

Early predictors of hyperlipidemic acute pancreatitis

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Abstract. The present study aimed to investigate early risk factors for hyperlipidemic acute pancreatitis (HLAP) in order to open up novel routes for its prevention and treatment. Demographics, laboratory data obtained within 48 h, enhanced computed tomography (CT) imaging data and the modified CT severity index (MCTSI) for 111 patients with HLAP who were assessed at Ordos Central Hospital (Ordos, China) between January 2015 and October 2017 were retrospectively analyzed. Of these, 17 patients progressed to infectious pancreatic necrosis (IPN) and 14 patients progressed to organ failure (OF), the occurrence of which were the study outcomes. The patients were divided into pairs groups: IPN and non-IPN, as well as OF and non-OF, and differences between the groups were determined regarding various clinicopathological parameters. Furthermore, univariate and multivariate regression analyses were performed to identify parameters associated with the risk of progression to IPN or OP. On univariate analysis, the following parameters were deemed as being significantly associated with the risk of IPN: Serum calcium ions, C-reactive protein (CRP), extent of necrosis, procalcitonin (PTC) and the MCTSI. Furthermore, calcium ions, red cell distribution width (RDW), extent of necrosis and the MCTSI were significantly associated with the risk of OF on univariate analysis. Multivariate logistic regression analysis for these parameters then indicated that CRP ($P=0.014$), RDW ($P=0.025$) and the extent of necrosis ($P=0.022$) were significant and independent predictors of progression; thus, these are early risk factors for patients with HLAP. Receiver operating characteristic curves were generated to evaluate the predictive value of these factors, and the area under the curve for the three parameters was 0.863 [95% confidence interval (CI), 0.646-0.886], 0.727 (95% CI, 0.651-0.803) and 0.833 (95% CI, 0.739-0.936), respectively. Therefore, CRP, RDW and the extent of necrosis are early predictive indexes for the risk of progression in HLAP.

Introduction

Acute pancreatitis (AP) is a frequently occurring acute abdominal condition with characteristics of acute onset and rapid progression; however, its severity differs considerably among affected patients. In the majority of cases, AP is classified as mild, which is a self-limited disease. Only 10-20% of patients with AP progress to severe AP (SAP) (1), which is an acute, life-threatening condition with a case fatality rate of ~20%. SAP may result in persistent organ failure (OF) with local and/or systemic complications (2). AP may be classified into two types: Acute interstitial edematous pancreatitis and acute necrotizing pancreatitis (NP) (3). Furthermore, the necrosis may be classified as aseptic or infective. For instance, secondary infection of pancreatic or peri-pancreatic tissue in advanced NP may induce infectious pancreatic necrosis (IPN). The major causes of secondary infection of NP include bacterial translocation, biliary-system source and hematogenous dissemination. The infection is closely correlated with the degree of PN (4).

AP has numerous causes, with the major ones being excessive alcohol consumption and intrabiliary calculi. Certain studies suggested that hyperlipidemia is another major cause of AP, and that the prevalence of hyperlipidemic AP (HLAP) has increased (5). Furthermore, HLAP is generally considered to have no correlation with elevated blood cholesterol levels, but to be closely associated with elevated blood triglycerides (TG). Compared with biliary pancreatitis and alcoholic pancreatitis, HLAP is more dangerous, with a larger amount of associated complications and a higher mortality rate (6); in addition, HLAP cases more easily and rapidly progress to NP and OF (7).

Numerous studies have investigated the differences in clinical characteristics between HLAP and non-HLAP. However, to date, only few studies have assessed the early risk factors of HLAP. In the present study, data from patients with HLAP obtained within 48 h of admission were analyzed in order to characterize the early risk factors of HLAP and provide novel approaches for its prevention and treatment.

Materials and methods

Case information. The complete case data for a total of 111 patients with HLAP, who were admitted to Ordos Central Hospital (Ordos, China) between January 2015 and October 2017, were retrospectively analyzed. The present study was

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approved by the Ethics Committee of Ordos Central Hospital (Ordos, China) and all patients provided written informed consent.

The inclusion criteria were as follows: i) Patients who meet the diagnostic criteria for AP. If the patient satisfied two of the following three criteria, they were considered to have AP: Abdominal pain; serum amylase and (or) lipase concentration ≥ 3 times higher than the normal value; and abdominal imaging examination in line with imaging changes typical for AP (8). ii) Patients who meet the criteria for hyperlipidemia: Serum TG levels of $\geq 1,000$ mg/dl or TG levels between 500 and 1,000 mg/dl, accompanied by lactescent serum in the absence of other causes of pancreatitis, including gallstone disease, alcoholism or trauma (9-11). iii) Patients who underwent abdominal enhanced computed tomography (CT) imaging within 48 h of admission.

The exclusion criteria were traumatic, biliary, alcoholic, medical, self-limited, pregnant and tumorous pancreatitis.

Data collection. The clinical characteristics of the subjects, including age, sex, body mass index (BMI) and history of diabetes were recorded. Within 48 h of admission, the following laboratory parameters were determined: Hematocrit, albumin, glucose, calcium ions, urea nitrogen, C-reactive protein (CRP), white blood cell (WBC) count, procalcitonin (PTC), fibrinogen (FIB) and red cell distribution width (RDW). Enhanced CT was performed to determine the necrotic tissue extent and the fluid locus. The modified CT severity index (MCTSI) was also determined within 48 h of onset (12). Abdominal enhanced CT was used to diagnose AP and determine the volume ratio between necrotic and non-necrotic pancreatic tissues, as well as peri-pancreatic effusion (13). A roentgenologist and a surgeon co-analyzed 3-dimensional reconstructions of abdominally-enhanced CT images of necrotic and non-necrotic pancreatic tissues to determine the volume of necrotic and non-necrotic pancreatic tissues as exemplified in Fig. 1.

Treatment. Initially, all enrolled patients received targeted lipidemia-lowering and general therapy, including fasting, gastrointestinal decompression, fluid resuscitation, nutritional therapy, organ function maintenance, preventive usage of antibiotics against gram-negative *bacilli* and Traditional Chinese Medicine approaches, including Radix Bupleuri, Radix Paeoniae Alba and Radix et Rhizoma Rhei, in order to restore gastrointestinal tract dynamics and treat the pancreatitis.

Study outcomes. The outcome of the study was the progression of HLAP to IPN or OF at discharge; patients were not involved in a subsequent follow-up. Pancreatic and peri-PN tissues may remain uninfected or become infected; most of the studies available suggest no correlation between the extent of necrosis and the risk of infection and symptom duration (14,15). The presence of IPN may be presumed when extraluminal gas is visible in pancreatic and/or peri-pancreatic tissues on CECT, or when percutaneous, image-guided, fine-needle aspiration is positive for bacteria and/or fungi on Gram stain and culture. Three organ systems should be assessed to determine OF: The respiratory, cardiovascular and renal systems. OF is defined by a score of ≥ 2 for one of these three organ systems using the modified Marshall scoring system, which has the merit of

simplicity, universal applicability and the ability to easily and objectively determine disease severity (8).

Statistical analysis. SPSS v.20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. After stratification of the patients into INP and non-INP, or OF and non-OF groups, inter-group differences in measurement data were analyzed using a two independent samples t-test and Mann-Whitney U test, while differences in enumeration data were analyzed using a chi-square test. In order to identify early risk factors of HLAP, the data initially underwent univariate logistic regression analysis to obtain odds ratios (OR) and 95% confidence intervals (CIs), and then the parameters that were significantly associated with progression of HLAP to INP or OF were further subjected to a multivariate logistic regression analysis. $P < 0.05$ was considered to indicate a statistically significant difference. The area under the receiver operating characteristic (ROC) curve (AUC) was determined to evaluate the performance of the predictive model. The AUC ranged from 0-1, and a variable with an AUC of > 0.7 was considered useful, while an AUC between 0.8 and 0.9 was considered to indicate excellent diagnostic accuracy.

Results

Clinicopathological characteristics associated with the progression of HLAP. Of the 111 patients with HLAP that were enrolled in the present study, 17 (15.3%) patients progressed to IPN and 14 (12.6%) progressed to OF at the time of discharged. Between the IPN and non-IPN groups, no significant differences in sex, age, BMI and diabetes history were present ($P > 0.05$). Furthermore, differences in calcium ions, CRP, necrotic tissue extent, PTC and MCTSI were statistically significant ($P < 0.05$). However, differences in hematocrit, albumin, blood sugar, urea nitrogen, white blood cell count, fibrinogen, RDW and effusion focus were not statistically significant ($P > 0.05$; Table I).

Between the OF and non-OF groups, no significant differences in sex, age, BMI and diabetes history were determined ($P > 0.05$). Furthermore, differences in calcium ions, RDW, necrotic tissue extent and MCTSI were statistically significant ($P < 0.05$). However, differences in hematocrit, albumin, blood glucose, urea nitrogen, white blood cell count, procalcitonin, fibrinogen, CRP and effusion focus were not statistically significant ($P > 0.05$; Table I).

Multivariate logistic regression analysis indicated that CRP was significantly and independently associated with IPN ($P = 0.014$). RDW ($P = 0.025$) and the extent of necrosis ($P = 0.022$) were significant independent factors associated with the progression to OF (Table II).

CRP, RDW and extent of necrosis are independent prognostic factors for the progression of HLAP. The prognostic value of CRP regarding the progression to IPN, and that of RDW and the extent of necrosis regarding the progression to OF, was then evaluated by ROC curve analysis (Figs. 2-4, respectively). The AUC for CRP, RDW and the extent of necrosis was 0.863 (95% CI, 0.646-0.886), 0.727 (95% CI, 0.651-0.803) and 0.833 (95% CI, 0.739-0.936), respectively. The optimal cut-off value of CRP to predict IPN was 77.2 mg/l. Additionally, the optimal

Table I. Univariate regression analysis of the comparison of patients with and without IPN, and of patients with and without OF.

Characteristics	IPN	non-IPN	P-value	OR (95% CI)	OF	non-OF	P-value	OR (95% CI)
Number of patients	17	94			14	97		
Age (years)	42±11.3	40±10.3	0.969	1.824 (-3.638-7.287)	43.2±8.6	40.1±10.6	0.498	3.172 (-2.735-9.079)
Sex (male/female)	11/6	79/15	0.061	0.262 (0.062-0.463)	10/4	80/17	0.324	-8.451 (-45.571-28.668)
History of diabetes	3 (17.6%)	23 (23.4%)	0.188	-0.068 (-0.291-0.154)	3 (21.4%)	23 (23.7%)	0.700	-0.022 (-0.264-0.219)
Body mass index (kg/m ²)	29±5.4	28±4.2	0.742	1.543 (0.348-9.661)	29±3.6	27±4.9	0.823	2.672 (-1.622-6.841)
Hematocrit (%)	45.9±3.98	36.3±4.39	0.876	-0.445 (-2.713-1.821)	44.9±4.46	46.5±4.28	0.637	-1.537 (-3.981-0.905)
Albumin (g/l)	40.7±6.28	43.8±5.72	0.477	-3.105 (-6.144-0.657)	43.1±6.28	43.3±5.87	0.742	-0.217 (-3.575-3.141)
Glucose (mmol/l)	9.6±3.14	9.3±2.86	0.732	-2.663 (-13.231-7.904)	9.01±3.78	8.7±2.25	0.701	-1.320 (-3.760-1.119)
Calcium ion (mmol/l)	1.6±0.42	2.2±0.24	0.006	-0.591 (-0.761-0.421)	1.5±0.23	2.0±0.39	0.004	-0.684 (-0.870 - -0.499)
BUN (mmol/l)	61.8±10.18	77.6±10.58	0.268	-15.808 (-49.928-18.310)	67.8±12.13	76.3±29.66	0.342	-8.451 (-45.571-28.668)
CRP (mg/l)	119.9±44.73	71.3±21.48	<0.001	38.528 (20.330-56.725)	99.7±26.38	76.5±29.49	0.405	6.227 (-15.014-27.469)
WBC (10 ⁹ /l)	15.4±5.87	13.7±7.00	0.943	1.671 (-1.916-5.259)	16.5±6.24	13.5±6.88	0.966	2.816 (-1.051-6.884)
PTC (ng/ml)	2.1±0.80	1.4±0.79	0.023	0.017 (-0.399-0.434)	1.5±0.75	1.2±0.78	0.988	0.501 (0.059-0.943)
Fibrinogen (g/l)	3.6±1.71	3.7±1.57	0.721	-0.093 (-0.928-0.741)	4.0±2.09	3.7±1.51	0.111	0.279 (-0.625-1.183)
RDW (%)	13.3±0.58	13.0±0.54	0.101	0.284 (-1.465-3.426)	13.6±0.41	12.9±0.66	0.003	0.943 (-0.148-2.465)
Extent of necrosis								
<30%	12 (12.5%)	84 (87.5%)	0.037	0.286 (0.083-0.980)	8 (8.5%)	86 (91.5%)	0.002	0.171 (0.050-0.584)
≥ 30%	5 (33.3%)	10 (66.7%)			6 (35.3)	11 (64.7%)		
Number of fluid collections								
1	14 (15.6%)	76 (84.4%)	0.884	1.105 (0.287-4.258)	12 (15.4%)	66 (84.6%)	0.176	2.818 (0.584-13.366)
≥2	3 (14.3%)	18 (85.7%)			2 (6.1%)	31 (93.9%)		
MCTSI	6.5±1.34	4.7±1.19	0.020	1.257 (0.384-2.311)	6.2±1.67	4.8±0.98	0.025	2.975 (0.521-3.643)

IPN, infective pancreatic necrosis; OF, organ failure; BUN, blood urea nitrogen; CRP, C-reactive protein; WBC, white blood cells; PTC, procalcitonin; FIB, fibrinogen; RDW, red cell distribution width; MCTSI, modified computerized tomography severity index.

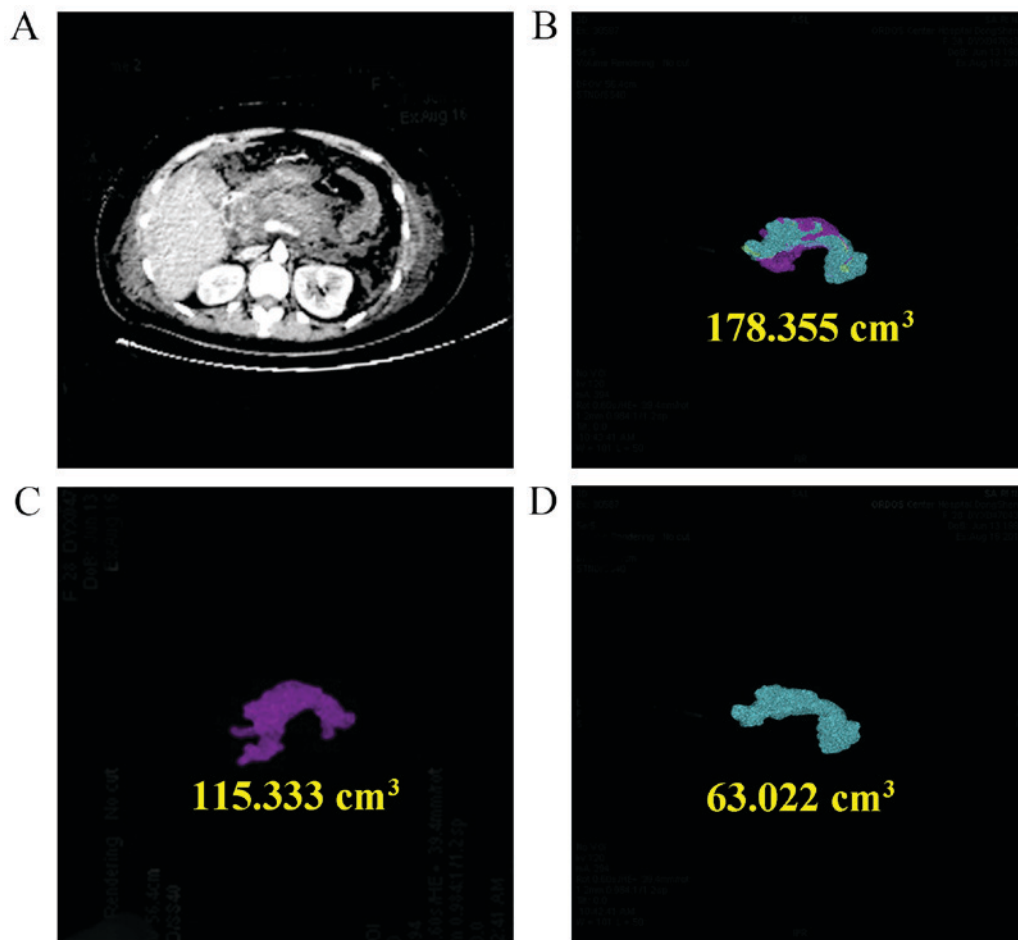


Figure 1. Peripancreatic necrosis extent was determined from computed tomography scanning. (A) Arterial phase imaging. (B) Whole pancreas. (C) The purple region represents the non-necrotic tissue of the pancreas. (D) The blue region represents the necrotic tissue of the pancreas.

cut-off value of RDW and the extent of necrosis to predict OF was 13.7 and 18.7%, respectively.

Discussion

HLAP is the third most frequent cause of AP. Multicenter, retrospective studies have revealed that the prevalence of HLAP has increased over the past 20 years (16). Other studies have revealed that increasing TG is a key factor in inducing HLAP, while obesity, fatty liver, male sex and concomitant diabetes are also important factors in inducing HLAP (17-19). In the present study, 90 patients were male, aged <45 years and had a relatively high BMI. HLAP is more common in younger males; this may be associated with unhealthy, high-lipid diets, overeating and excessive alcohol consumption. Similarly, transient increases in TG levels in the plasma are associated with the competitive simultaneous oxidation of ethanol and free fatty acids (FFA) in liver tissues (20).

CRP is a non-specific marker for tissue lesions and inflammation, and is an acute-phase reaction (APR) protein that activates the complement system, improves phagocytosis and adjusts immunity. When the body is damaged, an APR occurs and CRP levels increase. AP is an acute inflammation caused by pancreatitis and induces the autodigestion of pancreatic tissues. Among patients with severe AP, particularly in cases of PN complicated with bacterial infection, CRP may rapidly

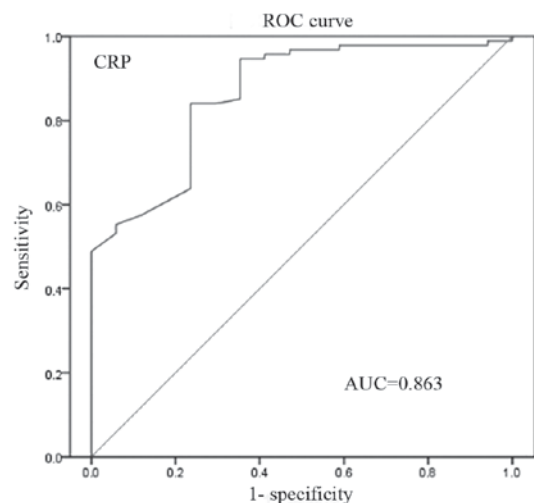


Figure 2. ROC curve for CRP to predict the development of infective pancreatic necrosis in hyperlipidemic acute pancreatitis. ROC, receiver operating characteristic; CRP, C-reactive protein; AUC, area under the curve.

increase. CRP levels reflect the extent of inflammation in AP and may predict important indexes of disease severity, complications and mortality. Detection of CRP has the advantages of low cost, simplicity, availability, accuracy and reliability.

Table II. Multivariate regression analysis of variables independently associated with progression to IPN and OF.

Event/variables	OR (95% CI)	P-value
IPN		
CRP	0.961 (0.933-0.991)	0.014
OF		
RDW	1.225 (1.051-1.648)	0.025
Extent of necrosis ($\geq 30\%$)	2.410 (1.210-3.612)	0.022

IPN, infective pancreatic necrosis; OF, organ failure; CRP, C-reactive protein; RDW, red cell distribution width; OR, odds ratio; CI, confidence interval.

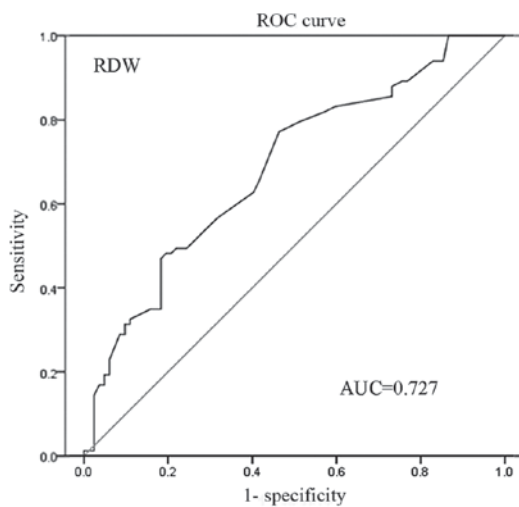


Figure 3. ROC curve for RDW to predict the development of organ failure in hyperlipidemic acute pancreatitis. RDW, red cell distribution width; ROC, receiver operating characteristic; AUC, area under the curve.

Furthermore, CRP determined within 48 h of presentation is more accurate in predicting SAP and PN, with a higher sensitivity and specificity compared with CRP determined at other time-points (21). Khanna *et al* (22) revealed that CRP had the highest sensitivity (100%) and specificity (81.4%) for the prediction of PN, while it had a sensitivity of 86.2% and a specificity of 100% for the prediction of SAP. The AUC for CRP for the prediction of PN was higher at 0.90 (95% CI, 0.82-0.77) compared with the AUC for the multiple organ system score, the acute physiology and chronic health evaluation II score, systemic inflammatory response syndrome, the bedside index for severe acute pancreatitis, interleukin (IL)-6 expression and the CT severity index. Yin *et al* (23) revealed that the for the accurate prediction of severity, the cutoff value for CRP in HLAP was required to be higher than that in non-HLAP. Furthermore, the serum CRP concentration in patients with HLAP, mild AP, moderately severe AP and SAP was notably higher within four days of disease onset. In the present study, univariate analysis of early risk factors for HLAP progression indicated that calcium ions, CRP, extent of necrotic tissue and MCTSI were significant predictors of IPN. Multivariate analysis then determined that CRP is an

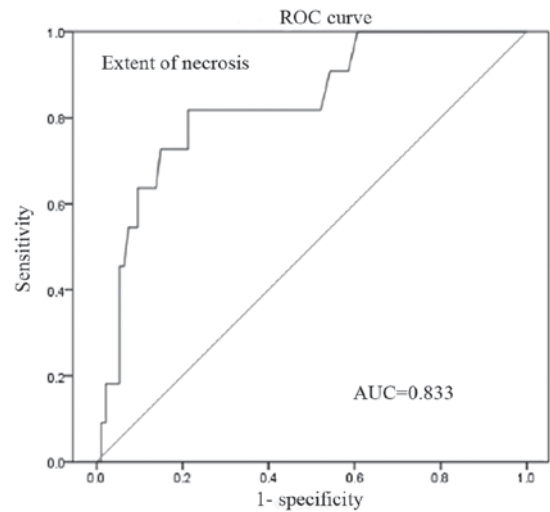


Figure 4. ROC curve for the extent of necrosis to predict the development of organ failure in hyperlipidemic acute pancreatitis. ROC, receiver operating characteristic; AUC, area under the curve.

independent predictive factor for progression of HLAP to IPN (OR, 0.961; 95% CI, 0.933-0.991; P=0.014).

The diagnostic criteria for OF are in line with the improved Marshall scoring system, which mainly involves the evaluation of respiratory, circulation and kidney function of patients with pancreatitis. In the present study, the clinical partial oxygen pressure/fraction of inspired oxygen index, contractive pressure and serum creatinine index were assessed for this. A score of ≥ 2 for any organ is regarded as indicative of OF (8). Studies have revealed that HLAP more easily progresses to OF through excessive TG levels causing the release of large quantities of FFA in the process of pancrelipase hydrolysis (24). Furthermore, the FFA form an acidic environment in the pancreas, and a number of cytokines and inflammatory mediators are activated and released, thereby leading to systemic inflammatory response syndrome (SIRS), which may in turn lead to multiple organ dysfunction syndrome.

The clinical presentation of early OF due to AP includes damage to the respiratory, circulatory and renal systems. If this is reliably predicted, targeted and appropriate treatments may be immediately applied and the duration and severity of OF may be decreased. Searching for markers whose assessment is simple, economic and non-invasive, and which have good sensitivity and specificity, is important for predicting OF in AP.

Several parameters, including the concentration of apolipoprotein (APO)A-I, high-density lipoprotein-cholesterol and combinations of APOA-I and scoring systems (25), lactate dehydrogenase (26) and calcium (27), have been used for predicting persistent OF in AP. Peng *et al* (28) concluded that RDW is independently associated with persistent OF in AP and may serve as an early predictor. The predictive value of RDW was superior to that of SIRS and glucose levels. Another study indicated that RDW is a potential novel and sensitive predictor of mortality in patients with AP (29). The AUC for RDW was 0.894 (95% CI, 0.823-0.966) and the optimal cut-off value to predict mortality was 14.35 (sensitivity, 88.2%; specificity, 91.8%).

RDW, the assessment of which is part of routine blood tests, is used as a parameter to quantify the extent of erythrocyte anisocytosis. A meta-analysis has determined that RDW is an independent prognostic marker for determining the risk of mortality in numerous pathophysiological conditions, including cardiovascular diseases and cancer (30). The univariate logistic regression analysis regarding the early prediction of HLAP progression to OF performed in the present study revealed that calcium ions, oxygen partial pressure, extent of necrosis and MCTSI scores are significant risk factors. Multivariate analysis then indicated that RDW is an early independent predictor of OF in HLAP ($P=0.025$).

Meyrignac *et al* (31) investigated the aptness of the extra-PN volume for early prediction of AP severity. The AUC for extra-PN in the prediction of OF was 0.94 (95% CI, 0.90-0.97), which was significantly higher than that of the Balthazar score (AUC, 0.83; 95% CI, 0.76-0.88), the CTSI (AUC, 0.84; 95% CI, 0.78-0.89) and CRP levels (AUC, 0.78; 95% CI, 0.72-0.84). With a cutoff value of 100 ml, extra-PN had a sensitivity of 95% (19/20) and a specificity of 83% (142/172) in the prediction of OF. Mentula *et al* (32) demonstrated that IL-10, high blood sugar and serum calcium are independent predictive factors for the progression of AP to OF. Furthermore, calcium levels were identified to be associated with the clinical onset of OF. The combined predictive value of IL-10 ($>50 \mu\text{g/ml}$) and calcium ($<1.65 \text{ mmol/l}$) was greater than that of any single factor or of the APACHE II score, with a sensitivity of 88%, a specificity of 93% and an adjusted OR of 94. In conclusion, the extent of necrosis is another independent prognostic/predictive factor of the progression of HLAP to OF, while serum calcium is also closely associated with OF in HLAP. However, calcium ions are not an independent predictive factor, as indicated by multivariate logistic regression analysis.

The aim of the present study was to investigate the early risk factors of HLAP progression in order to facilitate intervention/prevention, as well as to open up novel avenues for its clinical treatment. However, due to its retrospective nature, the present study only included a limited number of subjects with correlative factors. Further studies with larger sample sizes and multicenter studies are therefore required to verify the present results.

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Availability of data and materials

The analyzed data sets generated during the present study are available from the corresponding author on reasonable request.

Authors' contributions

XC and ZS designed the study. HW, XY, HD, EC, SW and YD collected the data. XC analyzed the data and drafted

the manuscript. All authors have read and approved the final manuscript.

Ethical approval and consent to participate

The present study was approved by the ethical review committee of Ordos Central Hospital (Ordos, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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