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ORIGINAL ARTICLE

New Risk Factors for Infected Pancreatic Necrosis Secondary to Severe Acute Pancreatitis: The Role of Initial Contrast-Enhanced Computed Tomography

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Abstract

Background and Aims Pancreatic necrosis is a risk factor for poor prognosis of acute pancreatitis (AP). However, the associations between the findings on initial contrast-enhanced computed tomography (CT) of the pancreas and infected pancreatic necrosis (IPN) are unclear.

Methods This was a retrospective cohort study. Patients with severe AP (SAP) from January 2014 to December 2016 at the First Affiliated Hospital of Nanchang University were enrolled and assigned to an IPN group and a non-IPN group. Univariate and multivariate logistic regression analyses were sequentially performed to assess the associations between the variables and IPN development. A receiver operating characteristic (ROC) curve was generated for the qualified independent risk factor.

Results Forty-two patients with IPN were compared with 100 patients without IPN. Contrast-enhanced CT was performed 7 (range 3–10) days after AP onset. Multivariate stepwise logistic regression analyses showed that the number of acute peripancreatic fluid collections (APFCs) (OR 1.328, $P=0.006$), presence of peripancreatic and pancreatic parenchymal necrosis (OR 4.001, $P=0.001$), and gastrointestinal wall thickening (OR 3.353, $P=0.006$) were independent risk factors for IPN secondary to SAP. The area under an ROC curve for the number of APFCs was 0.714, the sensitivity was 78.60%, and the specificity was 57.30% at a cutoff value of 4.5.

Conclusions The number of APFCs, presence of peripancreatic and pancreatic parenchymal necrosis, and gastrointestinal wall thickening were independent risk factors associated with IPN. As initial contrast-enhanced CT (about 7 days from AP onset) plays an important role in predicting IPN, it is important for clinicians to consider initial imaging of the pancreas.

Keywords Pancreatitis · Infection · Risk factors · Multidetector computed tomography

Abbreviations

AP	Acute pancreatitis
IPN	Infected pancreatic necrosis
SAP	Severe AP
APFC	Acute peripancreatic fluid collection
CT	Computed tomography
ROC	Receiver operating characteristic
ORs	Odds ratios
CIs	Confidence intervals
SD	Standard deviation

Background

Acute pancreatitis (AP), an inflammatory disorder of the pancreas, is the leading cause of admission to hospital for gastrointestinal disorders in the USA and many other countries and can generate severe local and/or systemic complications. Infected pancreatic necrosis (IPN) is a life-threatening complication with a high morbidity rate of 33% [1] and a high mortality rate of 32% [2]. Thus, early identification of potential risk factors for IPN is necessary for active and early interventions and a more favorable prognosis.

Recent studies revealed that laboratory indicators such as C-reactive protein [3], procalcitonin [3, 4], D-dimer [5], blood urea nitrogen [6], interleukin-6 [7], interleukin-8 [4] and lymphocytes [8] and clinical indicators such as hypotension [9], and intraperitoneal pressure [5] were risk factors for IPN. However, all the above studies are limited to individual

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studies, and few publications provide precise and adequate early predictions of the development of IPN.

Contrast-enhanced computed tomography (CT) is highly accurate and sensitive in both diagnosing and demonstrating the extent of disease, and the use of contrast-enhanced CT is not routinely recommended for examining patients 72 h within the onset of abdominal pain [10]. Pancreatic necrosis is strongly associated with poor prognosis [11, 12]. However, there are few reports on the relationship between initial contrast-enhanced CT and the development of IPN. Thus, our investigation is the first study to evaluate the relationship between initial contrast-enhanced CT and IPN and to identify the independent risk factors for developing IPN.

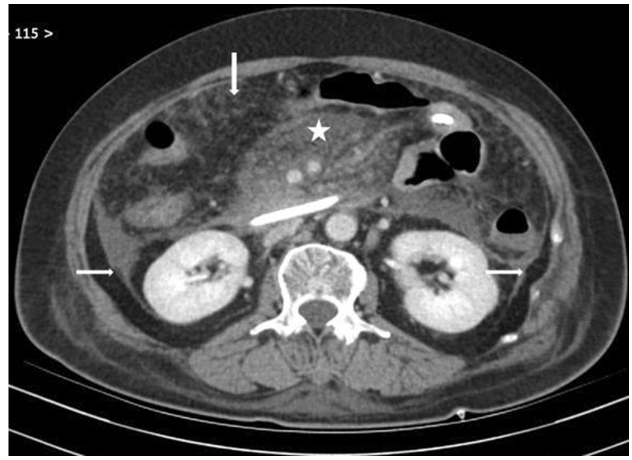

Fig. 1 Fluid spreads along the mesenteric root (star). Due to leakage of enzymes along the great omentum (down arrow), a collection forms. Fluid is seen in the paracolic sulci (right arrow)

Fig. 2 Peripancreatic necrosis alone with fat necrosis in the anterior renal space (triangle) and no pancreatic parenchymal necrosis (star)

Methods

Patients

This was a retrospective cohort study and was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. This study was initiated by the authors.

Consecutive adult patients (age ≥ 18 years old) with severe AP (SAP) who were admitted to the First Affiliated Hospital of Nanchang University between January 2014 and December 2016 were enrolled in this study. Patient exclusion criteria included: (1) admission > 7 days after onset of AP; (2) history of AP, chronic pancreatitis or other pancreatic pathologies, such as pancreatic malignancy or cysts; (3) not contrast-enhanced CT examination within 10 days (≤ 10 days) of AP onset; (4) pregnancy; or (5) missing images or incomplete data.

Data Collection

The following demographic data were assessed: age, sex, AP etiology, organ failure, and clinical outcomes including clinical treatment, microbiological outcomes, length of hospital stay, duration of intensive care, patient discharge, and death.

Imaging Protocols

Initial contrast-enhanced CT was generally performed approximately 3–10 days after AP onset, with an average of 7 days. All CT examinations were performed using a 64-channel multidetector CT scanner (Somatom Definition AS +, Siemens Medical Systems, Erlangen, Germany). After noncontrast scans were obtained, 1.3 mL/kg iopromide (Ultravist 370; Bayer Schering Pharma, Berlin, Germany) was intravenously injected at a rate of 3 mL/s with a high-pressure injector. Then, when the attenuation of the aorta at the thoracolumbar junction had reached 180 HU and a fixed 60-s delay, contrasted arterial and portal phase scans were obtained. The scanned area extended from the diaphragmatic domes to the pubic symphysis. Scan parameters were as follows: detector collimation of 64 × 0.625 mm, beam pitch of 0.984, 120 kVp, automated dose modulation using a maximum allowable tube current set at 200 mAs, and a section thickness/reconstruction interval of 3 mm/3 mm.

Image Analysis

All CT studies were re-assessed and reviewed by a radiologist who specialized in abdominal imaging and were blinded to the clinical data and outcome parameters. The following features (Figs. 1, 2, 3, 4, 5) were recorded [13, 14]: (1) anatomical location of acute peripancreatic fluid

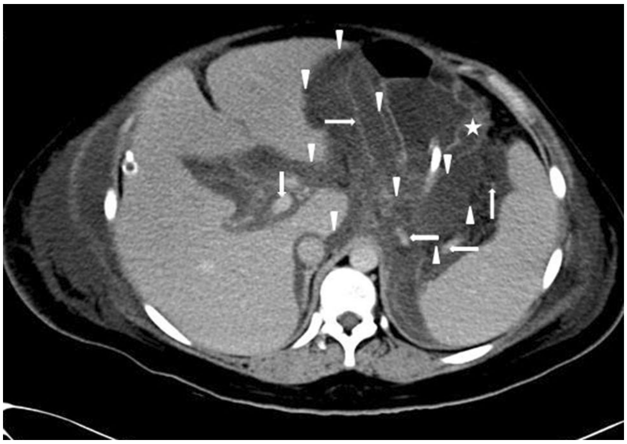

Fig. 3 Gastrointestinal wall thickening with thickening and edema of the gastrointestinal wall (star). Fluid commonly penetrates through the peritoneal layer and disseminates into the peritoneal cavity and forms an APFC in the lesser omentum (triangle). The left gastric artery (right arrow), portal vein (down arrow), splenic artery (left arrow), and left gastroepiploic artery (up arrow) are the vascular landmark for identifying the lesser omentum. APFC: acute peripancreatic fluid collection

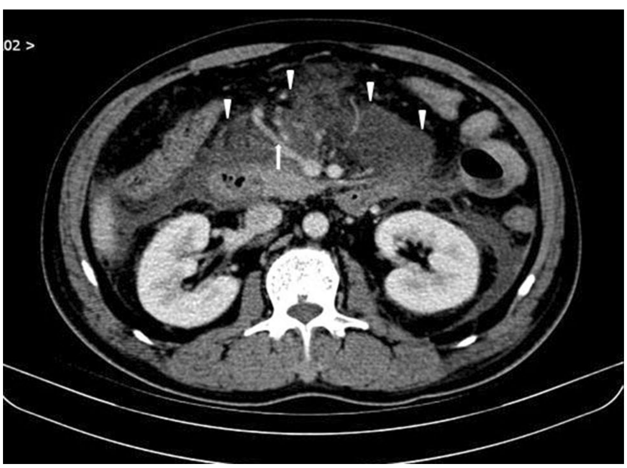

Fig. 4 Fluid spreads along the transverse mesocolon secondary to pancreatitis (triangle), adjacent to the gastrointestinal trunk (up arrow)

collections (APFCs): renal space (anterior, left posterior and right posterior), perirenal space (left and right), omentum (greater and lesser), paracolic sulci (left and right), mesenteric root, and transverse mesocolon. APFCs were recorded when the diameter was > 1 cm. (2) Form of necrotizing pancreatitis: peripancreatic necrosis alone, pancreatic parenchymal necrosis alone, and peripancreatic and pancreatic parenchymal necrosis. To further refine our assessment of the extent and location of pancreatic necrosis, according to location, the pancreas was divided into head, neck, body, and tail; necrosis was classified

Fig. 5 APFCs seen in the perirenal space (right arrow) and posterior renal space (up arrow)

according to extent as < 30%, 30% to 50%, and > 50%. (3) Other images out of pancreas: pleural effusion, ascites, pelvic fluid, fatty liver, cholecystitis, gastrointestinal wall thickening.

Definitions

The revised Atlanta classification of AP in 2012 identified two phases of the disease: early and late, and this early phase is usually over by the end of the first week but may extent into the second week [13]. In the present study, contrast-enhanced CT was generally performed approximately 3–10 days after AP onset, with an average of 7 days, which was defined as initial contrast-enhanced CT. IPN was confirmed by a positive bacterial or fungal culture or Gram stain of pancreatic or extrapancreatic necrosis obtained by fine-needle aspiration or from the first drainage procedure or the first necrosectomy.

APFCs were defined as peripancreatic fluid collections with homogeneous liquefied components and without well-defined walls that arise in patients with interstitial edematous pancreatitis during the first 4 weeks. Pancreatic parenchymal necrosis was defined as focal or diffuse non-enhancement of the pancreatic gland, as determined by contrast-enhanced CT. Extrapancreatic necrosis alone (without pancreatic parenchymal necrosis) was defined as extrapancreatic morphological changes exceeding fat stranding with complete enhancement of the pancreatic parenchyma without signs of focal or diffuse non-enhancement able to be determined on contrast-enhanced CT [13]. Gastrointestinal wall thickening was defined as thickening and edema of the gastrointestinal wall, with wall thickness greater than 4 mm, and as robust enhancement of the mucosa with reduced enhancement of the submucosa [14].

Data Statistics

Quantitative variables are presented as the mean ± SD (standard deviation) for normal distributions and were analyzed using a t test. Categorical variables are presented as absolute numbers and percentages and were analyzed using a Chi-square test. Variables found to be statistically significant in the univariate logistic regression analysis were introduced into a multivariate logistic analytic model (stepwise regression) to identify independent risk factors with odds ratios (ORs) and 95% confidence intervals (CIs). Furthermore, receiver operating characteristic (ROC) curves were generated for each of the qualified independent risk factors. A p value < 0.05 was considered statistically significant. Data were analyzed using SPSS software (v17.0; SPSS Inc., Chicago, IL, USA).

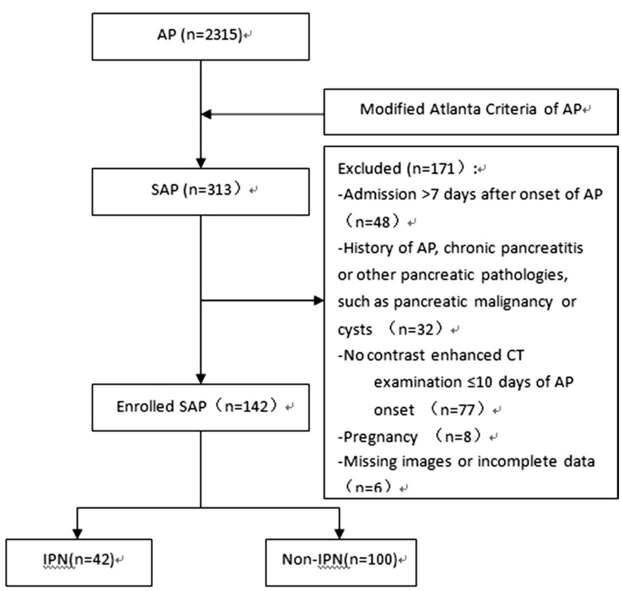

Fig. 6 Flowchart of patients with or without IPN secondary to SAP. AP: acute pancreatitis; SAP: severe acute pancreatitis; IPN: infected pancreatic necrosis; CT: computed tomography

Results

As shown in a flowchart in Fig. 6, 142 eligible patients were enrolled in this study, and 42 (29.58%) of these patients progressed to IPN. Demographic data and clinical characteristics of both the IPN and non-IPN groups are shown in Table 1. The average age of all patients was 55.87 ± 15.47 years (range 19–84 years), and the study included 74 males (52.11%) and 68 females (47.89%). Patient distributions based on cause of AP were as follows: 8 patients with alcoholic pancreatitis (5.63%), 34 with hypertriglyceridemia pancreatitis (23.94%), 95 with biliary pancreatitis (66.90%), and 5 others (3.52%). The two groups were matched by age, sex, and AP etiology. Patient distributions based on organ failure type were as follows: 132 patients with respiratory failure (92.96%), 34 with renal failure (23.94%), and 15 with circulation failure (10.56%). The incidence of circulation failure was higher in the IPN group than that in the non-IPN group (26.19% vs. 4.00%, $P = 0.000$). Average time from AP onset to admission was 2.42 ± 1.45 days (range 1–7 days), and there were no differences between the two groups.

Results of the univariate logistic regression analysis are shown in Table 2. The following were potential risk factors: the time from AP onset to examination by contrast-enhanced CT (OR 1.186, $P < 0.05$), the total number of APFCs (OR 1.427, $P = 0.000$) and the collections at the posterior renal space (OR 3.32, $P < 0.01$), lesser omentum (OR 3.056, $P < 0.01$), mesenteric root (OR 2.889, $P < 0.01$), or

Table 1 Demographic data and clinical characteristics of both the IPN and non-IPN groups

Variables	IPN group ($n = 42$)	Non-IPN group ($n = 100$)	P value
Age (year), mean ± SD	53.33 ± 13.72	56.93 ± 16.09	0.207
Sex, male/female	26/16	48/52	0.132
Etiology			0.355
Alcoholic	4	4	
Hypertriglyceridemia	12	22	
Biliary	24	71	
Others	2	3	
Organ failure			0.001
Respiratory failure	40	92	0.491
Renal failure	14	20	0.089
Circulation failure	11	4	0.000
Time form onset to admission (day), mean ± SD	2.33 ± 1.43	2.46 ± 1.47	0.637

SD mean ± standard

Table 2 Univariate logistic analysis of variables with the development of IPN as the endpoint

Variables	IPN group ($n=42$)	Non-IPN group ($n=100$)	OR (95% CI)	P value
Time form AP onset to examination by contrast-enhanced CT	6.90 ± 2.64	5.94 ± 2.29	1.186 (1.014–1.387)	0.032
Number of APFCs	5.86 ± 2.08	4.15 ± 2.20	1.427 (1.189–1.713)	0.000
Location of APFCs				
Anterior renal space, yes/no	39/0	94/6	2.489 (0.290–21.364)	0.406
Left posterior renal space, yes/no	17/25	17/83	3.320 (1.481–7.444)	0.004
Right posterior renal space, yes/no	10/32	11/89	2.528 (0.981–6.517)	0.055
Left perirenal space, yes/no	13/29	18/82	2.042 (0.891–4.681)	0.092
Right perirenal space, yes/no	9/33	11/89	2.207 (0.839–5.805)	0.109
Greater omentum, yes/no	12/30	26/74	1.138 (0.509–2.546)	0.752
Lesser omentum, yes/no	30/12	45/55	3.056 (1.405–6.644)	0.005
Left paracolic sulci, yes/no	34/8	65/35	2.288 (0.956–5.478)	0.063
Right paracolic sulci, yes/no	24/18	40/60	2.000 (0.963–4.152)	0.063
Mesenteric root, yes/no	26/16	36/64	2.889 (1.372–6.083)	0.005
Transverse mesocolon, yes/no	32/10	56/44	2.514 (1.116–5.666)	0.026
Peripancreatic necrosis alone, yes/no	17/25	61/39	0.435 (0.208–0.907)	0.026
Pancreatic parenchymal necrosis alone, yes/no	0/42	3/97	–	0.999
Peripancreatic and pancreatic parenchymal necrosis, yes/no	23/19	24/76	3.833 (1.790–8.209)	0.001
Location of pancreatic necrosis				
Head	8	8	2.706 (0.941–7.779)	0.065
Neck	12	10	3.600 (1.413–9.174)	0.007
Body	18	15	4.250 (1.869–9.664)	0.001
Tail	12	14	2.457 (1.023–5.9)	0.044
Extent of necrosis				
< 30%	9	19	1.163 (0.477–2.832)	0.740
30–50%	6	2	8.167 (1.576–42.323)	0.012
> 50%	8	5	4.471 (1.368–14.608)	0.013
Other images out of pancreas				
Pleural effusion, yes/no	41/1	99/1	–	1.000
Ascites, yes/no	17/25	41/59	0.979 (0.47–2.038)	0.954
Pelvic fluid, yes/no	14/28	35/65	0.929 (0.433–1.989)	0.849
Fatty liver, yes/no	14/28	34/66	0.971 (0.452–2.082)	0.939
Cholecystitis, yes/no	3/39	23/77	0.258 (0.073–0.911)	0.035
Gastrointestinal wall thickening, yes/no	23/19	23/77	4.053 (1.885–8.714)	0.000

APFC acute peripancreatic fluid collection, *OR* odds ratios, *CI* confidence intervals

transverse mesocolon (OR 2.514, $P < 0.05$). Peripancreatic and pancreatic parenchymal necrosis (OR 3.833, $P = 0.001$); its location on the neck (OR 3.6, $P < 0.01$), body (OR 4.25, $P = 0.001$), or tail (OR 2.457, $P < 0.05$) of the pancreas; an extent of pancreatic necrosis of 30–50% (OR 8.167, $P < 0.05$) or > 50% (OR 4.471, $P < 0.05$); and gastrointestinal wall thickening (OR 4.053, $P = 0.000$) were also risk factors. Patients with all the risk factors mentioned above might have a higher possibility to develop IPN.

Table 3 illustrates the results of multivariate analysis by stepwise regression. After adjustment for potential confounding factors with multivariable regression, the number of APFCs (OR 1.328, 95% CI 1.083–1.628, $P = 0.006$) and presence of peripancreatic and pancreatic parenchymal necrosis (OR 4.001, 95% CI 1.716–9.327, $P = 0.001$) and gastrointestinal wall thickening (OR 3.353, 95% CI

Table 3 Multivariate analysis of variables with the development of IPN as the endpoint

Variables	OR (95% CI)	P value
Number of APFCs	1.328 (1.083–1.628)	0.006
Peripancreatic and pancreatic parenchymal necrosis	4.001 (1.716–9.327)	0.001
Gastrointestinal wall thickening	3.353 (1.420–7.919)	0.006

1.420–7.919, $P = 0.006$) remained independent risk factors for IPN secondary to SAP. The number of APFCs (0.714, 95% CI 0.625–0.802, $P = 0.000$) had a favorable predictive value, of which the sensitivity was 78.60% and the specificity was 57.30% for APFCs at a cutoff value of 4.5. The ROC curve for number of APFCs in predicting IPN is shown in Fig. 7.

Discussions

IPN is a life-threatening complication with high morbidity and mortality rates and is the main cause of death at the late stage of AP. Therefore, early prediction of IPN and specific targeted interventions are imperative to assess the disease condition and reduce IPN-related mortalities. The new Atlanta classification of AP emphasizes the role of contrast-enhanced CT and redefines local complications. Contrast-enhanced CT plays an important role in the diagnosis of AP, but there are few reports on the relationships between initial contrast-enhanced CT (about 7 days from AP onset) and IPN, which usually developed in the late phase. To our knowledge, the present study is the first report to identify the independent risk factors for the development of IPN with regard to initial contrast-enhanced CT and to indicate that peripancreatic and pancreatic parenchymal necrosis, gastrointestinal wall thickening, and APFC number are independent risk factors associated with IPN.

The location (not extent) of pancreatic necrosis was useful in predicting the development of IPN [15]. A later study further found that pancreatic parenchymal necrosis causes significantly more severe pancreatic infection than

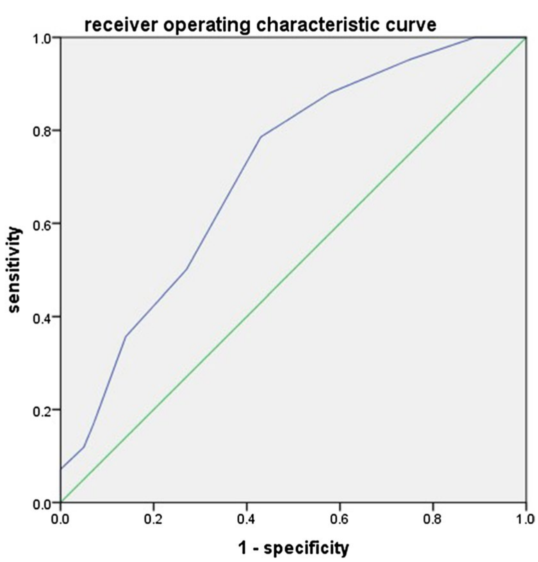

Fig. 7 Receiver operating characteristic curve for number of APFCs in predicting IPN

peripancreatic necrosis alone (47% vs. 16%) [16]. This study further suggested that peripancreatic and pancreatic parenchymal necrosis was an independent risk factor for IPN. Similarly, in this study, patients with peripancreatic necrosis alone were less prone to develop IPN than their counterparts, suggesting that it is important to clinically distinguish peripancreatic necrosis from the combined disease type. It is generally believed that trypsin activation within pancreatic acinar cells leads to autodigestion and local inflammation [17, 18]. Following a cascade of intracellular events, pancreatic acinar cells may become necrotic. The pathophysiological mechanism involved in the development of concomitant necrotizing pancreatitis and infection remains speculative.

This study revealed gastrointestinal wall thickening as an independent risk factor for IPN. It is speculated that intestinal bacteria and their products can infiltrate the blood circulation by passing through the damaged intestinal barrier, causing bacterial translocation and ultimately leading to sepsis and IPN [19]. Therefore, detection of gastrointestinal wall thickening by initial contrast-enhanced CT may indicate that the intestinal barrier is more vulnerable and prone to develop to IPN. Furthermore, regarding gastrointestinal wall thickening, it is imperative to identify the subgroups of patients with relatively higher risks of IPN development in a timely manner; as such, proper surveillance and interventions, such as timely liquid resuscitation and enteral nutrition and maintenance of the rhythm of intestinal peristalsis, can be implemented.

The previous studies showed that the presence and extent of extrapancreatic fluid collection are indicators of SAP [20, 21]. These findings further suggested that IPN could be predicted better when the number of APFCs is 4.5, and APFCs in the posterior renal space, lesser omentum, mesenteric root and transverse mesocolon were more closely associated with IPN than other tested factors. However, the specificity of the cutoff value for the number of APFCs was relatively low (57.30%), and we sacrificed the specificity to obtain a higher sensitivity of 78.60%. The pathophysiological mechanism underlying the relationship between IPN and APFCs remains speculative. APFCs are caused by pancreatic and peripancreatic inflammation or rupture of one or more small peripheral pancreatic side duct branches. Ductal disruption might facilitate bacterial invasion of pancreatic tissue. Of note, collections that fail to dissolve early in the course of disease will most likely contain some degree of peripancreatic tissue necrosis and hence have a greater chance of being detected. The presence of APFCs should not change overall management but does provide clinicians with information for risk stratification.

The limitations of this study are as follows: (1) A retrospective study has its own limitations. However, by reassessing images from initial contrast-enhanced CT and introducing the updated definition of SAP, we were able to minimize information bias. (2) Imaging itself is an objective indicator; however, imaging is affected by subjective factors introduced by the radiologist, and the results may be slightly different due to the radiologists' assessment [22]. (3) Because peripancreatic and pancreatic necrosis and gastrointestinal wall thickening are count data, it was not suitable to apply a ROC curve to assess the accuracy. However, it is still important to alert physicians of the possibility of developing IPN when the above factors appear. (4) We only enrolled patients with SAP, not included patients with moderately severe AP, which limited generalizability of findings and needed further study.

In conclusion, the present study suggested that peripancreatic and pancreatic parenchymal necrosis, APFC number, and gastrointestinal wall thickening might be indicative of the likelihood of IPN secondary to SAP. As initial contrast-enhanced CT (about 7 days from AP onset) plays an important role in predicting IPN, it is imperative that clinicians consider initial imaging of the pancreas.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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