

Ultra-Early Indicators of Acute Hypertriglyceridemic Pancreatitis May Influence Treatment Decision-Making By Chinese Doctors

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Abstract

Background: This study investigates whether ultra-early indicators can predict severity of acute hypertriglyceridemic pancreatitis (HTGP) and affect clinical decisions.

Methods: For this observational retrospective study, we analyzed data of 110 HTGP patients enrolled between January 2017 and February 2020. HTGP patients were categorized into mild acute pancreatitis (MAP) and moderately severe acute pancreatitis-severe acute pancreatitis (MSAP-SAP) groups, based on their final clinical outcomes. Demographic and clinical data were collected and ultra-early indicators (serum calcium, triglyceride (TG), interleukin-6(IL-6), D-dimer, hemoglobin A1c(HbAc1), arterial lactate) levels were measured within 6 hours of admission. A multivariate logistic regression analysis model and receiver operating characteristic curve were used to determine ultra-early indicators values of high-risk patients. The chi-square test method was applied to estimate the hospitalization time and associated complications in MSAP-SAP group post-plasma exchange within or more than 24 hours.

Results: Among the 110 HTGP patients, 56 were in the MAP group whereas, 54 were in the MSAP-SAP group. TG, IL-6, D-dimer, HbAc1, and arterial lactate levels measured within 6 hours after admission were significantly higher in the MSAP-SAP group, but serum calcium was significantly lower, versus the mild AP group. IL-6, D-dimer and serum calcium were identified as the risk factors for MSAP-SAP and were potential ultra-early indicators for predicting HTGP severity within 6 hours of admission. MSAP-SAP patients that underwent blood purification therapy within 24 hours of admission had a shorter hospitalization time than those treated 24 hours post-admission.

Conclusion: The present study reveals IL-6, D-dimer, and serum calcium - ultra-early indicators - as promising biomarkers in the assessment of AP severity in HTGP patients within 6 hours. Early blood purification presents a novel therapy among MSAP-SAP patients within 24 hours and is associated with fewer complications and a shorter hospitalization time. However, traditional therapy can be further integrated to manage MAP patients effectively with less medical expenses.

Background

Acute pancreatitis is a common acute abdominal disease associated with urgent hospitalization worldwide. Despite having a mortality rate of 5%-10%, severe pancreatitis accounts for a high mortality rate between 30% and 50% [1–3]. Change in people's diet and lifestyle in recent years is attributed to hyperlipidemic acute pancreatitis (HTGP) which has surpassed alcoholic pancreatitis and is the second leading cause of acute pancreatitis in China [4]. HTGP incidence increases yearly. Unlike other types of AP, HTGP patients are characterized by severe clinical symptoms, occasional recurrence and poor prognosis. In addition, the mortality rate of severe HTGP is significantly higher than that of severe biliary pancreatitis [5, 6].

High triglycerides consequences are severe regardless of their occurrence in the human body. For instance, in the heart, it can cause coronary heart disease and myocardial infarction whereas, it induces

stroke in the brain. The occurrence of high triglycerides in the fundus of the eye can cause impaired vision and blindness and renal failure in the kidney. The presence of blood in the limbs is attributed to high triglycerides. Consequently, poor blood flow causes necrosis. Hypertriglyceridemia is the main risk factor for HTGP. Triglycerides are broken down into a large amount of free fatty acids that exceed the binding capacity of albumin, causing cell membranes toxicity through lipid peroxidation. This mechanism consequently damages acinar cells and capillary endothelial cells [7]. Moreover, hypertriglyceridemia is associated with the hypercoagulable state of blood and induces pancreatic microcirculation disturbance [8].

Reduction in blood lipid level is the key treatment for hyperlipidemic pancreatitis. Integration of targeted lipidemia-suppression with general therapy, for example, fasting and administration of low molecular weight heparin and insulin can reduce blood lipid and recuperation among non-severe patients. The use of drug therapy alone in severe patients is unlikely to reduce blood lipid rapidly. Early application of blood purification therapy has been widely adopted to rapidly reduce blood lipid level among patients with severe pancreatitis. Therefore, identifying high-risk patients at the early stages of the disease is crucial since it can help clinicians to formulate an effective management approach or refer the diagnosed patients to expert care for advanced clinical prognosis.

Methods of risk stratification and severity prediction at the early stage of AP have been developed for decades, including some clinical scoring systems and laboratory parameters. Previous studies had identified several indicators that could predict severity of acute pancreatitis such as D dimer [9], serum calcium [10], IL-6 [11, 12], arterial lactate [13], C-reactive protein(CRP), red cell distribution width (RDW) [14, 15], MCTSI [16], TG [5], among other indicators. However, these indicators are frequently detected within 24–48 hours post-admission. In most cases, patients with severe pancreatitis do not enjoy, the best opportunity for blood purification therapy, which prolong their hospitalization time and increase medical expenses. Early identification of severe form of pancreatitis is among the major challenges for its management.

Numerous studies have investigated the differences in clinical characteristics between HTGP and non-HTGP [13, 17]. To date, only a few studies have assessed the ultra-early risk factors of HTGP. In this study, we collected blood samples and tested the six indicators within 6 hours after the patients are admitted to the hospital. Data from HTGP patients obtained within 6 hours of admission were analyzed to characterize their early risk factors of HTGP and provide novel approaches for its prevention and treatment. Early evaluation of HTGP is key in determining the immediate use of blood purification and drug lipid-lowering therapies. Therefore, drug lipid reduction therapy will be beneficial in the recovery of patients condition and save medical expenses when blood purification therapy is not needed.

Methods

Study population and study design

We acquired data for 110 patients with HTGP during admission at the Second Affiliated Hospital, Fujian Medical University, (Quanzhou, China) between January 2017 to February 2020. Complete case data for the participants were retrospectively analyzed. The present study was approved by the Ethics Committee of the Second Affiliated Hospital, Fujian Medical University. Because this was a retrospective study, approved by the ethics committee of our hospital, there was no patient informed consent. However, all patients' personal information was kept confidential and the principle of confidentiality was observed. This was a retrospective study performed in accordance with local and national laws and abiding by the guidelines of the Helsinki Declaration.

The inclusion criteria were: i) Patients who meet the diagnostic criteria for AP. The AP was diagnosed based on two of the following factors (determined ≥ 3 times); abdominal pain, increased serum amylase and/or lipase and abdominal imaging examination in line with imaging changes typical for AP. ii) The serum TG level of ≥ 11.3 mmol/L at the onset of the disease. However, TG levels between 5.65 and 11.3 mmol/L were accepted except for AP caused by other factors such as cholelithiasis and alcoholism. iii) Patients who underwent abdominal enhanced computed tomography (CT) imaging within 72 hours of admission. Patients with alcoholic AP, post-ERCP pancreatitis, chronic pancreatitis and chronic renal dysfunction were excluded [18, 19]. The classification of acute pancreatitis is well recognized according to the latest 2012 revision of the Atlanta classification as follows: i) MAP: It meets the diagnostic criteria of AP and is not associated with organ failure and either local or systemic complications; ii) MSAP: associated with transient organ failure (recovery within 48 hours) and either local or systemic complications; iii) SAP: with persistent organ failure (> 48 h) and a modified Marshall score of ≥ 2 . Initially, the enrolled patients received targeted lipidemia-lowering and general therapies which include fasting, low molecular weight heparin and insulin to reduce blood lipid, gastrointestinal decompression, fluid resuscitation, nutritional therapy, organ function maintenance, preventive usage of antibiotics against gram-negative bacilli and Traditional Chinese Medicine approach, taking raw rhubarb to restore gastrointestinal tract dynamics and treat pancreatitis. Blood purification therapy which includes plasma exchange and hemofiltration were conducted in patients diagnosed with a severe tendency on admission. According to the final clinical outcomes, HTGP patients were divided into MAP and MSAP-SAP groups. Patients demographic and clinical data were collected and their ultra-early indicators (serum calcium, TG, IL-6, D-dimer, HbAc1, arterial lactate) levels were measured within 6 hours of admission. A multivariate logistic regression analysis model and receiver operating characteristic curve were used to determine the value of ultra-early indicators in high-risk patients. A chi-square test method was applied to estimate the time of hospitalization and complications in the MSAP-SAP group post-plasma exchange within or more than 24 hours.

Data collection

We recorded information on patient's, age, sex, body mass index (BMI), medical history, admission data and length of stay were collected to form the baseline demographic data. Moreover, on admission, data on vital signs were collected also, whereas important laboratory tests, radiological data and clinical outcomes were determined after hospitalization. Within 6 hours of admission, the following laboratory parameters were determined: TG, IL-6, D-dimer, HbAc1, and arterial lactate levels. Enhanced CT was

performed to examine the extent of necrotic tissue and the fluid locus. The modified Marshall score was used to evaluate the severity of acute pancreatitis.

Statistical methods

IBM Statistical Package for Social Sciences (SPSS) software version 20.0 (Chicago, USA) was used to perform the statistical analysis. The results were presented as a percentage (%) or mean \pm SD. Comparisons were performed using the Student's t-test and Mann-Whitney U test for two groups of independent samples. Categorical data were presented as n (%) prevalence whereas the between-group differences were assessed using either χ^2 -test or Fisher's exact test, accordingly. Logistic regression analysis was performed to predict risk factors with categorical dependent variables. Differences were statistically significant at $p < 0.05$. The area under the receiver operating characteristic (ROC) curve (AUC) was determined to evaluate the performance of the predictive model. Given the range of 0–1 of AUC, a variable with > 0.7 was considered useful whereas an AUC value of 0.8–0.9 denoted excellent diagnostic accuracy.

Results

Demographic and clinical characteristics of the study population

Of the 110 patients with HTGP, 56 were classified with mild AP and 54 with moderately severe and severe AP (MSAP-SAP). Though the age of onset in the mild AP group was higher (44.3 ± 4.1 versus 33.6 ± 4.9 years), their incidence of type 2 diabetes mellitus disease was lower (32 versus 43 patients) compared with the MSAP-SAP group ($P < 0.05$). The sex of patients among the groups was not statistically different ($P > 0.05$). MAP group have patients with a lower BMI than in SAP group ($P < 0.05$) as shown in **Table 1**.

Table 1

Clinical and demographic characteristics of patients with HTGP, stratified into MAP and MSAP-SAP group.

Characteristic	MAP (n = 56)	MSAP-SAP (n = 54)	Statistical significance ^a
Age, years	44.3 ± 4.1	33.6 ± 4.9	<i>P</i> < 0.01
Sex, male/female	38/18	40/14	NS
Concomitant type 2 diabetes mellitus	32	43	<i>P</i> < 0.05
Fatty liver disease	52	53	NS
BMI, Kg/m ²	26.2 ± 1.7	27.1 ± 2.2	<i>P</i> < 0.05
Data presented as mean ± SD or n patients. ^a MAP group compared with MSAP-SAP group; independentsamples t-test or χ^2 -test. MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis. BMI, Body mass index; NS, no significant between-group difference (<i>P</i> > 0.05).			

MSAP-SAP group had significantly high Triglyceride (17.10 ± 5.06 versus 13.94 ± 2.37 mmol/l), IL-6 (32.61 ± 5.09 versus 25.26 ± 4.29 pg/ml), CRP (42.51 ± 14.21 versus 37.42 ± 15.99 mg/l), HbA1c (6.7 ± 0.6 versus 6.2 ± 0.6 %), Arterial lactate (1.82 ± 0.45 versus 1.47 ± 0.36 mmol/l) than MAP group (**Table 2**). However, serum calcium was significantly lower in the MSAP-SAP group than in the MAP group (2.01 ± 0.13 versus 2.29 ± 0.21 mmol/l). The C-reactive protein was not statistically significant between the MAP and MSAP-SAP patients.

Table 2

Routine blood parameters for patients with HTGP, stratified into MAP and MSAP-SAP group.

Characteristic	MAP (n = 56)	MSAP-SAP (n = 54)	Statistical significance ^a
Ca, mmol/l	2.29 ± 0.21	2.01 ± 0.13	<i>P</i> < 0.01
TG, mmol/l	13.94 ± 2.37	17.10 ± 5.06	<i>P</i> < 0.01
IL-6, pg/ml	25.26 ± 4.29	32.61 ± 5.09	<i>P</i> < 0.01
CRP, mg/L	37.42 ± 15.99	42.51 ± 14.21	NS
D-dimer, mg/L	1.81 ± 0.74	2.93 ± 0.93	<i>P</i> < 0.01
HbA1c (%)	6.2 ± 0.6	6.7 ± 0.6	<i>P</i> < 0.05
Arterial lactate, mmol/L	1.47 ± 0.36	1.82 ± 0.45	<i>P</i> < 0.01
Data presented as mean ± SD or n patients. ^a MAP group compared with MSAP-SAP group; independentsamples t-test or U-test. TG, Triglyceride. HbA1c, hemoglobin A1c; CRP, C-reactive protein. IL-6, Interleukin-6; NS, no significant between-group difference (<i>P</i> > 0.05).			

Indicators for predicting the severity of HTGP

We summarized the sensitivity, specificity and AUC results in the prediction of HTGP severity in Fig. 1. Some parameters were highly accurate in the prediction of HTGP severity. In the prediction of MSAP-SAP, IL-6 \geq 27.4 pg/ml had the highest accuracy with 87% sensitivity, 73% specificity and 0.86 area under the curve. D-dimer \geq 2.65 mg/l had 63% sensitivity, 94% specificity and 0.82 area under the curve for serum D-dimer in the prediction of HTGP severity. Arterial lactate \geq 1.69 mmol/L had 57% sensitivity, 79% specificity and 0.73 AUC in the prediction of HTGP severity. Serum calcium $<$ 2.14 mmol/l had 72% sensitivity, 70% specificity and 0.77 AUC (**Table 3**).

Table 3
Sensitivity, specificity and AUC of different indicators in predicting MSAP-SAP in HTGP.

Indicators	Organ failure		Sensitivity %	Specificity %	Cut off	AUC
	Yes	No				
IL-6						
\geq 27.4 pg/ml	47	15	87	73	27.4	0.86
$<$ 27.4 pg/ml	7	41				
D-dimer						
\geq 2.65 mg/L	41	16	63	94	2.65	0.82
$<$ 2.65 mg/L	13	40				
Arterial lactate						
\geq 1.69 mmol/L	31	12	57	79	1.69	0.73
$<$ 1.69 mmol/L	23	44				
Serum calcium						
\geq 2.14 mmol/L	15	40	72	70	2.14	0.77
$<$ 2.14 mmol/L	39	16				

Independent prognostic factors in the MSAP-SAP group at admission

To further evaluate the relationship between admission indicators and MSAP-SAP, we constructed a multivariate logistic regression analysis model consisting of four parameters (IL-6, D-dimer, Arterial lactate, Serum calcium) within 6 hours of admission. The multivariate logistic regression model identified IL-6, D-dimer, and Serum calcium as independent risk factors for AP. The odds ratio (OR) were respectively listed in **Table 4**. With a D-dimer \geq 2.65 mg/l, IL-6 \geq 27.4 pg/ml or serum calcium $<$ 2.14 mmol/l, greatly increased the risk of transformation of HTGP to severe. Therefore, the combination of the three independent risk factors in the prediction of HTGP severity further improved the prediction accuracy with a 0.88 AUC (**Fig. 2**).

Table 4
Uni- and multi-variate logistic regression analyses of risk factors for MSAP-SAP.

Variables	Uni-variate Odds Ratio(95%CI)	Statistical significance	Multi-variate Odds	Statistical significance
			Ratio(95%CI)	
IL-6 \geq 27.4 pg/ml	18.35 (6.82, 49.4)	$P < 0.01$	10.36(3.644, 31.304)	$P < 0.01$
D-dimer \geq 2.65 mg/L	7.89 (3.36, 18.48)	$P < 0.01$	3.29(1.12, 9.65)	$P < 0.05$
Arterial lactate \geq 1.69 mmol/L	4.94 (2.14, 11.4)	$P < 0.01$	2.39 (0.8, 7.11)	NS
Serum calcium < 2.14 mmol/L	6.5 (2.83, 14.92)	$P < 0.01$	3.64 (1.25, 10.58)	$P < 0.05$

The effect of early blood purification treatment on MSAP-SAP patients

Early blood purification therapy within 24 hours after admission could shorten the hospitalization time of HTGP patients with severe tendency. Among the 50 SAP patients with higher-level clinical indicators (D-dimer \geq 2.35 mg/L or IL-6 \geq 27.4 pg/ml) at admission, 28 received early blood purification therapy within 24h whereas the 22 were delayed. Patients who received early blood purification therapy had a shorter time of hospitalization with fewer complications than those whose treatment was delayed as shown in **Table 5**. Blood purification treatment could not shorten hospitalization time and greatly increased medical expenses, however, the traditional lipidemia-lowering treatment scheme could yield a better therapeutic effect on MAP patients.

Table 5
Early blood purification therapy could improve clinical outcomes in MSAP-SAP patients

	MSAP-SAP ^a			MAP ^b		
	Blood purification (< 24h, N = 28)	Blood purification (> 24h, N = 22)	P	Blood purification (n = 8)	Conventional treatment (n = 48)	P
Hospitalization time (day)	12 \pm 4	17 \pm 6	$P < 0.05$	10 \pm 4	7 \pm 2	$P < 0.05$
Complications (%)	18%	36%	$P < 0.05$	None	None	

a. For MSAP-SAP patients, 28 patients received early blood purification therapy within 24h, the other 22 patients delayed blood purification therapy over 24h. **b.** For MAP patients, 8 patients received early blood purification therapy, the other 48 patients received conventional lipidemia-lowering treatment (low molecular weight heparin and insulin).

Discussion

Recently, the incidence of HTGP has been increasing and is frequently associated with more severe clinical processes. HTGP is mostly reported in young people especially those who are obese, alcoholic and diabetic. Hypertriglyceridemia is the main risk factor for HTGP. Studies have shown that HTGP patients are prone to persistent organ failure and the incidence of complications and mortality are significantly higher than those of AP due to other causes. Therefore, an immediate decrease in serum triglyceride level to below 5.65 mmol/L in the early stage of the disease interrupts the vicious cycle between triglyceride and inflammation, hence lowers the disease severity and improve the prognosis. Heparin and insulin have a synergistic effect to reduce serum triglyceride. The synergistic effect of heparin and insulin on HTGP has been clinically recognized and is adopted as a first-line treatment on severe HTGP [20, 21]. Blood purification including plasma exchange and hemofiltration can be used in HTGP treatment. A recent systematic review showed that serum triglyceride in most HTGP patients decreases significantly after plasma exchange followed by improvement of clinical symptoms or laboratory indicators, but cannot reduce the mortality of patients [22]. Moreover, the blood purification is not superior in terms of clinical outcomes and costs. There are some research deviations in these conclusions. For example, the patients in the HTGP group are not graded for severity, which cannot reflect the advantages of blood purification therapy for severe patients and whether blood purification therapy is necessary for non-severe patients. On the other hand, the time of plasma exchange might be the critical point. If severe patients with HTGP can receive plasma exchange as soon as possible, a better result may be predicted [23]. In addition, at present, the main drugs for HTG are fenofibrate, gemfibrozil and other fibrates, niacin, statins and omega-3 fatty acids. Niacin is restricted due to its multiple side effects [24]. In a randomized double-blind controlled trial, the dual treatment of omega-3 fatty acids and fenofibrate reduced the median TG concentration by 60.8% whereas, fenofibrate monotherapy alone reduced it by 53.8%. However, these two treatments were not statistically significant[25]. The role of statins is controversial. For instance, statins mainly act on hyperlipidemia with elevated cholesterol but some studies have shown that it has a protective effect while others have reported it to cause pancreatitis [26]. Currently, fibrates are the recommended first-line drug treatment in clinical practice.

Our research has two main findings. First, we found that during the ultra-early stage of HTGP, there still exist indicators that can better predict the severity of pancreatitis. This is key for an immediate evaluation of the disease progression and actively adopt targeted treatment measures. Therefore, effective intervention can be performed in the early stage of HTGP to achieve the goal of timely control of disease development. We found that ultra-early indicators of IL-6, D-dimer may be useful biomarkers in the assessment of AP severity in patients with HTGP, which facilitate the timely identification of HTGP patients with severe tendency using these indicators. Numerous studies have shown that HTG is often accompanied by leukocyte chemoattractant protein-1 (MCP-1), malondialdehyde (MDA), nitric oxide (NO) and catalase (catalase, CAT) and other indicators of oxidative stress[27]. Clinical studies have also found that for patients with LPL or Apo-C2 gene defects and repeated HTG-AP [28, 29], the use of antioxidant therapy has a clear clinical effect in the prevention of AP and suggests that oxidative stress may be an

important mechanism for HTG to induce AP [27]. Given these approaches, early intervention can be suggested as they are conducive to the rehabilitation of patients.

Second, we found that for patients diagnosed with MSAP-SAP, blood purification therapy within 24 hours of admission can shorten their hospitalization time. This shows that early blood purification therapy to reduce blood lipid level and eliminate inflammatory factors can block the progress of pancreatitis and is conducive for disease recovery. Considering the high medical cost of blood purification therapy and the potential risk of blood-borne infection, our research found that for patients diagnosed with MAP, the conventional treatment scheme can still result in a good therapeutic effect whereas the blood purification method will prolong their hospitalization time. Therefore, early assessment after admission is important and can determine the preliminary outcome of the disease through indicative indicators. Immediate blood purification therapy should be implemented in patients with severe manifestations, however, for patients without severe manifestations, cheap traditional treatment schemes can be adopted cheap which have a shorter hospitalization time. Our study has limitations in several aspects. This is a retrospective study that is prone to selection bias. To minimize the possibility of selection bias, we adopted strict inclusion criteria and expanded the sample size. Despite these limitations, this retrospective study provides effective information on treatment strategies for HTGP. We are currently conducting a prospective cohort study to obtain more accurate data to support our view.

Conclusion

Our results indicate that early detection of IL-6, D-dimer and blood calcium concentration may predict the development of pancreatitis after admission of patients with HTGP. Therefore, early detection facilitates the implementation of different effective treatment schemes in the early stage of HTGP which accelerate the recovery of pancreatitis and reduce medical expenses.

Abbreviations

hypertriglyceridemic pancreatitis (HTGP)

mild acute pancreatitis (MAP)

triglyceride (TG)

interleukin-6(IL-6)

hemoglobin A1c(HbA1c)

C-reactive protein (CRP)

computed tomography (CT)

Statistical Package for Social Sciences (SPSS)

chemoattractant protein-1 (MCP-1)

malondialdehyde (MDA)

nitric oxide (NO)

Declarations

Ethics approval and consent to participate

The present study was approved by the ethical review committee of the Second Affiliated Hospital, Fujian Medical University (Quanzhou, China).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JW and TYF conceived the study. YZL, XTT, ZLR, CWL, and XPP participated in the study design. JW collected the data. YZL, XTT and ZLR performed the statistical analyses. JW and CWL drafted the manuscript. XPP edited and checked the manuscript. The authors have read and approved the final manuscript.

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Figures

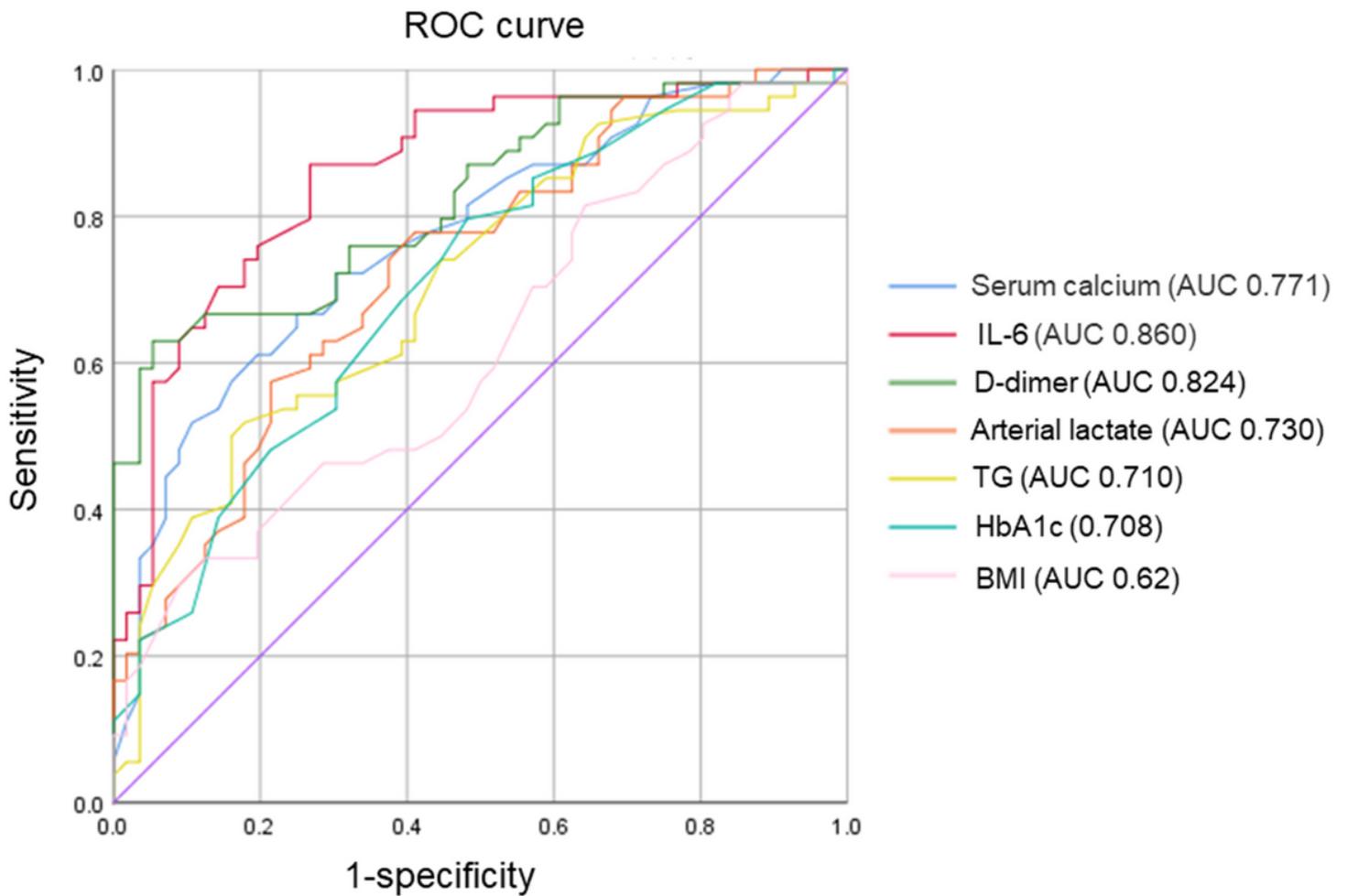


Figure 1

ROC curve for blood parameters to predict the MSAP-SAP in HTGP within 6h after admission. ROC curve for ultra-early indicators measured within 6h after admission to predict MSAP-SAP in HTGP. ROC, receiver operating characteristic; AUC, area under the curve.

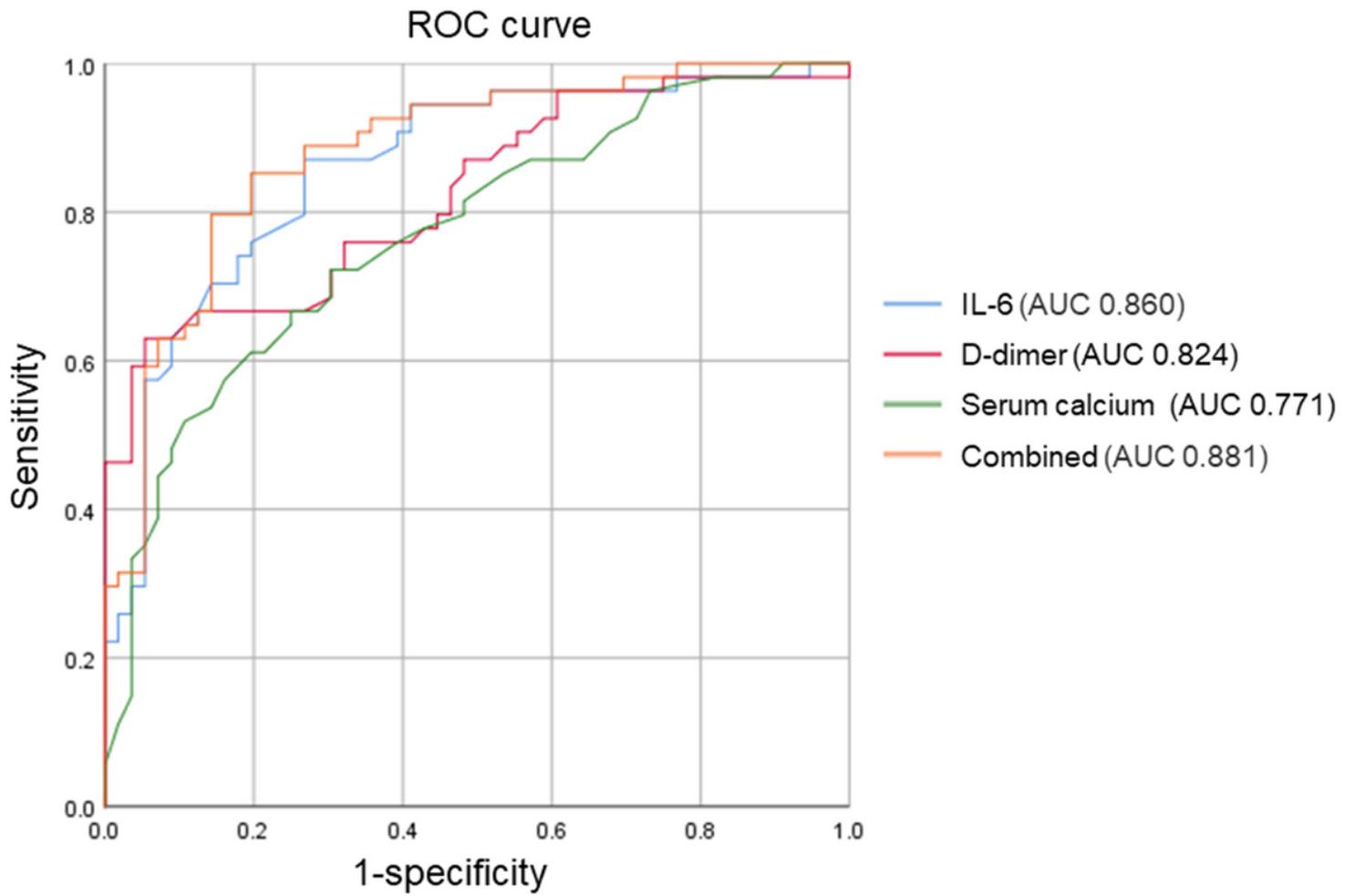


Figure 2

ROC curve for combined diagnosis to predict the MSAP-SAP in HTGP within 6h after admission. ROC curve for ultra-early indicators measured within 6h after admission to predict MSAP-SAP in HTGP. ROC, receiver operating characteristic; AUC, area under the curve.