Pancreatology 19 (2019) 230–236

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

The product value of serum albumin and prothrombin time activity could be a useful biomarker for severity prediction in AP: An ordinal retrospective study

Shoukang Li [a], Zhiqiang Liu [b], Heshui Wu [b, *]

[a] Department of Thoracic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China
[b] Department of Pancreatic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China

ARTICLE INFO

Article history:
Received 6 October 2018
Received in revised form
1 February 2019
Accepted 2 February 2019
Available online 5 February 2019

Keywords:
Acute pancreatitis
The product value of serum albumin and prothrombin time activity
Severity
Organ failure
Death

ABSTRACT

Aim: To appraise the predictive function of 'the product value of serum albumin and prothrombin time activity' (PAA) on admission for the organ failure related events of acute pancreatitis (AP).
Background: 789 patients with AP were included in this retrospective study. 468 patients generated transient organ failure (TOF). 242 were diagnosed with persistent organ failure (POF), of which 63 patients died.
Study: All the values of laboratory parameters were measured upon admission to hospital. Dunnett'T3 test, Uni- and multi-variate ordinal logistic regression were used. ROC curve was utilized to evaluate the ultimate predictive values.
Results: Among the patients with 4 different levels of severity of acute pancreatitis, PAA observably reduced as the disease aggravated (32.20 vs 29.56 vs 23.54 vs 17.89). PAA was also an independent risk factor for the aggravation of AP (OR: 0.873, 95% CI: 0.848, 0.899; $p < 0.01$). The Area Under the Curve (AUC) of PAA for OF was 0.828 (0.783, 0.872), 0.828 for POF (0.790, 0.865) and 0.905 for death cases (0.862, 0.948).
Conclusion: The product value of serum albumin and prothrombin time activity is a good predictor of the severity, especially the events related to organ failure of acute pancreatitis.

Introduction

Acute pancreatitis (AP) is known as an inflammatory disorder characterized by local or systemic immuno-inflammation, which undergoes the development observed clinically from local pancreatitis through the systemic inflammatory response to organ dysfunction and death. Though most patients experienced a mild, self-limiting inflammatory process, the others will develop a severe disease with local or systemic complications and/or organ failure (OF), even death in the terminal stage [1]. According to the 2012 revised Atlanta classification for AP, the severity of the disease is categorized into 3 levels: mild (without OF), moderately severe (with transient organ failure; TOF, OF persists for < 48 h), and severe (with persistent organ failure; POF, OF persists for ≥ 48 h) [2–7].

Thus, it is important to assess the disease severity in order to study out the therapeutic strategy soon as the admission of the patient for the fact that effective treatments could significantly decrease the mortality of patients with severe pancreatitis [8,9]. A lot of invasive and non-invasive methods, including radiological imaging modalities, biochemical parameters and scoring systems are used for early diagnosing and evaluating the severity of AP.

At present, both serum albumin and prothrombin time (PT) are easy to detect. Though different examine-methods can lead to deviations in the results of PT, prothrombin time activity (PTA) can be a good way to standardize PT values [10,11].

Abnormal low-level of serum albumin signals act as a pivotal starter in the pathogenesis of AP. The hypoproteinemia has been observed in AP patients and the mechanism of it was studied too [12,13]. The dysfunction of coagulation was also found in many AP patients. Such as 'the levels of Antithrombin III (APTT)' and 'D-dimer', have been found to be closely connected with the severity of AP [14,15].

* Corresponding author.
E-mail addresses: shoukangli@hust.edu.cn (S. Li), heshuiwu@hust.edu.cn (H. Wu).

https://doi.org/10.1016/j.pan.2019.02.001
1424-3903/

The main aim of our study is to confirm that the product value of serum albumin and prothrombin time activity (PAA) on admission could be used to evaluate the severity of acute pancreatitis (AP).

Material and method

Patients

In total, 789 patients with AP in the Department of Pancreatic Surgery of Wuhan Union Hospital were recruited to our study from Jan.1st, 2010 to Dec.31st, 2016. The diagnosis was based on the presence of two or more of the following three criteria: 1) abdominal pain consistent with AP; 2) serum amylase and/or lipase elevation ≥ three times the upper limit of normal value; 3) contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI) or abdominal ultrasonography findings characteristic of AP [2]. The exclusion criteria included: 1) patients aged less than 18 years old; 2) the time from abdominal pain onset to hospital admission ≥72 h; 3) chronic pancreatitis; 4) pancreatitis induced by trauma or pregnancy; 5) diagnosed with chronic diseases of other organs (heart, liver, lung, kidney, etc.) before AP; 6) unavailable laboratory measurements or medical records. The information of those patients who were excluded due to the loss of medical records were shown in supplemental Table 1.

Laboratory data were obtained from the blood screening test at hospitalization. Patient's paper charts and electronic medical records were reviewed for information on demographics, physiologic characteristics, and disease severity by one independent physician.

The study was conducted according to the principles of the Declaration of Helsinki. For the reason that all data were retrieved retrospectively from the laboratory test information system without additional laboratory analysis or blood samples tests, informed consent for individual patient was not obtained. This study was approved by the ethics review board of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Definition

'PAA' was calculated from 'ALB' multiply by 'PTA'.

According to Modified Marshall score as described in the revised 2012 Atlanta classification, OF was diagnosed when at least one of the following cutoffs were exceeded: 1) respiratory failure if the ratio of PaO2/FiO2 was <300 mmHg; 2) renal failure if serum creatinine was ≥169 μmol/L; and 3) cardiovascular failure if systolic blood pressure was <90 mmHg despite fluid replacement. TOF was identified when OF lasts for less than 48 h, and POF if lasts for more than 48 h [2].

In our study, the death cases were all caused by OF after detailed analyses. The patients who died from severe complications at late-stage were not included.

Therefore, we divided all 789 patients into 4 different levels. 'Level 1' means those patients were without any OF. All patients in 'Level 2' only experienced a TOF. 'Level 3' consisted of all that patients who suffered from POF but survived. All the patients died from POF were included into 'Level 4'.

Statistical analysis

Statistical analysis were performed using SPSS 17.0 (SPSS Inc, Chicago IL, USA). Data were tested for normality and homogeneity of variance.

All the collected factors were analyzed by 'Dunnett'T3′ test first. Secondly, 'Parallel Lines' Test was used to test whether the ordinary regression was applicable. The remaining risk factors were selected out and joined in 'Ordinal logistic regression'. We used both 'univariate analysis' and 'multivariate analysis' to test the remaining factors together. We also used the ROC curve to describe the value in predictions of PAA. According to the three cut-off values of PAA, all 789 patients were then divided into 4 groups and the combination of the 4 groups were analyzed.

P value smaller than 0.05 was considered statistically significant.

Results

Patient characteristics

The male-female ratio (479/310) was 1.55, with a median age of 45 years. The numbers of patients in 'Level' 1–4 (without OF, with TOF, with POF but survived, died from POF) were 79, 468, 179 and 63 respectively.

In 'Level 2', 446 patients got through respiratory failure and 22 patients experienced renal failure. No patients had Multiple TOF or died in 'Level 2'.

In 'Level 3' and 'Level 4', there were 164 patients developing solitary POF (152 of respiratory system with 16 deaths, 11 of renal system with 4 deaths, 1 of cardiovascular and died). Multiple POF was observed in 78 patients (49 of lung and kidney, 18 of lung and heart, and 11 of lung, kidney and heart) and 42 of them died.

In total, 63 patients with POF died with a mortality of 8.0% (Table 1).

Comparison among all patients in different 'levels'

'Dunnett'T3′ test was applied to analyze the differences among the 4 'Levels'. All kinds of related factors were tested, including 'general information', 'laboratory examination', 'etiology'. For each factor, the comparison was done between any two 'Levels' and the result was considered 'significant' only when the values of all 4 'Levels' were totally different. There were only 7 factors which were significant, HDL-C, LDH, ALB, PTA, Ca, Ranson, PAA (Table 2). The details of 'Dunnett'T3′ test are shown in Table 3.

For each factor, we use the ratio of the corresponding value of different grades to the maximum value of the four grades to make a graph to indicate its changing trend. The variation trend of the above 7 factors among the 4 'Levels' is shown in Supplemental Figure 1.

PAA, the product value of serum albumin and prothrombin time activity, as an independent predictor of organ failure related events in acute pancreatitis

All those risk factors were first checked by'Parallel Lines' Test. Thus, Age, WBC, ALT, AST, HDL-C, Na, K, Cl, Ca, Ranson cannot be analyzed by ordinal logistic regression.

Table 1
Types of organ failure and the corresponding mortality.

	Transient organ failure		Persistent organ failure	
	Live	Dead	Live	Dead
Solitary	**468**	**0**	**143**	**21**
Respiratory	446	0	136	16
Renal	22	0	7	4
Cardiovascular	0	0	0	1
Multiple POF	**0**	**0**	**36**	**42**
Respiratory + renal	0	0	32	17
Respiratory + cardiovascular	0	0	4	14
Respiratory + cardiovascular + renal	0	0	0	11
Total	**468**	**0**	**179**	**63**

Table 2
Results of comparison among all patients in different 'Levels'.

	Level-1 (n = 79)	Level-2 (n = 468)	Level-3 (n = 179)	Level-4 (n = 63)	Dunnett'T3 test
General information					
Sex (M/F = 1/2)	45/34	284/184	108/71	42/21	NS
Age (year)	42 (24–50.75)	45 (36–57)	46 (38–60)	45 (28–73.75)	NS
Laboratory examination					
WBC (G/L)	10.75 (8.24–13.54)	12.74 (9.45–15.93)	14.33 (10.97–18.96)	11.55 (9.59–14.15)	NS
PLT (G/L)	179.5 (153–227.75)	179 (140–220)	163 (126–209)	137.5 (81–201.25)	NS
Tbil (umol/L)	19.5 (13.575–27.125)	22.9 (15.75–34.975)	26.1 (17.4–36.0)	27.75 (15.05–61.4)	NS
ALT (U/L)	30 (26–75)	34 (20–109)	37 (23–63)	47 (37–77)	NS
AST (U/L)	23.5 (21–49.5)	30.5 (20–73)	42 (29–86)	91 (51.5–233.25)	NS
ALP (U/L)	78.5 (68.25–103.5)	85 (64–111)	77 (58–109)	69 (41–128)	NS
GGT (U/L)	26.5 (14.75–103)	67 (28–222)	71 (39.75–158.75)	66 (38.25–168)	NS
HDL-C (mmol/L)	1.12 (1.04–1.55)	0.99 (0.76–1.34)	0.71 (0.45–0.97)	0.48 (0.22–0.765)	Significant
LDL-C (mmol/L)	2.18 (1.91–2.33)	1.795 (1.24–2.53)	1.48 (1.01–2.07)	1.18 (0.485–1.4)	NS
LDH (U/L)	178 (167–211)	231 (177–326)	415 (265.5–648)	928 (501–1279)	Significant
Cr (umol/L)	57.4 (50.3–66.025)	62.8 (52.85–74.975)	75.5 (63.5–106.8)	221.75 (136.1–358.1)	NS
ALB (g/L)	40.6 (38–46.1)	36 (33.6–39.55)	31.7 (26–35.8)	26 (21.275–31.525)	Significant
PT (s)	14.05 (13.125–14.4)	14.4 (13.5–14.425)	14.5 (14.2–15.8)	15.5 (14.575–15.8)	NS
PTA	0.837 (0.800–0.952)	0.800 (0.798–0.901)	0.790 (0.681–0.821)	0.703 (0.681–0.783)	Significant
Na (mmol/L)	140.75 (138.95–143)	138 (135.5–141)	137 (133–140)	138 (133–143)	NS
K (mmol/L)	4.1 (3.74–4.4)	4 (3.76–4.3)	4.1 (3.8–4.6)	4.35 (3.8–5.5)	NS
Cl (mmol/L)	105 (102.05–106)	104 (100.4–106)	106 (101–108)	110 (105.4–114)	NS
Ca (mmol/L)	2.36 (2.16–2.46)	2.095 (2–2.23)	1.85 (1.6–2.03)	1.47 (1.175–1.855)	Significant
Ranson	2 (1–2)	4 (3–5)	6 (5–7)	8 (6–9)	Significant
PAA	32.20 (29.08–39.20)	29.56 (26.07–33.90)	23.54 (18.84–28.80)	17.89 (14.38–22.14)	Significant
Etiology					
Biliary	41 (51.9%)	236 (50.4%)	86 (48.0%)	32 (50.8%)	NS
Alcoholic	21 (26.6%)	99 (21.2%)	60 (33.5%)	17 (27.0%)	NS
Hyperlipidemia	15 (19.0%)	79 (16.9%)	30 (16.8%)	14 (22.2%)	NS
Other cause	2 (2.5%)	54 (11.5%)	3 (1.7%)	0	NS

Data are presented as median value (interquartile range). ALB: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate amino transferase, Ca: calcium, Cl: chlorine, Cr: creatinine, GGT: γ-glutamyl transpeptidase, HDL-C: high density lipoprotein cholesterol, K: potassium, LDH: lactate dehydrogenase, LDL-C: low density lipoprotein cholesterol, Na: sodium, PLT: platelets, PAA: product value of serum albumin and prothrombin time activity, PT: Prothrombin Time, PTA: prothrombin time activity, Ranson: Ranson scoring system, Tbil: total bilirubin, WBC: white blood cell. NS: not significant.

Table 3
Details of Dunnett'T3 test among 4 'Levels'.

	P for Dunnett'T3 test					
	Level 1 and 2	Level 1 and 3	Level 1 and 4	Level 2 and 3	Level 2 and 4	Level 3 and 4
General information						
Sex (M/F = 1/2)	NS	NS	NS	NS	NS	NS
Age (year)	0.003	0.000	0.003	NS	NS	NS
Laboratory examination						
WBC (G/L)	0.001	0.000	NS	0.000	NS	0.000
PLT (G/L)	NS	NS	0.003	NS	0.045	NS
Tbil (umol/L)	NS	NS	0.011	NS	NS	NS
ALT (U/L)	NS	NS	NS	0.031	NS	NS
AST (U/L)	0.011	NS	0.000	NS	0.002	0.000
ALP (U/L)	NS	NS	NS	NS	0.012	NS
GGT (U/L)	NS	NS	NS	NS	NS	NS
HDL-C (mmol/L)	0.000	0.000	0.000	0.000	0.000	0.001
LDL-C (mmol/L)	NS	0.000	0.000	0.001	0.000	NS
LDH (U/L)	0.000	0.000	0.000	0.000	0.000	0.000
Cr (umol/L)	0.000	0.000	0.000	0.000	0.000	NS
ALB (g/L)	0.000	0.000	0.000	0.000	0.000	0.000
PT (s)	0.000	0.000	0.000	0.000	0.000	NS
PTA	0.000	0.000	0.000	0.000	0.000	0.011
Na (mmol/L)	0.000	0.000	0.016	0.006	NS	NS
K (mmol/L)	NS	NS	NS	0.001	0.000	NS
Cl (mmol/L)	NS	NS	0.000	0.003	0.000	0.006
Ca (mmol/L)	0.000	0.000	0.000	0.000	0.000	0.000
Ranson	0.000	0.000	0.000	0.000	0.000	0.000
PAA	0.000	0.000	0.000	0.000	0.000	0.000
Etiology						
Biliary	NS	NS	NS	NS	NS	NS
Alcoholic	NS	NS	NS	NS	NS	NS
Hyperlipidemia	NS	NS	NS	NS	NS	NS
Other cause	NS	NS	NS	NS	NS	NS

The study was done regarding the rest parameters. According to the results of multivariate ordinal analysis, PAA remained an independent risk factor. The odds ratio of PAA is 0.873, 95%CI: 0.848–0.899, $p < 0.01$ (Table 4).

Predictive value of PAA for OF, POF and death

The 'ROC curve' of PTA, ALB, LDH, Ranson and PAA for OF, POF and death were shown separately (Fig. 1).

For OF, PAA on admission was shown to have an area under curve (AUC) of 0.828 (95%CI: 0.783, 0.872), with a sensitivity of 54.2%, specificity of 96.9%. The optimal threshold was 28.655. The AUC of Ranson was 0.943 (95%CI: 0.919, 0.966) respectively.

For POF, the AUC of PAA was 0.828 (95%CI: 0.790, 0.865), with a sensitivity of 61.2%, specificity of 91.9%. The optimal threshold was 23.555.

For death event, the AUC of PAA was 0.905 (95%CI: 0.862, 0.948), even larger than that of Ranson, 0.887 (95%CI: 0.842, 0.933) (Table 5).

It turned out that PAA is a good predictor in predicting OF related events in AP.

All patients can be divided into new groups according to the cut-off values of PAA

The cut-off values for OF, POF and death of PTA, ALB, LDH, Ranson and PAA are shown in Table 6 and the variation trend can be found in Supplemental Figure 2.

We divided all the patients into 4 different groups again according to the cut-off value of PAA, that were Group A: PAA>28.655, Group B: 28.655 > PAA>23.555, Group C: 23.555 > PAA>22.895, Group D: PAA<22.895. The total number of patients in each group (A, B, C, D) and the distribution of four 'levels' (without OF, with TOF, with POF, die from POF) patients in each group was shown in Table 7 and Fig. 2.

Discussion

Albumin is a stable but flexible heart-shape-molecule with 585 residues. It can only be synthesized by liver but can be catabolized in most organs of the body at a similar rate by uptake into endocytotic vesicles on the endothelial surface and finally turned into amino acids as breakdown products [16,17].

Prothrombin time (PT) is one of the most important parameters to assess coagulation function. In view of many kinds of blood coagulation factors are synthesized by liver, PT is always tightly related with liver function [18,19].

In the 1930s, two groups developed the first versions of the prothrombin time test. PT was developed as an assay for the level of prothrombin based on the prevailing model of coagulation since that time. However, variability in thromboplastin reagents leads to large interlaboratory differences in PT results. Activity percentage expression (PTA) may provide a common international scale of PT reporting as a supplement [10,18,19].

Both hypoalbuminemia and decreased PTA are common in liver dysfunction which can be either a cause or result of system inflammation response.

As a result of inflammatory response, the consumption of albumin and coagulation factors increased, while the synthesis of them decreased, eventually leading to hypoalbuminemia and PTA falling. Organ metabolism and hemodynamics changes, a vicious circle is created then. Organ failure or death arises as a result [20–28]. What's more, because of the effects, serum albumin level decreased as well as PTA, so the value product of both decreased more significantly.

Acute pancreatitis, especially the severe type, is one of the most serious emergencies in abdominal surgery department. The

Table 4
Results of Uni/Multi-variate ordinal logistic regression analysis.

	P of Parallel Lines Test	P of Uni/Multi-variate analysis	Estimate (95%CI)	Odds ratio (95% CI)
Univariate Analysis				
Sex	0.638	NS	0.112 (−0.167, 0.391)	1.119 (0.846, 1.478)
Age (year)	0.044	Not Applicable		
WBC (G/L)	0.000	Not Applicable		
PLT (G/L)	0.232	0.000	−0.004 (−0,006, −0.002)	0.996 (0.994, 0.998)
Tbil (umol/L)	0.077	NS	0.004 (−0.001,0.009)	1.004 (0.999, 1.009)
ALT (U/L)	0.026	Not Applicable		
AST (U/L)	0.001	Not Applicable		
ALP (U/L)	0.150	NS	−0.002 (−0.004, 0.000)	0.998 (0.996, 1.000)
GGT (U/L)	0.191	NS	0.000 (0.000, 0.001)	1.000 (1.000, 1.001)
HDL-C (mmol/L)	0.007	Not Applicable		
LDL-C (mmol/L)	0.088	0.000	−0.510 (−0.673, −0.347)	0.600 (0.510, 0.707)
LDH (U/L)	0.216	0.000	0.006 (0.005, 0.006)	1.006 (1.005, 1.006)
Cr (umol/L)	0.665	0.000	0.022 (0.019, 0.025)	1.022 (1.019, 1.025)
ALB (g/L)	0.726	0.000	−0.212 (−0.238, −0.186)	0.808 (0.788, 0.830)
PT (s)	0.331	0.000	0.466 (0.368, 0.564)	1.594 (1.445, 1.758)
PTA	0.893	0.000	−6.451 (−7.695, −5.207)	0.002 (0.000, 0.005)
Na (mmol/L)	0.000	Not Applicable		
K (mmol/L)	0.000	Not Applicable		
Cl (mmol/L)	0.000	Not Applicable		
Ca (mmol/L)	0.000	Not Applicable		
Ranson	0.000	Not Applicable		
PAA	0.659	0.000	−0.186 (−0.209, −0.163)	0.830 (0.811, 0.850)
Multivariate Analysis				
PAA	0.185	0.000	−0.136 (−0.165, −0.106)	0.873 (0.848, 0.899)
LDL-C (mmol/L)		NS	−0.144 (−0.351, 0.064)	0.866 (0.704, 1.066)
LDH (U/L)		0.000	0.003 (0.002, 0.004)	1.003 (1.002, 1.004)
PLT (G/L)		NS	0.001 (−0.001, 0.004)	1.001 (0.999, 1.004)
Cr (umol/L)		NS	0.010 (0.000, 0.019)	1.010 (1.000, 1.019)
ALB (g/L)	Tightly connected with PAA.			
PT (s)	Tightly connected with PAA.			
PTA	Tightly connected with PAA.			

ALB and PT are tightly connected with PAA, we choose PAA rather than ALB, PTA or PT.

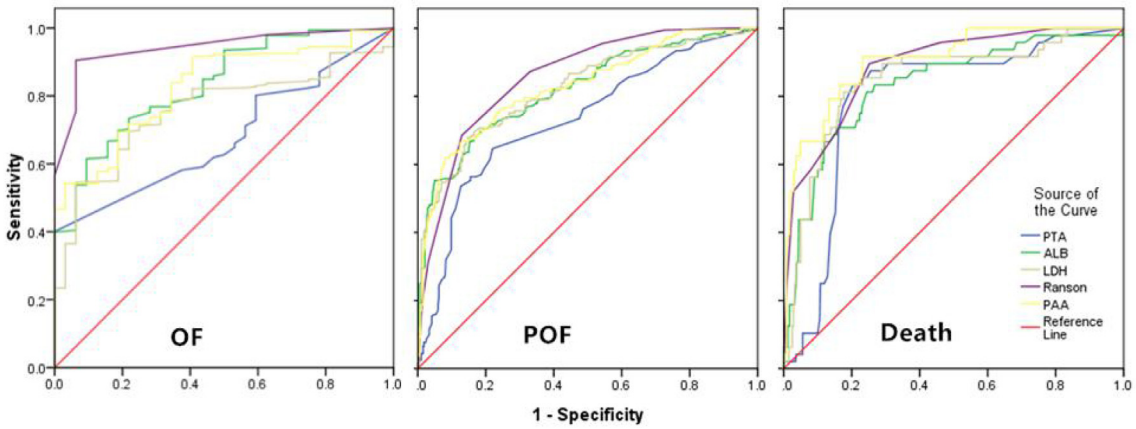

Fig. 1. The 'ROC curve' predicting OF, POF and death.

Table 5
AUC of PAA and other factors predicting OF, POF, death.

	AUC (95%CI)	Cut-off	sensitivity	specificity	PPV	NPV
OF						
PTA	0.680 (0.626, 0.734)	0.795	0.401	1.000	1.000	0.146
ALB	0.833 (0.787, 0.880)	35.85	0.615	0.906	0.981	0.194
LDH	0.760 (0.711, 0.809)	270.5	0.546	0.937	0.986	0.146
Ranson	0.943 (0.919, 0.966)	2.5	0.905	0.937	0.994	0.535
PAA	0.828 (0.783, 0.872)	28.655	0.542	0.969	0.990	0.184
POF						
PTA	0.732 (0.687, 0.777)	0.795	0.639	0.779	0.566	0.808
ALB	0.820 (0.782, 0.859)	33.45	0.721	0.787	0.596	0.848
LDH	0.820 (0.781, 0.859)	366.5	0.672	0.852	0.683	0.796
Ranson	0.857 (0.826, 0.889)	5.5	0.678	0.870	0.716	0.858
PAA	0.828 (0.790, 0.865)	23.555	0.612	0.919	0.754	0.831
Death						
PTA	0.794 (0.733, 0.856)	0.731	0.833	0.796	0.257	0.971
ALB	0.833 (0.770, 0.896)	32.05	0.813	0.756	0.227	0.979
LDH	0.847 (0.786, 0.909)	404.5	0.813	0.823	0.299	0.981
Ranson	0.887 (0.842, 0.933)	5.5	0.896	0.748	0.229	0.982
PAA	0.905 (0.862, 0.948)	22.895	0.917	0.767	0.267	0.968

AUC: Area Under The Curve, NPV: negative Predictive value, PPV: positive predictive value.

Table 6
Three 'Cut-off Value' of PAA and other factors.

	<mild>	Cut-off 1	<TOF>	Cut-off 2	<POF>	Cut-off 3	<death>
PTA	–	0.795	–	0.795	–	0.731	–
ALB		35.85		33.45		32.05	
LDH		270.5		366.5		404.5	
Ranson		2.5		5.5		5.5	
PAA		28.655		23.555		22.895	

Cut-off 1: the cut-off value for the prediction of OF; Cut-off 2: the cut-off value for the prediction of POF; Cut-off 3: the cut-off value for the prediction of death.

Table 7
Distribution of patients in different levels/groups.

	Group A (%)	Group B (%)	Group C (%)	Group D (%)	Total
Level 1	76 (18.58%)	3 (1.55%)	0	0	79
Level 2	280 (68.46%)	142 (73.58%)	6 (37.50%)	40 (23.39%)	468
Level 3	47 (11.49%)	42 (21.76%)	10 (62.50%)	80 (46.78%)	179
Level 4	6 (1.47%)	6 (3.11%)	0	51 (29.82%)	63
Total	409	193	16	171	789

phenomena of both hypoalbuminemia and derangements of the coagulation system have also been found in AP, especially in severe acute pancreatitis patients [12–15].

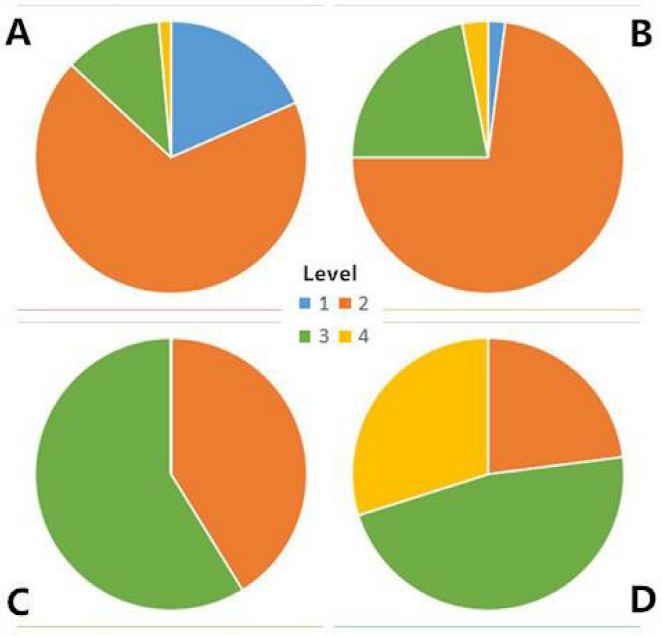

Fig. 2. The combination of the Group A-D.

We designed our research according to the 2012 revision of the Atlanta Classification of acute pancreatitis and found the product value of serum albumin and prothrombin time activity is closely related to the severity of the disease.

OF, especially POF, is the most important cause of mortality within the first 2 weeks of AP onset. POF develops in 10%–20% of AP patients, with a mortality rate between 20% and 50% [2,3]. The ability to assess the risk of AP patients developing POF earlier upon hospitalization is critical, both for triaging patients to the appropriate grade of care and for designing appropriate medical treatment and intervention [29].

The method of "ordinal regression" used in our study is applicable for those dependent variables which are ordered classification variables. In this study, the severity of AP, mild without OF, with TOF, with POF and die from POF are in order and can be progressively aggravated. 'Parallel Lines' Test was necessary to verify the value of the factor increases uniformly no matter where the cut-off value is. This test was used to make sure ordinal analysis is applicable.

In our research, ordinal regression analysis turned out that PAA, the product value of serum albumin and prothrombin time activity, is always decreasing as AP aggravates. Patients with smaller PAA get more serious AP, and it is highly possible for them to suffer from OF, POF and even die.

PAA does well in the prediction of severity of AP. For OF and POF, the AUC under ROC curve of PAA is 0.828. For death, the AUC of PAA is 0.905, larger than ALB, PTA and even Ranson scoring system. In addition, PAA is much more easily and quickly to measure than Ranson.

No previous study discussed the meaningful parameter, PAA. What's more, we divided the patients into four ordered groups according to their OF conditions. And we used an ordinal analysis method to analyze the data. In previous studies, other researchers tried different methods to classify AP patients into four groups [30]. The 'determinant-based classification' has different emphasis. It also considers the effects of acute pancreatitis complications, which makes it more comprehensive than our approach. But ours is more accurate in differentiating OF-related events.

However, there are still several limitations of the present study. Our study was an observational retrospective study which implicated that cause and effect relationships could not be discerned, though it didn't affect the predictive function. Therefore, further studies, in particular large-scale prospective studies, are needed to investigate the influence of PAA on the terminal acute pancreatitis.

A single-center study was limited by the special characteristics of patients. Our department is one of the most important centers for diagnosis and treatment of pancreatic diseases in our country, so the patients in our department were always with a more serious AP. In our center, only 79 out of 789 patients suffered a mild acute pancreatitis. But as our concerned, the mild type should be the majority of the disease. A multi-center study can be a good supplement. Therefore, we plan to cooperate with our primary hospital to conduct multi-center clinical studies to make the sample composition more reasonable.

POF is an important cause of death in AP but not the only one. Another study including all kinds of patients especially those suffering from local or systemic complications can be a supplement to our study. Within that study, however, ordinal regression may be not applicable.

Conclusions

In conclusion, our present study revealed that the product value of serum albumin and prothrombin time activity was always decreasing as AP aggravates. We suggest that PAA on admission is a valuable tool for a rapid assessment of disease severity in patients with AP.

Ethics approval and consent to participate statement

The study was conducted according to the principles of the Declaration of Helsinki. The ethics review board of Wuhan Union Hospital approved this study. Informed consent for individual patient was not obtained since all data were retrieved retrospectively from the laboratory test information system without additional blood samples or laboratory analysis.

Availability of data and materials statement

No additional data are available, for the reason that we promised to our patients to keep their information in secret.

Conflicts of interest

The authors declare that they have no competing interests.

Consent to publish statement

Not applicable.

Authors' contributions

Shoukang Li, Zhiqiang Liu, Heshui Wu designed the research; Shoukang Li, Zhiqiang Liu collected the data; Shoukang Li performed the research; Shoukang Li analyzed the data; Shoukang Li wrote the manuscript; Heshui Wu revised the manuscript for important intellectual content.

Funding statement

No funding.

Acknowledgements

We are grateful to Dr. Yushun Zhang of Department of Pancreatic Surgery, Union Hospital of Tongji Medical College of Huazhong University of Science and Technology.

List of abbreviations

ALB	albumin at admission
PT	Prothrombin Time
PTA	prothrombin time activity
PAA	the product value of serum albumin and prothrombin time activity
OF	organ failure
TOF	transient organ failure
POF	persistent organ failure
AP	acute pancreatitis
SAP	severe acute pancreatitis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate amino transferase
Ca	calcium
Cl	chlorine
Cr	creatinine
GGT	γ-glutamyl transpeptidase
HDL-C	high density lipoprotein cholesterol
K	potassium
LDH	lactate dehydrogenase
LDL-C	low density lipoprotein cholesterol
Na	sodium
PLT	platelets
Ranson	Ranson scoring system
Tbil	total bilirubin
WBC	white blood cell
NS	not significant
OR	odds ratio
AUC	Area Under The Curve
NPV	negative Predictive value
PPV	positive predictive value

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.02.001.

References

[1] Oiva J, Mustonen H, Kylanpaa ML, Kyhala L, Kuuliala K, Siitonen S, et al. Acute pancreatitis with organ dysfunction associates with abnormal blood lymphocyte signaling: controlled laboratory study. Crit Care 2010;14:R207 [PMID: 21087472].

[2] Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–11 [PMID: 23100216].

[3] Nawaz H, Mounzer R, Yadav D, Yabes JG, Slivka A, Whitcomb DC, et al. Revised Atlanta and determinant-based classification: application in a prospective cohort of acute pancreatitis patients. Am J Gastroenterol 2013;108:1911–7 [PMID: 24126632].

[4] Johnson CD, Abu-Hilal M. Persistent organ failure during the first week as a marker of fatal outcome in acute pancreatitis. Gut 2004;53:1340–4 [PMCID: PMC1774183].

[5] Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW. Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis. Br J Surg 2006;93:738–44 [PMID: 16671062].

[6] Lytras D, Manes K, Triantopoulou C, Paraskeva C, Delis S, Avgerinos C, et al. Persistent early organ failure: defining the high-risk group of patients with severe acute pancreatitis? Pancreas 2008;36:249–54 [PMID: 18362837].

[7] Pitchumoni CS, Patel NM, Shah P. Factors influencing mortality in acute pancreatitis: can we alter them? J Clin Gastroenterol 2005;39:798–814 [PMID: 16145344].

[8] Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. Am J Gastroenterol 2005;100:432–9 [PMID: 15667504].

[9] Oría A, Cimmino D, Ocampo C, et al. Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: a randomized clinical trial. Ann Surg 2007;245:10–7 [PMID: 17197959].

[10] Robert A, Chazouillères O. Prothrombin time in liver failure: time, ratio, activity percentage, or international normalized ratio? Hepatology 1996 Dec;24(6):1392–4 [PMID: 8938167].

[11] Mischke R. Prothrombin time standardisation in canine samples with regard to inter-batch and inter-reagent variability. Vet J 2011 Jun;188(3):301–6 [PMID: 20655250].

[12] Li S, Zhang Y, Li M, et al. Serum albumin, a good indicator of persistent organ failure in acute pancreatitis. BMC Gastroenterol 2017 Apr 26;17(1):59 [PMID: 28446147].

[13] Bona DD, Cefal AB, et al. Albumin versus solvent/detergent–treated pooled plasma as replacement fluid for long-term plasma exchange therapy in a patient with primary hypertriglyceridemia and recurrent hyperlipidemic pancreatitis. Transfusion March 2016;56:755–60 [PMID: 26536493].

[14] Gupta S, Shekhawat VP, Kaushik GG. D-dimer, a potential marker for the prediction of severity of acute pancreatitis. Clin Lab 2015;61(9):1187–95 [PMID: 26554237].

[15] Yang N, Hao J, Zhang D. Antithrombin III and D-dimer levels as indicators of disease severity in patients with hyperlipidaemic or biliary acute pancreatitis. J Int Med Res 2017 Feb;45(1):147–58 [PMID: 28222624].

[16] Peters T. All about albumin. San Diego: Academic Press; 1995, ISBN 978-0-12-552110-9.

[17] Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000;85:599–610 [PMID: 11064620].

[18] Hoffman M. Coagulation in liver disease. Semin Thromb Hemost 2015;41:447–54 [PMID: 26049068].

[19] Saito M, Seo Y, Yano Y, et al. Serum albumin and prothrombin time before entecavir treatment in chronic hepatitis B or cirrhosis are related to amelioration of liver function after treatment. Eur J Gastroenterol Hepatol 2013 Dec;25(12):1369–76 [PMID: 23974961].

[20] Arroyo V, Martinez RG, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014;61:396–407 [PMID: 24751830].

[21] Kim Y, Molnar MZ, et al. Relative contributions of inflammation and inadequate protein intake to hypoalbuminemia in patients on maintenance hemodialysis. Int Urol Nephrol 2013;45:215–27 [PMID: 22528583].

[22] Dubois Marc-Jacques, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med 2006;34(10) [PMID: 16915107].

[23] Otaki Yoichiro, et al. Comorbid renal tubular damage and hypoalbuminemia exacerbate cardiac prognosis in patients with chronic heart failure. Clin Res Cardiol 2016;105:162–71 [PMID: 26220048].

[24] de Castro Lais Lima, et al. Hypoalbuminemia and oxidative stress in patients on renal hemodialysis program. Nutr Hosp 2014;30(4):952–9 [PMID: 25335687].

[25] Eljaiek Roberto, et al. Hypoalbuminemia in the first 24 h of admission is associated with organ dysfunction in burned patients. Burns 2013;39:113–8 [PMID: 22683139].

[26] De Campos Tercio, et al. Morbimortality indicators in severe acute pancreatitis (Online) JOP. J Pancreas 2008;9(6):690–7 [PMID: 18981549].

[27] McKay CJ, et al. High early mortality rate from acute pancreatitis in Scotland, 1984-1995. Br J Surg 1999;86:1302–5 [PMID 10540138].

[28] McKay CJ, et al. The continuing challenge of early mortality in acute pancreatitis. Br J Surg 2004;91:1243–4 [PMID 15382103].

[29] Qiu L, Sun RQ, Jia RR, Ma XY, Cheng L, Tang MC, et al. Comparison of existing clinical scoring systems in predicting severity and prognoses of hyperlipidemic acute pancreatitis in Chinese patients: a retrospective study. Medicine June 2015;94(23):e957 [PMID: 26061329].

[30] Dellinger EP, Forsmark CE, Layer P, et al. Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. Ann Surg 2012;256:875–80.