Serum Hydroxybutyrate dehydrogenase as an early predictive marker of the severity of acute pancreatitis: a retrospective study

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Abstract

Background: Acute pancreatitis (AP) is an inflammatory disease caused by premature activation of the zymogen, which could lead to systemic inflammatory response syndrome (SIRS) and organ failure. Currently, some clinical multi-factor scoring systems have already been used to predict the occurrence of SAP, However, all these methods are complicated and difficult to obtain the first data.

Methods: Patients diagnosed with AP from January 2013 to December 2018 were included in this retrospective study. Patients were divided into the normal serum HBDH levels group (n-HBDH group) and the high serum HBDH levels group (h-HBDH group) according to the HBDH ≥ 182U/L after admission. The demographic parameters, laboratory data and the severity of AP in the two groups were compared. The receiver operating curve (ROC) was used to evaluate the efficacy of serum HBDH in predicting persistent organ failure and systemic inflammatory response syndrome (SIRS).

Results: A total of 260 AP patients were enrolled, including 176 cases in the n-HBDH group and 84 cases in the h-HBDH group. The incidence of SIRS and organ failure in the h-HBDH group were significantly higher than those in n-HBDH group (both $P < 0.001$). In addition, the serum HBDH levels were positively correlated with Atlanta classification, Ranson score, and BISAP score (all $P < 0.05$). ROC analysis showed that a serum HBDH cut-off point of 195.0 U/L had optimal predictive value for the development of persistent organ failure (AUC = 77.8%) and 166.5 U/L for the development of SIRS (AUC = 72.4%).

Conclusion: The elevated serum HBDH in early stage of AP is closely related to the adverse prognosis of AP patients, which can be used as a potential early biomarker for the severity of AP.

Background

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases of hospitalized patients in China, the United States and other countries, and its incidence rate continues to rise globally. The incidence and mortality of AP were estimated to be 33.74 cases per 100 000 person-years and 1.60 deaths per 100 000 person-years [1]. 80% of AP are self-limiting with no complications, and the remainder progresses to severe cases with local or systemic complications [2],systemic inflammatory response syndrome (SIRS) and organ failure, which ultimately led to a significant increase in mortality[3].

Early assessment of the severity of AP is a key factor in determining treatment strategies [4]. At present, some clinical multi-factor scoring systems, including Ranson score, BISAP score, Glasgow coma score and acute physiology and chronic health assessment-II (APACHA-II) score have already been used to predict the occurrence of SAP [5–6]. However, according to reports in the literature, different scoring systems have a certain predictive function on the severity of AP, but all these methods are complicated and difficult to obtain the first data [7–8]. Therefore, there is an urgent need for a novel, simple and effective evaluation method, or indicator to predict the severity of AP.

Lactate dehydrogenase (LDH) is a key enzyme in all biological anaerobic glycolysis, catalyzing the mutual conversion of lactic acid and pyruvate [9]. The level of serum LDH is associated with sepsis, AP, and tumor growth and metastasis [10–12]. Hydroxybutyrate dehydrogenase (HBDH) was measured by using α- ketoacid as a substrateis, because of the high affinity of H subunits to this substrate, HBDH mainly represents the activity of LDH1 and LDH2 which content more H subunits. Isozyme LDH1 and LDH2 dominate in the myocardium, red blood cells, and kidneys,which show more specific. Therefore, in recent years, scholars have gradually focused on the clinical application value of LDH isozyme HBDH. Studies have found that serum HBDH has significantly changes in myocardial infarction, atherothrombotic and liver injury [13–15].

At present, LDH has been incorporated into the Ranson scoring system to assess the severity of AP and is used to predict persistent organ failure of AP [16]. Whether there are significant changes in circulating HBDH levels in AP and whether they have predictive value for AP has not been reported. The purpose of this study was to determine the serum of HBDH in AP and to find a possible correlation between the severity of AP.

Method

2.1 Inclusion and Exclusion Criteria

Patients diagnosed with AP from January 2013 to December 2018 in the Department of Gastroenterology in a large regional hospital in Yangzhou of China, were admitted to our study. The diagnosis of AP was based on the existence of two or more of the following criteria: (1) typical clinical symptoms with persistent abdominal pain; (2) serum amylase and / or lipase levels 3 times higher than the normal upper limit; (3) characteristic results of abdominal imaging [17].Exclusion criteria include any of the following: younger than 18 years old, pregnant pancreatitis, traumatic pancreatitis, pancreatic cancer, and patients without serum HBDH values.

2.2 Data collection

Laboratory data was obtained from a blood screening test during hospitalization. HBDH (BIOSINO) was tested by enzymatic kit , and its reference value ranges from 72U / L to 182U / L.In order to obtain relevant demographics, physiological variables, disease severity, etc., the patient's electronic medical records and laboratory test results were checked by an independent doctor. This study was conducted in accordance with the principles of the "Helsinki Declaration". Due to the retrospective characteristics of the study from 2013 to 2018, informed consent was waived and the study was approved by the ethics committee of the affiliated hospital of Yangzhou University.

2.3 Severity assessment of AP

According to the Atlanta classification revised in 2012, AP was divided into three groups: mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP).

MAP refers to AP patients with no organ failure, and no local or systemic complications. MSAP refers to those suffering from transient organ failure and / or local or systemic complications (within 48 hours). Finally, patients with SAP are those who have organ failure and / or local or systemic complications which last longer than 48 hours. Diagnosis of organ failure required assessment of the respiratory, circulatory, and renal functions. According to the Atlanta classification revised in 2012, organ failure was defined as a score of 2 or more for one of these three organ systems using the modified Marshall scoring system [17].

2.4 Diagnostic criteria for systemic inflammatory response syndrome (SIRS)

SIRS was defined as the existence of two or more of the following four criteria: (1) temperature> 38◦C or <36◦C; (2) heart rate> 90 beats / min or hypotension;(3) Shortness of breath (> 20 breaths / min) or hyperventilation (PaCO2 <32 mmHg); (4) Peripheral blood leukocyte count> 12 × 10^9 / L or neutral rod-shaped granulocyte ratio> 10%. In addition, other conditions that may cause the above acute abnormal changes should be excluded [17].

2.5 Statistical analysis

All continuous variables were represented as the mean ± standard deviation (SD). Data were analyzed with SPSS 16.0 (SPSS Inc., Chicago, USA). Independent sample t test and chi-square test were used to compare continuous variables and categorical variables respectively. Person correlation analysis was used to examine the correlation between serum HBDH levels and other Laboratory indicators. Receiver operating characteristic (ROCs) curves were applied to assess the sensitivity and specificity of the indicators by GraphPad Prism 5.0 software. A bilateral $P < 0.05$ was considered to be a statistically significant difference.

Results

3.1 Comparison of clinical characteristics

A total of 842 patients diagnosed with AP from 2013 to 2018 were reviewed in this study, 582 patients were excluded according to the exclusion criteria, and finally 260 AP patients were enrolled, 176 (67.7%) patients had normal serum HBDH levels, whereas 84 patients (32.3%) had elevated serum HBDH levels.

Of all 260 patients, 162 patients (62.3%) were male, and the average age was 51.7 years old. Hypertriglyceridemia was the most common AP etiology (40.4%), followed by Biliary diseases (24.2%) and alcohol consumption (14.2%), and other causes accounted for 21.2% of cases. Among these patients, 81 (31.2%) patients suffered from organ failure, and 75(28.8%) had SIRS, as showed in Table 1.

Table 1
Comparison of clinical characteristics and outcomes between AP patients with vs. without high serum HBDH levels

	ALL	High HBDH	Normal HBDH	
	N = 260	N = 84	N = 176	P value
Age (mean ± sd), yrs	51.7 ± 16.1	52.4 ± 16.6	51.3 ± 16.0	0.617
Male sex, N (%)	162(62.3)	48 (57.1)	114 (64.8)	0.235
Smoking, N(%)	80(30.8)	26 (31.0)	54(30.7)	0.965
Drinking, N (%)	57(21.9)	22 (26.2)	35 (19.9)	0.251
Underlying diseases, N (%)				
Diabetes	52(20.0)	19(22.6)	33(18.8)	0.466
Hypertriglyceridemia	65(25.0)	21(25.0)	44(25.0)	1.000
hypertension	93(35.8)	36(42.9)	57(32.4)	0.100
NAFLD	108(41.5)	32(38.1)	76(43.2)	0.436
Etiology, N (%)				0.241
Biliary	63(24.2)	22(26.2)	41 (23.3)	
Alcohol	37(14.2)	11 (13.1)	26 (14.8)	
Hypertriglyceridemia	105(40.4)	39 (46.4)	66 (37.5)	
Others	55(21.2)	12 (14.3)	43 (24.4)	
Severity, N (%)				0.001***
MAP	179(68.8)	40 (47.6)	139 (79.0)	
MSAP	65(25.0)	32 (38.1)	33(18.8)	
SAP	16(6.2)	12(14.3)	4(2.3)	
OF	81(31.2)	44(52.4)	37(21.0)	0.001***
SIRS	75(28.8)	39(46.4)	36(20.5)	0.001***
*P < 0.05, **P < 0.01, ***P < 0.001.				

3.2 Serum HBDH levels and the severity of AP

There was no significant difference in terms of age, gender, history of tobacco and alcohol, and underling disease between the n-HBDH group and h-HBDH group. Compared with the n-HBDH group, the incidence of MAP was lower (47.6% vs 79.0%), whereas the incidence of SAP (14.3% vs 2.3%) and MSAP (38.1% vs 18.8%) were higher in the h-HBDH group (both P0.001). Moreover, there was a higher proportion of organ

failure (52.4% vs 21.0%) and SIRS (46.4% vs 20.5%) in the h-HBDH group, as showed in Table 1.(Both P<0.001). In addition, in the h-HBDH group, patients had higher levels of white blood cell, percentage of neutrophils (N%), LDH, AST, BUN, Alanine: Transpeptidase and Gamma glutamyl transferase (all P <0.05). Whereas, there was no significant difference in the serum levels of Cr between the two groups,as showed in Table 2.

Table 2
Comparison of laboratory data between AP patients with vs. without high serum HBDH levels

	ALL	High HBDH	Normal HBDH	
	N = 260	N = 84	N = 176	P value
WBC,×10*9/L	12.4 ± 5.1	13.9 ± 5.6	11.7 ± 4.7	0.002**
N%	79.7 ± 13.5	83.0 ± 9.8	78.1 ± 14.8	0.007**
LDH,U/L	253.1 ± 131.1	335.9 ± 160.1	213.5 ± 91.7	0.001***
DB, μmol/L	6.3 ± 14.1	9.0 ± 19.8	5.0 ± 10.2	0.080*
AST, U/L	91.2 ± 145.9	130.6 ± 202.9	72.4 ± 104.3	0.015*
ALT, U/L	88.7 ± 133.7	121.2 ± 186.6	73.2 ± 95.8	0.028*
GGT, U/L	183.2 ± 273.9	269.5 ± 360.7	142.0 ± 209.9	0.003**
BUN, mmol/L	5.1 ± 2.2	5.5 ± 2.8	4.9 ± 1.9	0.046*
Cr, μmol/L	63.5 ± 25.1	67.0 ± 33.2	61.8 ± 20.1	0.189
Glu	8.8 ± 0.3	9.6 ± 0.6	8.4 ± 0.4	0.066
*P < 0.05, **P < 0.01, ***P < 0.001.				

3.3 Serum HBDH levels and clinical scoring systems in AP

The scoring systems for the severity of AP are varied and each has its own emphasis. We observed the correlation between serum HBDH levels and clinical scoring systems. As shown in Figure 1, the results showed that serum HBDH levels were significantly related to the clinical scoring systems of AP. We found that the serum HBDH levels were significantly increased in patients with organ failure and SIRS, and were positively correlated with Atlanta classification, Ranson score, and BISAP score.

3.4 Correlation between serum HBDH levels and other clinical indicators

To further evaluate the predictive value of HBDH level for AP prognosis, correlation analysis was carried out between the serum HBDH level and other clinical markers. As shown in Table 3, serum HBDH levels were positively correlated with the serum levels of WBC (R=0.273; p <0.001), N% (R=0.162; p = 0.009), LDH (R=0.467; p <0.001), AST (R=0.152; p = 0.014), GGT (R=0.150; p = 0.015), BUN (R=0.165; p =

0.008),TG (R=0.195; p = 0.002),CHO (R=0.132; p = 0.037),GLU (R=0.171; p = 0.006). Whereas, there was no significant correlation between serum HBDH and ALT, Cr, TB, DB, ALP, HDL, and LDL.

Table 3
Correlation between HBDH and other clinical indicators in AP patients.

Index	R(with HBDH)	*P* value	Index	R(with HBDH)	*P* value
WBC	0.273	< 0.001***	**Glu**	0.171	0.006**
N%	0.162	0.009**	**TB**	0.021	.738
ldh	0.467	< 0.001***	**DB**	0.052	0.399
ast	0.152	0.014*	**ALP**	0.030	0.632
ggt	0.150	0.015*	**cr**	0.107	0.084
bun	0.165	0.008**	**HDL**	0.057	0.368
TG	0.195	0.002**	**LDL**	-0.062	0.325
CHO	0.132	0.037*	**alt**	0.103	0.096
*P < 0.05, **P < 0.01,***P < 0.001.					

3.5 ROC curve analysis of HBDH to diagnose organ failure

ROC curve analysis was performed to determine the cutoff value of HBDH for predicting AP with persistent organ failure or SIRS. As shown in Figure 2, the results revealed that the area under the ROC curve of HBDH for persistent organ failure was 0.778 and the optimal cutoff level was 195.0 U/L, which provided a 75.0% sensitivity and a 74.6% specificity. It also revealed that the area under the ROC curve of HBDH for SIRS was 0.724 and the optimal clinical cutoff level was 166.5 U/L, which provided a 66.7% sensitivity and a 68.4% specificity. In addition, our study found that the ability of serum HBDH for predicting persistent organ failure or SIRS is superior to LDH.

Discussion

AP is a non-infectious inflammatory disease that usually presents as self-limiting. Most AP do not require treatment interventions, but some of them suffer organ failure when the inflammatory response is excessive and can lead to a poor prognosis [18]. The duration of organ failure is the main criterion for the Atlanta classification revised in 2012. Some studies have found that the proportion of organ failure developed by AP in the Han population is between 8% and 20%, and even up to 40% in certain areas. [19]. Our research results show that the incidence of organ failure caused by AP is about 31.3%, which is consistent with the above results. If organ failure and SIRS can be detected as early as possible and intervention measures can be taken, the prognosis can be effectively improved. In recent years, many scales, such as CTSI score, Ranson score, BISAP score, Glasgow coma score and acute physiology and chronic health assessment-II (APACHA-II), have been designed to predict the prognosis of AP, but due to

its complexity, such as too many indexes, too long time span etc., each scale has different limitations in clinical application. So, it is necessary to find a clinically applicable biomarker to predict SAP.

Some studies have pointed out the value of LDH in AP disease assessment. Yin et al found that the patient's LDH level can be used as an indicator to assess the severity and prognosis of AP [20]. Cui et al observed that serum LDH at admission was independently associated with POF in AP and may be a potential prognostic factor [11]. Komolafe et al suggested that LDH can be used as an index for distinguishing edema pancreatitis and necrotizing pancreatitis [21].

Our study focused on the predictive value of serum HBDH in the early assessment of AP. HBDH is an isoenzyme of LDH and exhibits LDH activity. Previous studies have shown that HBDH can be used to assess the severity of systemic lupus erythematosus-associated liver injury diseases, intrahepatic cholestasis of pregnancy and AIDS-related pneumocystis pneumonia [22–24]. All these studies indicate the possibility of serum HBDH in clinical practice. In this study, 32.8% of patients had high serum HBDH levels. The incidence of SIRS and organ failure in the h-HBDH group was significantly higher than that in the n-HBDH group. In addition, the serum HBDH levels in patients were significantly increased with organ failure and SIRS were positively correlated with Atlanta classification, Ranson score, and BISAP score. These results suggest that elevated serum HBDH levels are closely associated with the poor prognosis of AP, but not with the pathogeny, gender, and age. Furthermore, based on the ROC curve analysis, we observed the ability of HBDH for predicting persistent organ failure in AP is about 77.8%, which is significantly better than LDH, so serum HBDH may be more suitable for SAP predicting.

Cells injury happens in all kinds of inflammatory disease. Cells injury or necrosis caused by different pathogens will release LDH isoenzymes with different structures, which can regulate the metabolism of lactate and pyruvate, resulting in increased lactate and reduced pyruvate, and eventually aggravated the inflammation [25–28]. Ferriero et al. proved that galloflavin as an LDH inhibitor reduced hepatocyte necrosis and apoptosis in mice model of hepatic failure [29]. Fantin et al. observed that LDH inhibitor can inhibit tumor growth and migration by reducing lactate release [30]. AP is a complex inflammatory syndrome that can develop into systemic inflammation and multiple organ failure, whether LDH inhibitors could be protective factors in AP needs further exploration.

Our study has the following limitations: First, this is a retrospective study that can only demonstrate the correlation between HBDH and AP, but cannot clarify the specific role of HBDH in the development of AP. Second, the study was conducted in a single center with a relatively small sample. Thirdly, we did not observe the dynamic changes of HBDH in AP.

Conclusion

In conclusion, our results provide evidence that serum HBDH indicates the adverse prognosis of AP patients. HBDH can be used as an early marker to distinguish SIRS and organ failure clinically.

Declarations

Authors' contributions

WMX and WLL contributed equally to this paper as first author. LY performed the statistical analysis. WMX wrote the first draft of the manuscript. GTL, XNL, WJG and YBD contributed intellectual content. All authors contributed to critical revisions to the manuscript. WMX and ZGY are the corresponding author. All authors approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

With Data Release Agreement with the ethics committee of the affiliated hospital of Yangzhou University. And no additional patient consent was required for the measurements in the data analysis.

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

HBDH : α - hydroxybutyrate dehydrogenase; NAFLD : nonalcoholic fatty liver disease; MAP : mild Acute pancreatitis; MSAP : moderately severe acute pancreatitis; SAP : severe acute pancreatitis; OF : organ failure; SIRS : systemic inflammatory response syndrome;WBC : White blood cell; N% : Percentage of neutrophils; LDH : lactate dehydrogenase; TB total bilirubin;DB : direct bilirubin;AST : aspartate transaminase;ALT: alanine transaminase;GGT :gamma glutamyltransferase;BUN :blood urea nitrogen; Cr :

Creatinine;TG : triglyceride; CHO : Cholesterol; HDL : high-density lipoprotein; LDL : low-density lipoprotein; Glu : glucose;POF : persistent organ failure;AUC : area under the curve;

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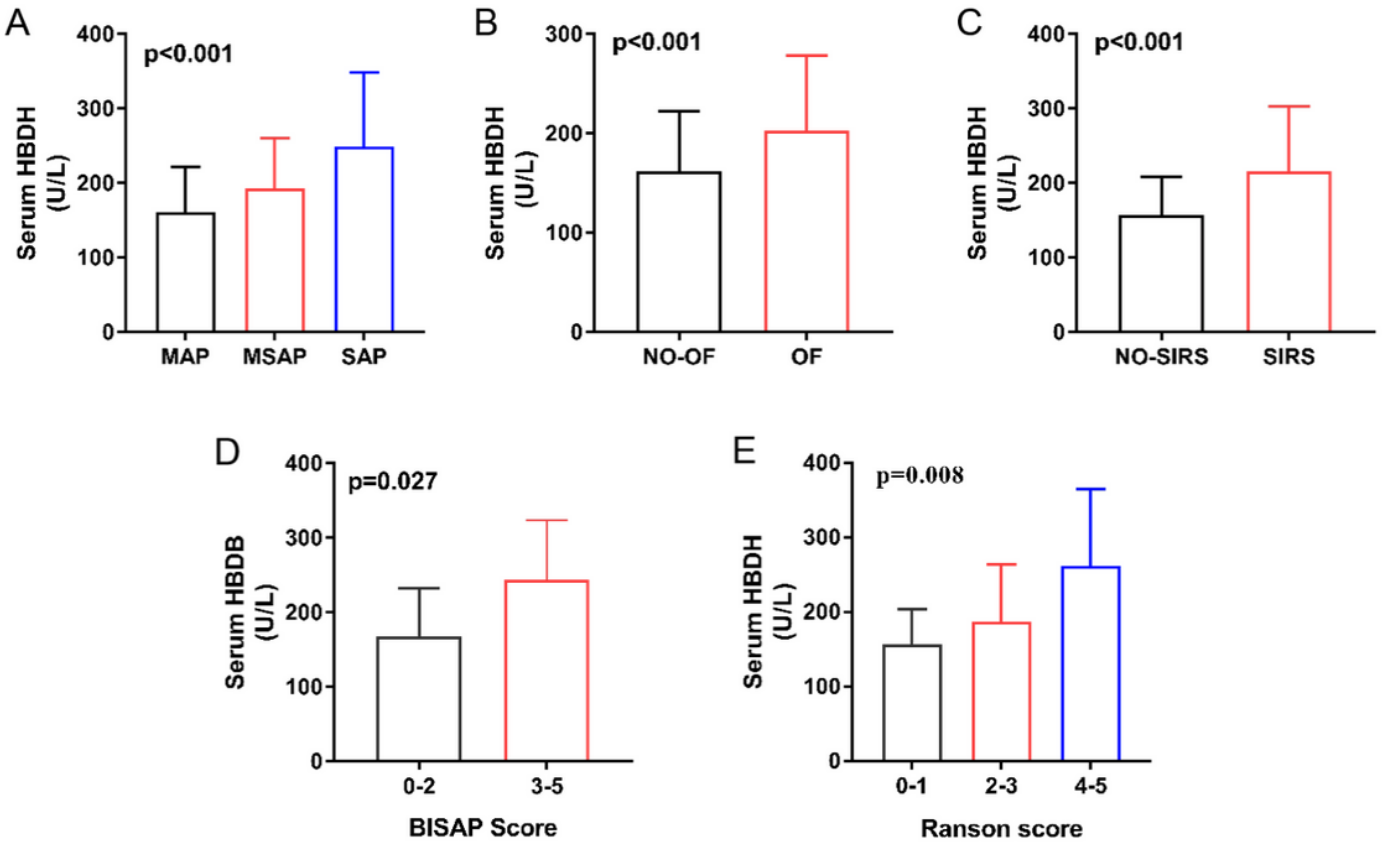
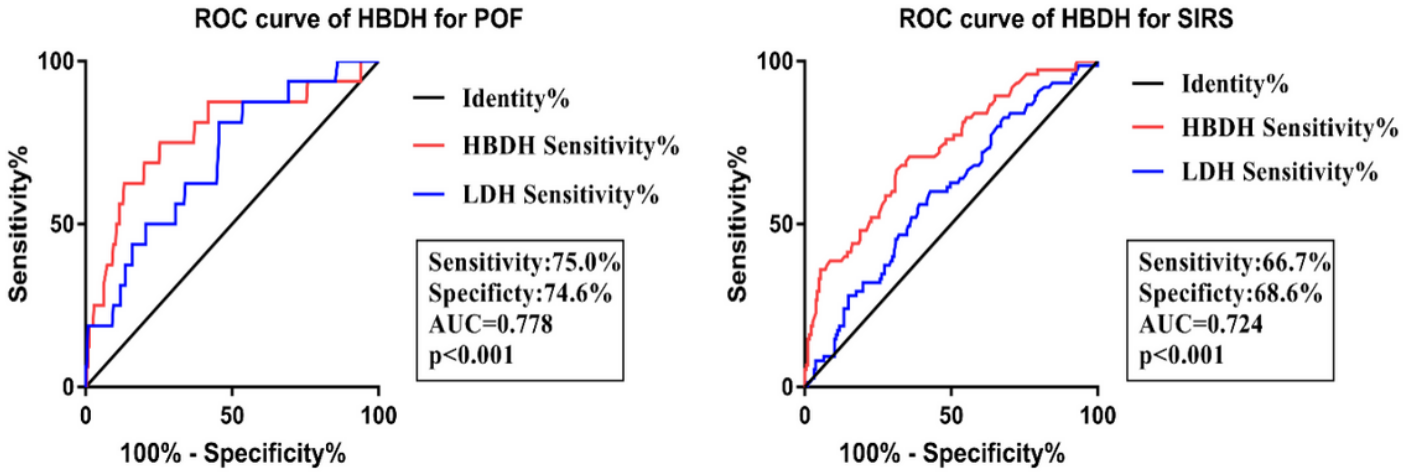
Figures



P < 0.05 was considered statistically significant.

Figure 1

Comparison of serum HBDH concentrations by Atlanta classification, Ranson, BISAP score.



The number of AP patients was 260. $P < 0.05$ was considered statisticallysignificant.

Figure 2

The ROC curve for determining the HBDH cut-off value for identifying POF and SIRS.