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Growth differentiation factor 15 is an early predictor for persistent organ failure and mortality in acute pancreatitis

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ABSTRACT

Objectives: Early prediction of persistent organ failure (POF) is crucial for patients with acute pancreatitis (AP). Growth differentiation factor 15 (GDF15), also known as macrophage inhibitory cytokine 1 (MIC-1), is associated with inflammatory responses. We investigated changes in plasma GDF15 and assessed its predictive value in AP.

Methods: The study included 290 consecutive patients with AP admitted within 36 h after symptoms onset. Clinical data obtained during hospitalization were collected. Plasma GDF15 levels were determined using enzyme-linked immunosorbent assays. The predictive value of GDF15 for POF was analyzed.

Results: There were 105 mild, 111 moderately severe, and 74 severe AP patients. Plasma GDF15 peak level were measured on admission, and significantly declined on the 3rd and 7th day. Admission GDF15 predicted POF and mortality with areas under the curve (AUC) of 0.847 (95% confidence interval [CI] 0.798–0.895) and 0.934 (95% CI 0.887–0.980), respectively. Admission GDF15, Bedside Index of Severity in Acute Pancreatitis, and hematocrit were independent factors for POF by univariate and multivariate logistic regression, and the nomogram built on these variables showed good performance (optimism-corrected c-statistic = 0.921). The combined predictive model increased the POF accuracy with an AUC 0.925 (95% CI 0.894–0.956), a net reclassification improvement of 0.3024 (95% CI: 0.1482–0.4565, $P < 0.001$), and an integrated discrimination index of 0.11 (95% CI 0.0497–0.1703; $P < 0.001$).

Conclusions: Plasma GDF15 measured within 48 h of symptom onset could help predict POF and mortality in AP patients.

1. Introduction

Acute pancreatitis (AP) is one of the most common gastrointestinal causes for hospitalization and has shown an increasing incidence in the last several decades [1]. Patients with AP experience variable clinical courses. Those with mild acute pancreatitis (MAP) do not typically develop any complications. Moderately severe acute pancreatitis (MSAP) can be accompanied by local complications or transient organ failure (TOF). Severe acute pancreatitis (SAP), which is defined by the occurrence of persistent organ failure (POF), is associated with increased mortality [2]. Predicting AP severity can identify at-risk patients and decrease mortality because it estimates whether organ failure (OF) will persist or resolve within 48 h. Accurate and early prediction of patients at risk of POF is clinically valuable, and a severity stratification to guide early management could improve clinical outcomes [3].

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Multiple scoring systems and biomarkers have been used to predict AP severity. Scoring systems such as the Bedside Index of Severity in Acute Pancreatitis (BISAP), Acute Physiology and Chronic Health Examination (APACHE II), and Systemic Inflammatory Response Syndrome (SIRS) are mostly based on a combination of clinical, laboratory, and radiographic findings, are of major limitation for their complex and cumbersome to implement in practice [4]. Although single laboratory tests including C-reactive protein (CRP), interleukin-6 (IL-6), blood urea nitrogen (BUN), hematocrit (HCT), and other markers have been studied as individual predictors of severe AP, they do not adequately predict SAP within 48 h after admission.

Growth differentiation factor 15 (GDF15), originally known as macrophage inhibitory cytokine-1 [5], is abundant in the placenta but has low or absent expression in several tissues [6]. However, GDF15 expression increases in hepatic [7], renal [8,9] and metabolic diseases [10–12]. Although the effects and biological significance of GDF15 in these diseases are largely indistinct, circulating GDF15 is associated with disease severity. In recent years, GDF15 was identified as a novel clinical biomarker with prognostic value for heart failure [13] or myocardial infarction [13–15], renal failure [16,17], acute respiratory distress syndrome [18], and sepsis [19]; however, no study has assessed plasma GDF15 expression in AP patients, and the prognostic value of GDF15 for AP is unknown. Given that elevated GDF15 levels were previously reported in cardiovascular, pulmonary, and renal failure, we hypothesized that GDF15 might be a predictive biomarker for POF and mortality in AP patients.

The present study was designed to measure longitudinal changes in plasma GDF15 levels in hospitalized AP patients and to determine the predictive value of plasma GDF15 for POF and mortality.

2. Materials and methods

2.1. Study population

A consecutive cohort of patients with AP admitted to our center at West China Hospital between December 9, 2016, and July 2, 2019, were enrolled. Eligible patients were 18–70 years old and had developed abdominal pain less than 36 h prior to admission. Patients were excluded if they had any known history of advanced comorbid diseases, trauma, tumor, pregnancy, lactation, or chronic pancreatitis.

The study protocol was approved by the West China Hospital of Sichuan University Clinical Trials and Biomedical Ethics Committee and was registered on the Chinese Clinical Trial Registry (No. ChiCTR2000034373). Informed consent was obtained from each patient included in this study.

2.2. Sample collection

The biobanking procedures were certified by the China Human Genetic Resources Management Office (2016, No. 406) as a part of the West China Biobank. Peripheral blood samples were taken from AP patients on admission (within 12 h after admission and on the), 3rd and 7th days after admission. The time interval between symptom onset and sample collection was less than 48 h.

Blood samples from healthy volunteers (HVs) were also obtained. Plasma samples were obtained after centrifugation at 1500*g* for 10 min and stored at −80 °C before use. Sample collection, processing, storage, monitoring, and use followed standard operating procedures (SOPs). All study procedures were in accordance with the ethical standards of the 1975 Helsinki Declaration as revised in 2013.

2.3. Clinical data collection

Demographic and clinical data were prospectively recorded in the database. The manual data collection process followed SOPs (WH and QX) by experienced medical students (QT, and LL) or attending doctors (CH, NS, XZ) with subsequent quality checks by more senior doctors (TJ and LD). SIRS, BISAP, APACHE II, and Modified Marshall Scores (MMS) were calculated.

2.4. AP diagnosis and severity stratification

Diagnosis and severity stratification were based on the Revised Atlanta Classification [2]. The diagnosis of AP was established when patients satisfied two out of the three following criteria: (1) characteristic epigastric abdominal pain, (2) elevation of amylase and/or lipase levels to threefold the upper limit of normal, and (3) abdominal imaging findings indicative of AP. OF was diagnosed if the scores of each organ was $\geq$2 points according to MMS. POF was defined as OF persisting longer than 48 h. TOF was defined as OF persisting no more than 48 h. Multiple organ failure was defined as at least two organs manifesting functional failure.

2.5. Outcomes

The primary outcome was POF in at least one of the respiratory, cardiovascular, or renal systems. Hospital mortality was recorded in hospitalization. Infection was defined as the appearance of infected pancreatic necrosis and/or extrapancreatic infection at least 3 days after admission. Local complications were defined according to the Revised Atlanta Classification [2]. Acute necrosis collection (ANC) was diagnosed when imaging reports from enhanced computerized tomographic scans clearly indicated the presence of “pancreatic necrosis or peripancreatic necrosis.” In a minority of the cases when this was equivocal, an experienced abdominal radiologist reviewed the scans and defined ANC as containing heterogenous contents (necrotic tissue with fluid) in the pancreatic parenchyma and/or peripancreatic tissues. Infected pancreatic necrosis was defined by microbiological diagnosis of pancreatic infection after the first sampling from drainage or debridement, or high suspicion of infection that eventually required necrosectomy in the absence of prior aspiration or drainage to confirm infection.

2.6. Laboratory analysis

Plasma GDF15 concentrations were determined by enzyme linked immunosorbent assay (DuoSet; R&D Systems, Inc. Minneapolis, MN, USA) in accordance with the manufacturer's instructions. CRP, IL-6, BUN, HCT, and other routine clinical biomarkers were determined and reported by the Laboratory Department of West China Hospital.

2.7. Statistical analysis

Statistical analyses were performed using IBM® SPSS® (version 24.0; IBM Corp., Armonk, NY, USA). Descriptive data are presented as median and interquartile range (IQR) for continuous variables. Categorical data are given as proportions. Bivariate relationships for categorical variables were assessed using Pearson chi-square tests and for continuous variables using Mann–Whitney *U* tests (2 groups) and Kruskal–Wallis *H* tests ($\geq$3 groups). Baseline characteristics were compared between different severity groups.

Univariate and multivariate logistic regression analyses were performed to investigate risk factors for POF. Factors that reached $P < 0.1$ in univariate analysis were introduced into a multivariate model that was built using stepwise regression from the set of

candidate variables. The model discrimination was reported together with Akaike information criterion (AIC) measures for comparing maximum likelihood models. Our final model is presented as a nomogram. Model discrimination was assessed by calculating the area under the receiver-operating characteristic curve (AUC, or c-statistic). Model calibration was determined with the Hosmer-Lemeshow technique, and a calibration curve was drawn. The bootstrap method was used for internal validation.

Receiver operating characteristic (ROC) curves were constructed for the predictive variables, and AUCs with 95% confidence intervals (95% CIs) were calculated. Optimal cut-off values for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) for each parameter were derived from the ROC curves. To assess whether there were any improvements in discrimination, we calculated the integrated discrimination index (IDI) and categorical net reclassification improvement (NRI). Two-sided $P < 0.05$ was considered statistically significant. Bonferroni corrections were used for multiple testing adjustments.

3. Results

The processes of patient selection and exclusion are shown in Fig. 1. A total of 290 patients had a diagnosis of AP fulfilling the inclusion criteria during the study period.

3.1. Baseline characteristics and clinical outcomes

The baseline characteristics and clinical outcomes are summarized in Table 1. Of 290 patients fulfilling the inclusion criteria, there were 105 (36.2%) MAP, 111 (38.3%) MSAP, and 74 (25.5%) SAP. The median age was 45.2 (IQR: 37.4–52.2) years, and 72.4% were male. A total of 123 among 290 (42.4%) developed OF, in which 49 were TOF and 74 were POF. Among patients developing POF, there were 74 (100%) for respiratory, 15 (20.3%) for circulatory, and 11 (18.9%) for renal. There were 102 (35.2%) patients who admitted to the high-dependency unit/intensive care unit (HDU/ICU). Among 290 patients, 164 (56.9%) were diagnosed with local pancreatic complications, including 91 (31.4%) who developed acute peripancreatic fluid collection (APFC), and 76 (26.2%) who developed ANC. Infections were found in 51 (17.6%) patients. Pancreatic necrosectomy was performed in 9 (3.1%) patients with (peri)pancreatic infection. The mortality of SAP was 9.5% with an overall mortality of 2.4%. SIRS, APACHE II, BISAP, SOFA, MMS, HCT, creatinine, IL-6, and CRP were significantly higher in patients with SAP compared to those with MAP or MSAP. In contrast, BUN levels on admission were not significantly different among the groups.

3.2. Features of plasma GDF15 for predicting AP severity

Plasma GDF15 measured at different time points showed a decreasing tendency (Fig. 2). The highest value was measured on admission [median (IQR): 1229.5 (724.6–1771.8) pg/ml] and then significantly declined on the 3rd [870.7 (553.4–1286.8) pg/ml] and 7th days [902.8 (574.1–1323.2) pg/ml] ($P < 0.001$) (Fig. 2A). GDF15 plasma levels were not significantly different on the 3rd and 7th days, but they were still above the normal levels measured in HVs [206.8 (154.4–238.8) pg/ml; $P < 0.001$]. We further performed subgroup analysis according to the interval from disease onset to the first sampling time. Within each severity group, there was no

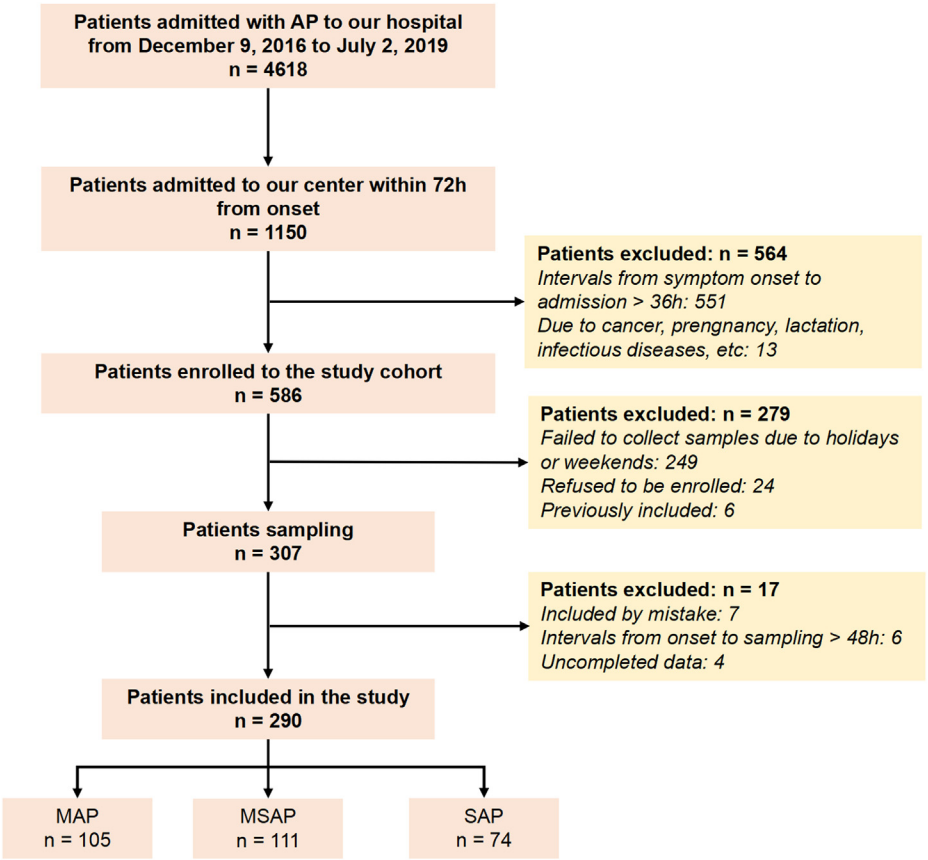


Fig. 1. Patient selection flow chart. AP: acute pancreatitis; MAP: acute pancreatitis; MSAP: moderate severe acute pancreatitis; SAP: severe acute pancreatitis.

Table 1
Baseline characteristics and clinical outcomes of the study population according to the severity of acute pancreatitis.

	Total (n = 290)	MAP (n = 105)	MSAP (n = 111)	SAP (n = 74)	*P* value[a]
Age, years[g]	45.2 (37.4–52.2)	45.03 (37.34–51.15)	45.15 (37.32–51.72)	45.78 (37.55–54.35)	0.093
Gender (male%)	210 (72.4)	76 (72.4)	83 (74.8)	51 (68.9)	0.676
Charlson comorbidity index[g]	0 (0–2)	0 (0–2)	0 (0–2)	2 (0–2)	0.18
Time from onset to sampling, hours[f]	26 (18.0–33.0)	27 (20–33.5)	26 (19–33)	22.5 (15–31.25)	0.093
Etiology					0.845
Biliary (%)	70 (24.1)	28 (26.7)	26 (23.4)	16 (21.6)	
Hypertriglyceridemia (%)	160 (55.2)	54 (51.4)	66 (59.5)	40 (54.1)	
Alcoholics (%)	11 (3.8)	5 (4.8)	3 (2.7)	3 (4.1)	
Others (%)	49 (16.9)	18 (17.1)	16 (14.4)	15 (20.3)	
Scoring systems[g]					
SIRS (on admission)	2 (1–3)	1 (0.5–2)	2 (1–3)	3 (2–3)	<0.001[d]
SIRS (24 h)	2 (1–3)	1 (0–2)	2 (1–2)	3 (2–3)	<0.001[d]
SIRS (48 h)	2 (0–3)	0 (0–1)	2 (0–2)	3 (2–3)	<0.001[d]
APACHE II	5 (3–7)	4 (2–6)	4 (2–6)	8 (6–12)	<0.001[b]
BISAP	1 (0–2)	1 (0–1)	1 (1–2)	2 (2–2)	<0.001[d]
SOFA	1 (0–2)	0 (0–1)	1 (0–2)	3 (1–4)	<0.001[b]
MMS	0 (0–1)	0 (0–0)	0 (0–1)	1.5 (0–3)	<0.001[d]
MCTSI	4 (2–6)	2 (2–4)	4 (4–6)	6 (4–8)	<0.001[d]
Single biomarkers[g]					
HCT, %	0.43 (0.4–0.47)	0.42 (0.39–0.45)	0.43 (0.4–0.47)	0.48 (0.43–0.52)	<0.001[b]
BUN, mmol/L	4.66 (3.5–6.13)	4.4 (3.43–5.5)	4.82 (3.5–5.9)	5.1 (3.1–7.3)	0.226
Creatinine, μmol/L	71 (57–82.25)	65 (52–79)	71 (58–80)	77.5 (59.5–111.25)	<0.001[b]
IL-6, pg/ml	86.89 (28.95–232.98)	35.66 (13.25–77.04)	97.23 (40.6–210.7)	297 (153.93–687.83)	<0.001[d]
CRP (on admission), mg/L	99.5 (27.2–223)	42.3 (11.4–101)	107 (42.95–221.5)	261 (134.5–373.5)	<0.001[d]
CRP (48 h), mg/L	139.5 (74.6–238)	139 (76.85–238.5)	144 (72.9–241.75)	139 (73.9–196.5)	<0.001[d]
Outcomes					
OF (%)	123 (42.4)	0 (0)	49 (44.1)	74 (100)	<0.001[d]
POF (%)	74 (25.5%)	0 (0)	0 (0)	74 (100)	<0.001[b]
MOF (%)	18 (6.2)	0 (0)	1 (0.9)	17 (23)	<0.001[b]
HDU/ICU admission (%)	102 (35.2)	0 (0)	28 (25.2)	74 (100)	<0.001[d]
Infection (%)	51 (17.6)	3 (2.9)	13 (11.7)	35 (47.3)	<0.001[d]
Necrosectomy (%)	9 (3.1)	0 (0)	0 (0)	9 (12.2)	<0.001[b]
Mortality (%)	7 (2.4)	0 (0)	0 (0)	7 (9.5)	<0.001[b]
Hospital LOS (days)[g,e]	10 (7–14)	8 (6–9)	10 (8–14)	16 (12–23)	<0.001[d]

[a] Indicates $\chi 2$ (or Fisher's exact test) for qualitative data and Kruskal–Wallis *H* test for quantitative data.
[b] $P < 0.05$, severe versus mild or moderate.[c] $P < 0.05$, mild versus moderate or severe.
[d] $P < 0.05$, between any two groups.
[e] Data from deceased patients are removed from the analysis.
[f] There was no significant difference within the group. APACHE II: Acute Physiology and Chronic Health Examination II; ANC: acute necrotic collection; APFC: acute peripancreatic fluid collection; BISAP: Bedside Index of Severity in Acute Pancreatitis; BUN: blood urea nitrogen; CRP: C-reactive protein; GDF15: growth differentiation factor 15; HCT: hematocrit; IL-6: interleukin-6; HDU: high-dependency unit; ICU: intensive care unit; LOS: length of stay; MAP: mild acute pancreatitis; MMS: Modified Marshall Score; MSAP: moderately severe acute pancreatitis; MOF: multiple organ failure; OF: organ failure; POF: persistent organ failure; SAP: severe acute pancreatitis; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential Organ Failure.
[g] Values are median (interquartile range).

significant variability among the time points within 48 h from abdominal pain onset (Fig. 2B). The results indicated that plasma GDF15 elevations were stable in different severity groups.

The SAP group [2086.2 (1477.4–2844.3) pg/ml] had significantly higher levels of GDF15 upon admission compared with MSAP [1230.6 (772.0–1614.3) pg/ml], MAP [740.8 (532.2–1167.2) pg/ml], or HVs [206.8 (154.4–238.8) pg/ml; $P < 0.001$] (Fig. 2C). Plasma GDF15 levels were higher in SAP than MSAP or MAP at each time point ($P < 0.001$) (Fig. 2A).

3.3. GDF15 in early prediction of POF development

It was of great interest to assess the predictive value of GDF15 in AP patients upon admission. We found a significant difference in admission GDF15 levels in patients who eventually developed POF (n = 74) and TOF (n = 49) [2086.2 (1477.4–2844.3) pg/ml vs. 1365.2 (1037.4–1775.7) pg/ml; $P < 0.001$] (Fig. 3A). Patients with OF upon admission (n = 63) had significantly higher GDF15 levels versus those without OF (n = 227) [1312.9 (1808.2–2782.9) pg/ml vs. 1070.2 (671.1–1535.1) pg/ml; $P < 0.001$] (Fig. 3B). We then investigated whether GDF15 could predict progression. Patients without OF on admission but who developed POF during their hospital stay had higher GDF15 levels compared with those who did not develop POF [1806.4 (1323.8–2674.6) pg/ml vs. 887.4 (591.8–1367.5); $P < 0.001$] (Fig. 3C). The results indicate that higher admission GDF15 could indicate the possible development of POF, even in patients who did not have OF on admission. In patients with OF on admission, plasma GDF15 was higher in those developing POF (n = 41) versus TOF (19) [2267.4 (1629.7–3265.3) vs. 1341.9 (957.2–1886.7); $P < 0.01$] (Fig. 3D). This indicates that elevated GDF15 level could be useful to distinguish POF from TOF in patients with OF on admission.

The results above showed a relevance of admission GDF15 to POF. Furthermore, ROC curve analysis identified that the AUC of admission GDF15 (AUC: 0.847; 95% CI 0.798–0.895) was higher than that on 3rd (AUC: 0.793; 95% CI 0.734–0.853) or 7th day (AUC: 0.786; 95% CI 0.719–0.853), which confirmed the accuracy of admission GDF15 in predicting POF. The absolute difference between plasma GDF15 levels on admission and the 3rd or 7th day of hospitalization had no adequate predictive value for POF. The AUC values for admission GDF15 and other well-established indicators of POF are summarized in Table 2. The data demonstrated that BISAP (AUC: 0.859; 95% CI 0.812–0.907) and admission GDF15 (AUC: 0.847; 95% CI 0.798–0.895) had strong predictive value for POF. The values for other clinical scores and markers were moderate (AUC: 0.551–0.835) in predicting POF with sensitivity

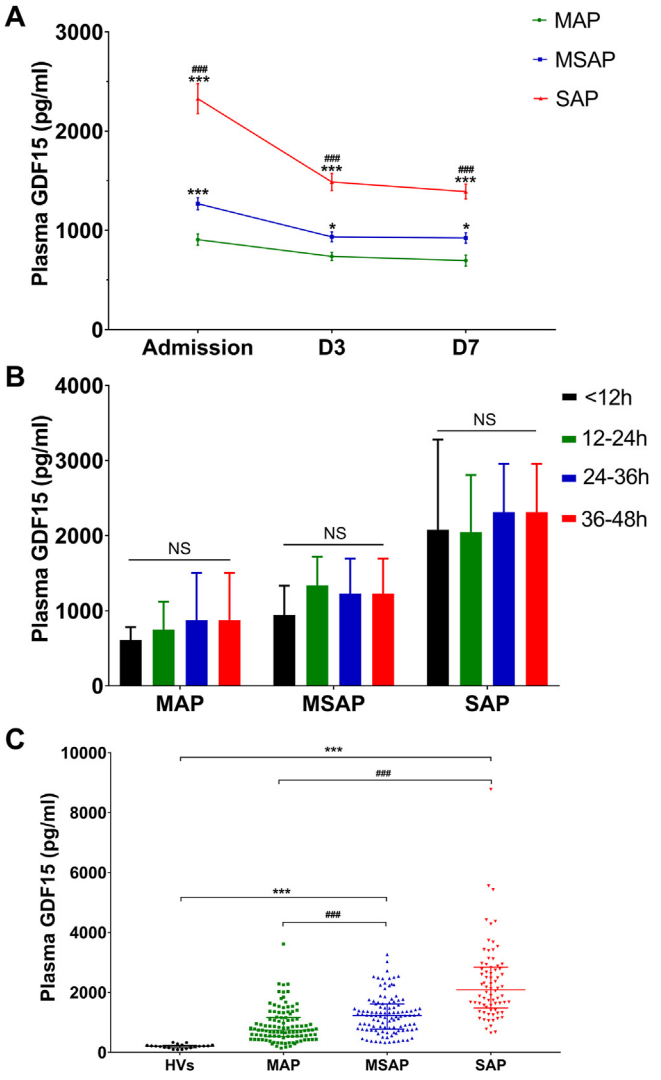


Fig. 2. Plasma GDF15 in patients with AP over time. **A.** Changes in plasma GDF15 levels on admission and on the 3rd and 7th days after admission. **B.** Plasma GDF15 levels at intervals of <12 h, 12–24 h, 24–36 h, and 36–48 h from abdominal pain symptoms to blood sampling upon admission. **C.** GDF15 levels on admission in SAP patients were significantly higher than those in MSAP, MAP or HV patients. GDF15: growth differentiation factor 15; HVs: healthy volunteers; MAP: acute pancreatitis; MSAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis. ***P < 0.001 versus MAP group at the corresponding time point; **P < 0.01 versus MAP group at the corresponding time point; *P < 0.05 versus MAP group at the corresponding time point; ###P < 0.001 versus MSAP group at the corresponding time point; NS, not significant.

(39.2–98.6%) and specificity (53.7–87.0%). Using the optimal cut-off value of 1549.43 pg/ml, plasma GDF15 predicted POF with sensitivity, specificity, PPV, and NPV of 74.3%, 80.6%, 56.7%, and 90.2%, respectively; the PLR and NLR values were 3.83 and 0.32, respectively (Supplementary Table 1). Patients with hypertriglyceridemic AP had higher levels of GDF15, IL-6, and CRP compared with other etiologies, but the predictive efficiency of GDF15 was equivalent (Supplementary Table 2).

Univariate logistic regression analysis showed that CRP, BISAP, GDF15, HCT, and IL-6 significantly correlated with POF (Supplementary Table 2). In the multivariate logistic analysis, only BISAP (odds ratio [OR] 5.254; 95% CI 2.877–9.593; P < 0.001), HCT (OR 1.122; 95% CI 1.044–1.205; P = 0.002), and GDF15 (OR 1.001; 95% CI 1.001–1.002; P < 0.001) were independently associated with POF. The discriminative ability of the final multivariate regression model performed well in predicting POF with a c-statistic value of 0.925 (95% CI 0.894–0.956). It showed proper discrimination and calibration (AIC = 182.95 and Hosmer-Lemeshow P value = 0.219) as depicted in the calibration plot (Supplementary Fig. 1).

A nomogram model to predict POF was developed based on the three independent variables (Fig. 4A). We performed internal validation of the nomograms according to a bootstrap method, which yielded an optimism-corrected c-statistic value of 0.921 (95% CI 0.912–0.969). The combined predictive model increased the accuracy for POF 0.925 (95% CI 0.894–0.956; P < 0.001) with a sensitivity and specificity of 94.6% and 84.7% respectively, and PLR and NLR of 6.16 and 0.064, respectively (Fig. 4B). Compared to BISAP, the NRI of the combined predictive model in predicting POF was 0.3024 (95% CI: 0.1482–0.4565; P < 0.001) and the IDI was 0.11 (95% CI 0.0497–0.1703; P < 0.001).

3.4. Plasma GDF15 in predicting mortality

We analyzed the association between GDF15 levels at admission and mortality (Fig. 5). Patients who died during hospitalization had significantly higher admission GDF15 levels than survivors [2933.4 (2364.7–3738.2) pg/ml vs. 1209.4 (716.2–1711.6) pg/ml, P < 0.001] (Fig. 5A). The same results were found for deceased and surviving SAP patients [2933.4 (2364.7–3738.2) pg/ml vs. 1880.1 (1404.2–2746.9) pg/ml; P = 0.01] (Fig. 5B).

The values of ROC curves for GDF15, clinical scores, and laboratory markers for predicting mortality are shown in Table 2. GDF15 had the highest predictive value with an AUC value of 0.934 (95% CI 0.887–0.980) (Fig. 5C). Using the optimal cutoff value of 2086.2 pg/ml, plasma GDF15 predicted death with sensitivity, specificity, PPV, and NPV of 100%, 82.7%, 66.45%, and 100% respectively, and a PLR and NLR of 5.78 and 0, respectively (Supplementary Table 3). There was no additive value for combinations of GDF15 and other parameters in predicting mortality.

3.5. Plasma GDF15 in patients with local complications

We further investigated plasma GDF15 in patients admitted to the HDU/ICU and those with local complications (Supplementary Fig. 2). Plasma GDF15 was higher in patients admitted to HDU/ICU versus those who were not [1756.6 (1268.8–2609.8) pg/ml vs. 881.5 (563.6–1366.6) pg/ml; P < 0.001]. When comparing patients with or without local complications, we observed a significant elevation in plasma GDF15 in patients who developed ANC [1869.0 (1268.5–2599.6) pg/ml vs. 1053.3 (650.3–1515.7) pg/ml; P < 0.001]. The plasma GDF15 ROC curve had no accurate predictive value for local complications. GDF15 levels in infected and non-infected patients were 2933.39 (2364.68–3738.16) pg/ml and 1880.09 (1404.16–2746.93) pg/ml, respectively (P = 0.272). Nine patients underwent necrosectomy due to infected pancreatic necrosis during hospitalization, and their GDF15 level on admission was significantly higher than that of other patients [2877.6 (2419.5–3328.9) vs. 1192.7 (706.9–1702.6) pg/ml; P < 0.001]. The AUC of GDF15 for predicting necrosectomy was 0.913 (95% CI 0.857–0.968), which was higher than other individual indicators. However, we only collected patient samples on admission and days 3 and 7; additional samples were not taken following necrosectomy. The changes of plasma GDF15 associated with necrosectomy remain to be determined.

3.6. Multivariate logistic regression analyses and ROC curves

Further analysis was performed to investigate the effects of referral. In the multivariate logistic regression analyses, 3 (GDF15,

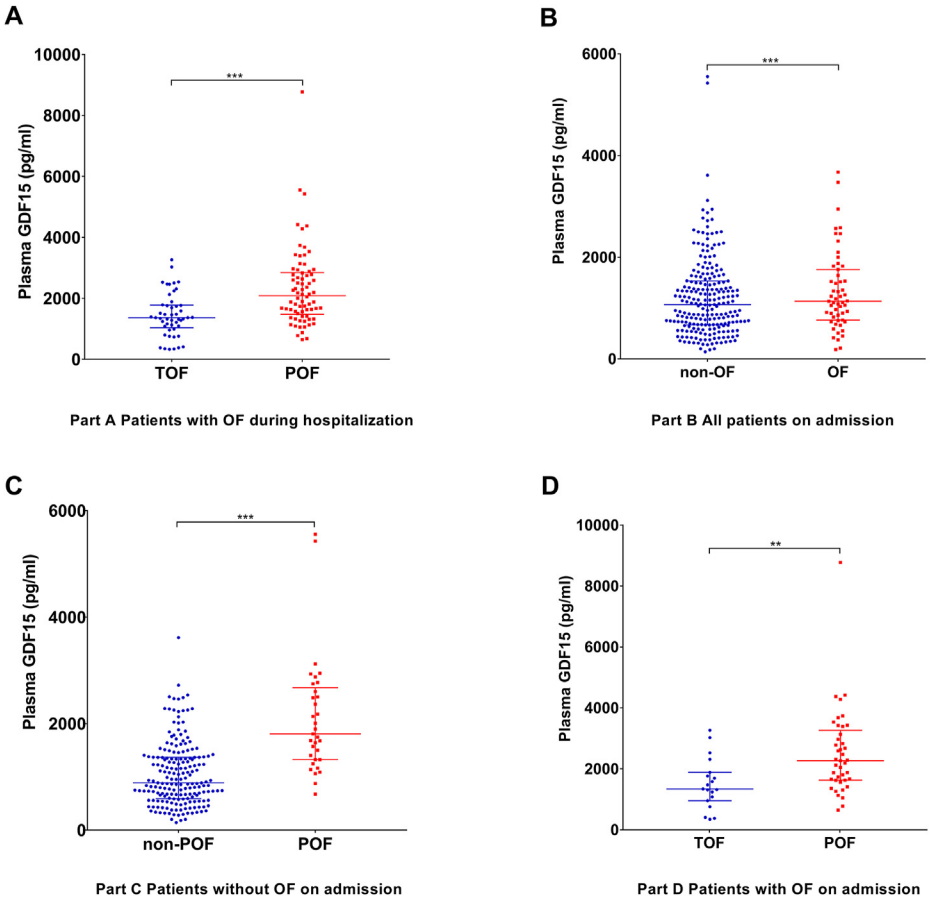


Fig. 3. Associations between admission GDF15 and OF in patients with AP. **A.** GDF15 levels in patients with POF were significantly higher versus those in patients with TOF. **B.** GDF15 levels in patients with OF on admission were significantly higher versus non-OF. **C.** Among patients without OF on admission, GDF15 levels in patients who developed POF were higher versus non-POF. **D.** Among patients with OF on admission, GDF15 levels were higher in patients developing POF compared to TOF. BISAP: Bedside Index of Severity in Acute Pancreatitis; CRP: C-reactive protein; GDF15: growth differentiation factor 15; MAP: acute pancreatitis; MSAP: moderately severe acute pancreatitis; organ: organ failure; POF: persistent organ failure; TOF: transient organ failure; SAP: severe acute pancreatitis . ***$P < 0.001$; **$P < 0.01$.

Table 2
Accuracy of potential predictors in predicting persistent organ failure and mortality on admission.

	Persistent organ failure			Mortality		
	AUC	95% CI	*P*	AUC	95% CI	*P*
BISAP	0.859	0.812–0.907	<0.001	0.844	0.710–0.977	0.002
GDF15	0.847	0.798–0.895	<0.001	0.934	0.887–0.98	<0.001
SIRS (48 h)	0.835	0.789–0.88	<0.001	0.799	0.673–0.926	0.012
SIRS (24 h)	0.832	0.786–0.878	<0.001	0.853	0.741–0.964	0.001
SOFA	0.82	0.762–0.877	<0.001	0.856	0.735–0.977	0.001
APACHEII	0.819	0.764–0.874	<0.001	0.877	0.745–1.00	0.001
IL–6	0.812	0.751–0.874	<0.001	0.922	0.846–0.997	<0.001
SIRS (on admission)	0.791	0.736–0.846	<0.001	0.783	0.656–0.911	0.01
CRP	0.78	0.716–0.844	<0.001	0.808	0.731–0.885	0.005
MCTSI	0.778	0.721–0.834	<0.001	0.679	0.521–0.837	0.106
HCT	0.751	0.685–0.817	<0.001	0.692	0.513–0.870	0.083
Creatinine	0.641	0.561–0.721	<0.001	0.885	0.761–1.00	<0.001
BUN	0.551	0.467–0.636	0.187	0.716	0.543–0.889	0.051

APACHE II: Acute Physiology and Chronic Health Examination II; BISAP: Bedside Index for Severity in Acute Pancreatitis; BUN: blood urea nitrogen; CRP: C-reactive protein; GDF15: growth differentiation factor 15; HCT: hematocrit; IL-6: interleukin-6; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential Organ Failure Assessment.

BISAP, and HCT) of 11 independent covariables were associated with POF, and 2 (age and GDF15) of 7 independent co-variables were associated with mortality. Referral was not an independent contributor to POF or mortality (Supplementary Table 4). However, ROC curves revealed that compared with non-referred patients, the AUCs of GDF15 [0.744 (95% CI 0.603–0.885) vs. 0.848 (95% CI 0.791–0.906)] and BISAP [95% CI 0.747 (0.574–0.92) vs. 0.846 (95% CI 0.788–0.904)] in predicting POF were lower than that of referred patients except HCT [0.871 (0.735–1) vs. 0.711 (0.631–0.79)]. Since there was only one death among non-referred patients, we did not perform ROC analysis to predict mortality.

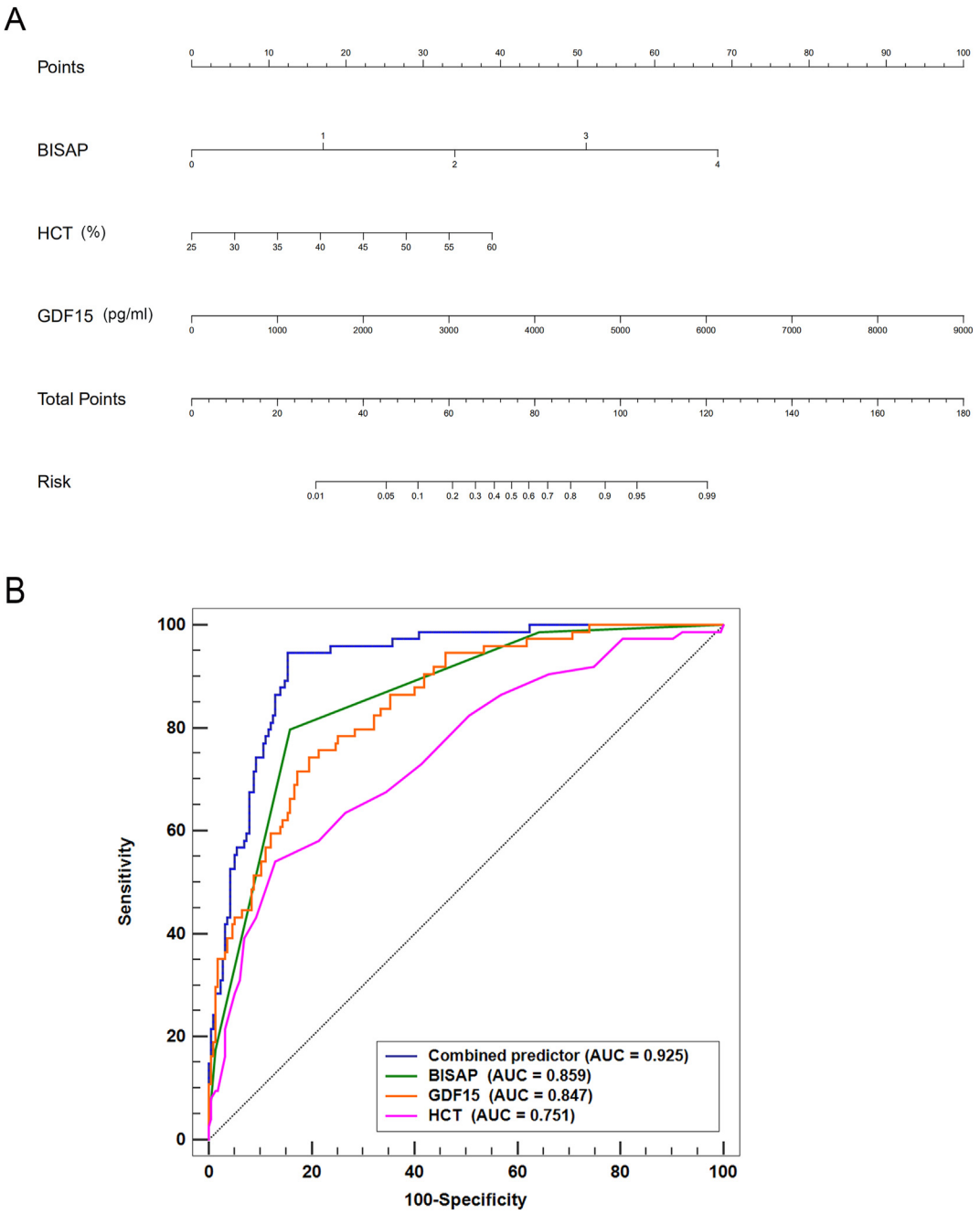


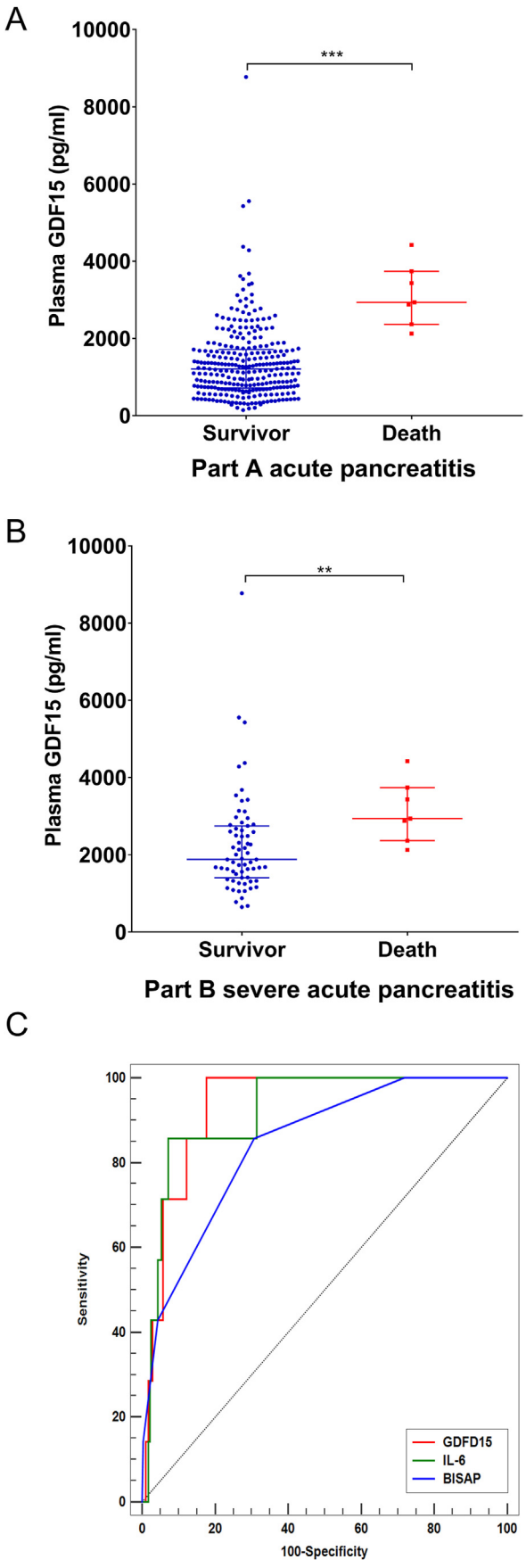
Fig. 4. Predictive model construction and predictor accuracy for POF. **A.** The Nomogram predicting the probability of POF in acute pancreatitis patients. **B.** Receiver-operating characteristic curves of BISAP, GDF15, HCT, and the predictive model for POF. BISAP: Bedside Index of Severity in Acute Pancreatitis; GDF15: growth differentiation factor 15; HCT, hematocrit; POF: persistent organ failure.

4. Discussion

A previous study determined that POF and infected pancreatic necrosis were major determinants for mortality in patients with AP [20]. A more recent report claimed that late mortality has diminished due to improved treatment for infected pancreatic necrosis, and the mortality pattern has changed to a single peak within 2 weeks followed by a steady decrease after 2 weeks [21]. Moreover, the importance of occurrence of during the first 24 h of admission was recognized, and OF duration was closely related to mortality [22]. These studies underscore the importance for early prediction of POF to offer intensive care and aggressive treatment to at-risk patients. It is necessary to identify a simple, accurate biomarker for POF to facilitate early prediction of AP severity.

GDF15 is lowly expressed under normal conditions. The mean value of circulating GDF15 in HVs was 206.8 (154.4–238.8) pg/ml, which is consistent with a previous study (319.4 ± 21.27 pg/ml) [11]. GDF15 can be elevated under a variety of environmental challenges such as age [23], smoking [24], hypoxia [25], and extreme endurance exercise [26]. In our study, we did not find any difference in GDF15 expression caused by sex, age, or smoking.

To the best of our knowledge, this is the first study to assess the longitudinal expression of plasma GDF15 in hospitalized AP patients. We found that plasma GDF15 was rapidly and dramatically



elevated in the initial stage of AP, especially in patients with severe disease. Our unpublished data in experimental AP models confirmed that GDF15 was remarkably increased in the early stage of AP and was associated with pancreatitis severity. Mice serum GDF15 levels were 18.58 (16.53–26.04) pg/ml in the control group, 33.94 (31.32–38.18) pg/ml in the mild AP group, and 456.6 (379.13–540.41) pg/ml in the severe AP group ($P < 0.001$ between groups). Circulating GDF15 was reportedly increased in chronic pancreatitis (2247.95 ± 179.27 pg/ml) and pancreatic ductal adenocarcinoma (7694.58 ± 1878.94 pg/ml) [27]. Other studies [27,28] found that GDF15 had a better performance compared with carbohydrate antigen 19–9 in distinguishing pancreatic ductal adenocarcinoma from normal serum or chronic pancreatitis.

Our results showed that plasma GDF15 was associated with POF occurrence and progression. Notably, in patients with OF on admission, higher levels of GDF15 were able to distinguish POF from TOF. More importantly, increased GDF15 could reveal a risk for progression to POF in patients without OF on admission. GDF15 levels also correlated with ANC and necrosectomy but did not show an accurate predictive value.

The AUC of GDF15 for POF was superior to those of IL-6, CRP, HCT, creatinine, BUN, SOFA, APACHE II, and SIRS but inferior to BISAP. Studies confirmed the predictive efficacy of BISAP in predicting AP severity [29,30] and death [31]. However, existing scoring systems have only modest accuracy in predicting POF [32]. A recent systematic review concluded that there is a lack of adequate predictors of POF within 48 h of hospital admission [33] and justifiable prediction models for mortality [34]. In our study, BISAP had a higher predictive value for POF with an AUC of 0.85, a sensitivity of 79.7%, and a specificity of 84.3%. Plasma GDF15 had a similar value to BISAP in predicting POF, but it is more convenient because it is a single marker. Although CRP is the most thoroughly investigated single marker, it could poorly predict severity on admission [35] and has the best predictive performance at 48 h after admission [36]. The accuracy of GDF15 in predicting POF in our study was higher than CRP levels both on admission and 48 h after admission. Moreover, GDF15 was the strongest in predicting death among all the indicators in our study. We constructed a logistic model to predict POF in AP patients using three independent variables and showed good performance; its efficacy was significantly higher than single predictors alone. The model improved efficiency in predicting POF by increasing the AUC to 0.925. The NLR was reduced to 0.064, which might help to exclude false-negative patients and identify patients at high risk who might benefit from more intensive treatments (e.g., fluid resuscitation) in the initial stage. We also developed a novel nomogram as a reference for clinical decision-making. Compared to BISAP, both the NRI and IDI of the combined model were significant in predicting POF. In summary, it might be useful for clinicians to measure GDF15 at admission to prevent POF and mortality in high-risk patients. In combination with BISAP and HCT, GDF15 could improve predictive accuracy.

As one of the largest single tertiary centers of China, our hospital admits a large number of referral patients with severe disease. To reduce the influence of the initial treatment on referral patient prognosis, we restrained the time window to 36 h from the onset of abdominal pain. Within this short time period, most transfer

Fig. 5. Admission GDF15 levels in deceased and surviving patients. **A.** Plasma GDF15 levels were significantly elevated in patients who died versus the survivors; **B.** Among SAP patients, plasma GDF15 levels were significantly higher in decreased compared to surviving patients; **C.** Receiver-operating characteristic curves of GDF15, IL-6, and BISAP in predicting mortality. AP: acute pancreatitis; BISAP: Bedside Index of Severity in Acute Pancreatitis; GDF15: growth differentiation factor 15; IL-6: interleukin-6; SAP: severe acute pancreatitis. ***$P < 0.001$; **$P < 0.01$.

patients only underwent diagnostic tests in an outside hospital and were immediately admitted to our center through a green delivery path in the hospital's emergency ward. According to our experience, AP abdominal pain is very intense, and patients often know the accurate time of onset with limited recall bias in a short time window. After admission, professional staff collected specimens and verified clinical data. The investigators determined the final enrollment and excluded patients with unclear information. We confirmed that all the patients in our study completed their specimen collection within 48 h whether they were transfer patients or not.

GDF15 has been implicated in various biological functions, but the mechanisms underlying OF remain obscure. GDF15 was increased in experimental conditions of ischemia/reperfusion injury and in clinical settings of organ dysfunction like heart failure [13], myocardial infarction [37,38], and pulmonary embolism [39]. GDF15 can be induced by inflammation and proinflammatory cytokines, suggesting that GDF15 might play a harmful role in sepsis by inhibiting neutrophil recruitment to the infected site [40]. These findings might explain the close association between GDF15 and organ dysfunction. We assume that circulating GDF15 and POF in AP was associated with inflammatory processes and macrophage activation. Paradoxically, evidence suggests that GDF15 may protect against injury. In lipopolysaccharide-induced sepsis models, GDF15 was required for survival following acute inflammatory states; it played a cardioprotective and reno-protective role as an “inflammation-induced central mediator of tissue tolerance” [41,42]. The contradiction of GDF15 upregulation in pathological conditions and its protective role might indicate that GDF15 plays a regulatory role as part of a compensatory mechanism in response to tissue damage [43]. The mechanisms of GDF15 in physiological and pathological regulation were poorly understood until glial cell line-derived neurotrophic factor-family receptor α-like, an orphan member of the GFR-α family, was identified as a high-affinity receptor for GDF15 [44–47]. Other signaling mechanisms also appear to be utilized by GDF15. The roles and molecular mechanisms of GDF15 association with AP severity are being studied.

There are some potential limitations that need to be acknowledged. First, the study was conducted at a large tertiary hospital that admits more seriously ill patients, which leads to a relatively low proportion of mild cases that represents our center's actual distribution in accordance with our previous reports [48,49]. While our results could be representative of large tertiary hospitals in China, the potential of bias calculation bias should be considered. Second, our cohort contained high proportion of AP with hypertriglyceridemia etiology (55%) which is consistent with our recent publications [22] and national trends [50]. Although we did not find any difference in GDF15 levels among etiologies in this study, we will investigate the effect of lipids on GDF15 expression in future work. Third, although nomogram performance was internally well-demonstrated through bootstrapping, further study is needed to perform external validation of the current model. A multi-center, prospective validation trial comparing more novel prognostic scoring and markers [51–54] of AP is required to clarify these issues.

5. Conclusions

In patients with AP, plasma GDF15 levels increased early, peaked at admission, and remained high on the 3rd and 7th days after admission. Plasma GDF15 is accurate in predicting POF and mortality in the early course of AP. Admission GDF15 level in combination with HCT and BISAP could improve prognostic predictive capabilities.

Declaration of competing interest

Authors state no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2021.12.001.

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