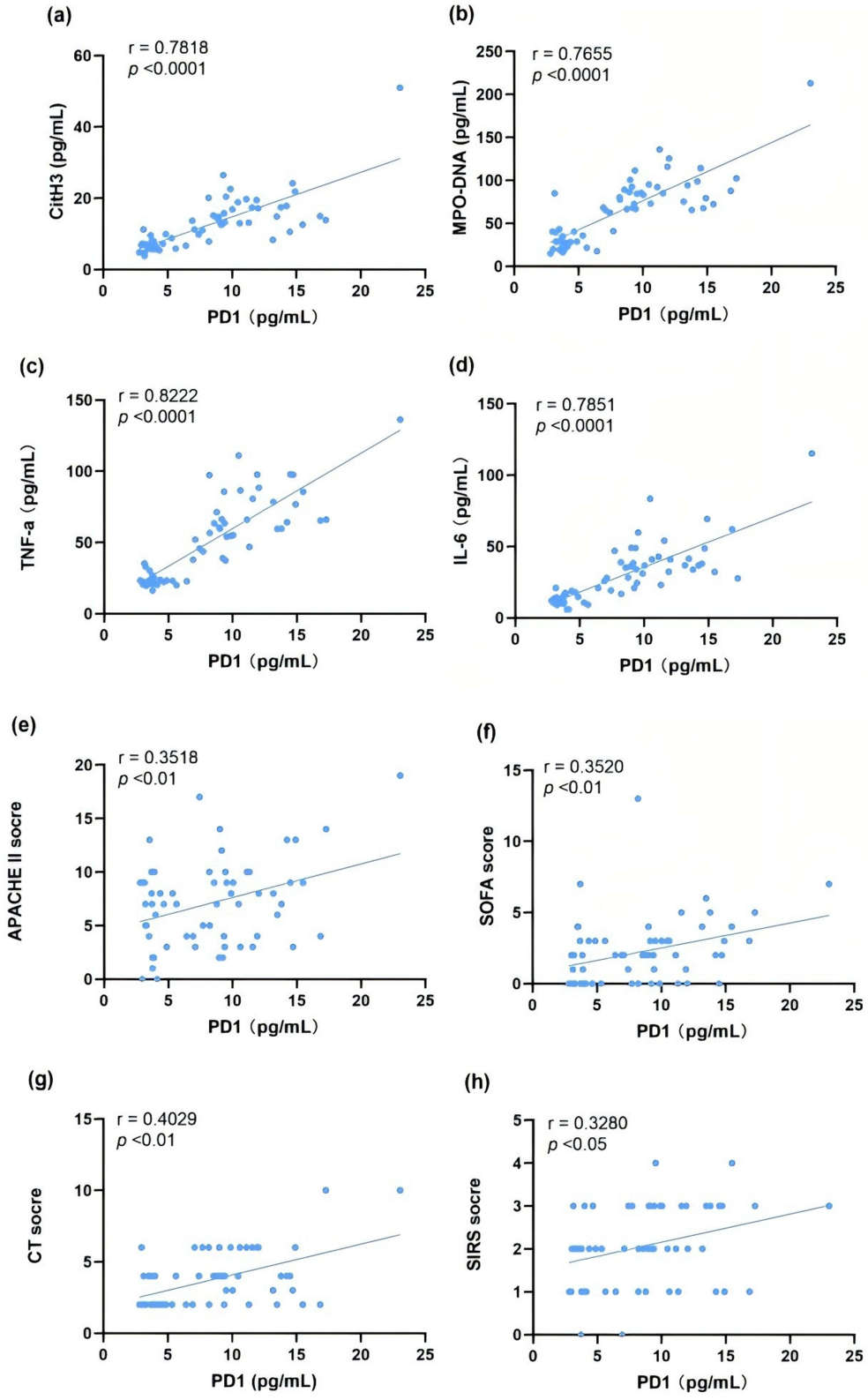

Figure 4 Correlation between serum PD1 and other indicators, p-value given in the figure (**a**) correlation between PD1 and CitH3. (**b**) correlation between PD1 and MPO-DNA. (**c**) correlation between PD1 and TNF-α. (**d**) correlation between PD1 and IL-6. (**e**) correlation between PD1 and APACHE II score. (**f**) correlation between PD1 and SOFA score. (**g**) correlation between PD1 and CT score. (**h**) correlation between PD1 and SIRS score.

release bactericidal enzymes and radicals, one the other hand, these enzymes and radicals can also be harmful to pancreatic tissue. Upon arrival at the site of injury, neutrophils are activated by various cytokines and bacterial products.[17] Neutrophils release DNA from their nuclei and bind it to intracellular proteins to form a network of NETs. In addition to neutralizing pathogens, NETs are involved in sterile inflammation, promote thrombosis and mediate tissue damage.[18] They also contribute to tissue remodeling. Merza et al[19] first found large amounts of NETs formation in pancreatic tissue in a mouse model of SAP, and NETs exacerbated pancreatitis. Our previous study also identified that NETs played a crucial role in the anti-inflammatory effects of PD1.[8] Consistent with prior findings, our current study demonstrated that circulating CitH3 and MPO-DNA—both indicators of NETs—were significantly elevated in patients with AP compared to healthy controls. Moreover, these markers exhibited an increase correlating with the severity of the disease.

PD1 is a potent lipid anti-inflammatory mediator that is produced on demand in the brain and other peripheral immune cells. Schwab et al[20] reported that PD1 promotes phagocytic clearance during acute inflammation by modulating leukocyte infiltration, increasing the uptake of apoptotic polymorphonuclear neutrophils by macrophages in vivo and in vitro, and enhancing the appearance of phagocytic enzyme-bearing phagocytes in lymph nodes and spleen. For the first time, PD1 has been demonstrated to exert a protective effect during the acute inflammatory regression phase in an animal model of self-limiting inflammation.[21] PD1 has a pro-inflammatory protective effect in cardiovascular disease, COVID19 and neurological disease.[22] Gobbetti et al[23] provides evidence that systemic treatment with PD1n-3 DPA had beneficial effects on leukocyte reactivity and cytokine production, modulating the outcome of intestinal inflammation. To date, there have been few studies investigating changes in serum PD1 levels in patients experiencing acute inflammation. Our research indicates that serum PD1 was elevated in patients during the acute phase of AP when compared to healthy individuals. Moreover, the degree of elevation correlated with disease severity. It can be hypothesized that this endogenous increase in PD1 serves a negative feedback mechanism within the body, aiming at limiting the progression of inflammation.

Over the past 40 years, various scoring systems have been proposed to predict the severity of AP.[24] However, there is no definitive scoring system with high sensitivity and specificity. The interest in identifying new biomarkers and predictive models for SAP demonstrates the clinical importance of early severity prediction. Several clinical scoring systems have been developed and employed and their effectiveness and accuracy compared.[25] The APACHE II and SOFA scores are currently commonly used in patients with AP. Our study compared the predictive value of serum PD1 levels with APACHE II and SOFA scores. We found a higher sensitivity and specificity of PD1 as a metric in predicting pancreatitis severity, IPN and OF incidence.

There are some limitations in our study, first, our study was a single-center observation and included a relatively small number of patients; it may be possible to include a larger sample size to obtain more accurate results later. Second, there were only 5 patients developed IPN and 4 patients developed OF, which made it challenging to assess the efficacy of PD1 in these patient populations. PD1 did not show a significant advantage in predicting OF, possibly related to the severity of pancreatitis in the patients included.

In conclusion, our results suggest that PD1 levels correlates with AP severity and predicts the occurrence of SAP, OF and IPN, which are a promising new prognostic marker of SAP.

Conclusion

In the early stage of AP, serum PD1 concentration risen much higher than milder patients and also developed a poorer prognosis. Our study found may be a new prognostic marker for AP.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author (Please contact Luyao Zhang, zhangluyao@njucm.edu.cn). The data are not publicly available due to privacy or ethical restrictions.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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