Ultra-early indicators of acute hypertriglyceridemic pancreatitis may affect treatment decision-making

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Research

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Ultra-early indicators of acute hypertriglyceridemic pancreatitis may affect treatment decision-making.

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Abstract

Background: The present study aimed to investigate whether the ultra-early indicators can predict severity of acute hypertriglyceridemic pancreatitis (HTGP) and affect clinical decisions.

Methods: We performed an observational retrospective study with data from 110 enrolled patients with HTGP from January 2017 to February 2020. According to the final clinical outcome, HTGP patients were divided into MAP group and MSAP-SAP group. Demographic and clinical data were collected, and ultra-early indicators (serum calcium, TG, IL-6, D-dimer, HbAc1, arterial lactate) levels were measured within 6 h of admission. A multivariate logistic regression analysis model and receiver operating characteristic curve were adopted to evaluate the value of ultra-early indicators for identifying high-risk patients. The chi-square test method was used to estimate the time of hospitalization and complications in MSAP-SAP group after plasma exchange within or more than 24 hours.

Results: Of the 110 HTGP patients, a total of 56 patients with mild AP and 54 MSAP-SAP HTGP patients included. TG, IL-6, D-dimer, HbAc1, and arterial lactate levels which measured within 6 h 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 found to be risk factors for MSAP-SAP and could ultra-early predict HTGP severity, particularly within 6 hours of admission. We found that patients of MSAP-SAP treated with Blood purification within 24 hours of admission have shorter hospital stay time than over 24 hours of admission.

Conclusion: Ultra-early indicators of IL-6, D-dimer, and serum calcium may be useful biomarkers for assessing AP severity in HTGP patients within 6 hours. Early blood purification therapy should be taken for MSAP-SAP patients within 24 hours, because fewer patients could suffer from complications and more patients had shorter hospital stay time. While traditional treatment could be implemented for MAP patients to reduce medical expenses and still obtain good therapeutic effect.

Keywords: Hypertriglyceridemic pancreatitis, Ultra-early indicators, Clinical decisions, Therapeutic effect

Background

Acute pancreatitis is one of the common acute abdominal diseases requiring emergency admission worldwide, with a high mortality rate of 5%-10%, of which the mortality rate of severe pancreatitis is as high as 30%-50%[1-3]. In recent years, with the change of people's diet and lifestyle, hyperlipidemic acute pancreatitis (HTGP) has surpassed alcoholic pancreatitis and has become the second leading cause of acute pancreatitis in China[4]. The incidence of HTGP is increasing year by year. Compared with other types of AP, HTGP patients have the characteristics of severe clinical symptoms, easy recurrence, and poor prognosis. The mortality of severe HTGP was significantly higher than that of severe biliary pancreatitis[5, 6]. Hypertriglyceridemia is the main risk factor for HTGP. Triglycerides are decomposed into a large amount of free fatty acids, which exceed the binding capacity of albumin and produce toxicity to cell membranes through lipid peroxidation. Eventually damage acinar cells and capillary endothelial cells[7]. Moreover, hypertriglyceridemia can make blood in hypercoagulable state and induce pancreatic microcirculation disturbance[8]. Reducing blood lipid is the key treatment for hyperlipidemic pancreatitis. For non-severe patients, targeted lipidemia-lowering and general therapy which including fasting, low molecular weight heparin and insulin could reducing blood lipid and get well. For severe

patients, drug therapy alone is far from achieving the goal of rapidly reducing blood lipid. Early application of blood purification to rapidly reduce blood lipid level has been recognized during the treatment of severe pancreatitis. So, the ability to identify high-risk patients at the early stage of the disease is crucial because it can help clinicians to formulate more effective management or quickly transfer patients to expert care to improve 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 have found many indicators that can predict the severity of acute pancreatitis, including 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], and other indicators. However, these indicators are often detected within 24-48 hours after admission. For patients with potentially severe pancreatitis, the best opportunity for blood purification treatment is often missed, which may prolong hospitalization time and increase medical expenses. Identifying the severe form early is one of the major challenges in managing severe acute pancreatitis. Numerous studies have investigated the differences in clinical characteristics between HTGP and non-HTGP[13, 17]. However, to date, only few studies have assessed the ultra-early risk factors of HTGP. Our research collected blood samples and tested them within 6 hours after the patients are admitted to hospital. In the present study, data from patients with HTGP obtained within 6 h of admission were analyzed to characterize the early risk factors of HTGP and provide novel approaches for its prevention and treatment. Early evaluation of HTGP can determine whether to implement blood purification and drug lipid-lowering therapy as soon as possible. This will be beneficial to the recovery of the patient's condition and save medical expenses when blood purification therapy is not needed.

Methods

Study population and study design

The complete case data for a total of 110 patients with HTGP, who were admitted to the Second Affiliated Hospital, Fujian Medical University, (Quanzhou, China) between January 2017 to February 2020, were retrospectively analyzed. The present study was approved by the Ethics Committee of the Second Affiliated Hospital, Fujian Medical University and all patients provided written informed consent. The inclusion criteria were as follows: i) Patients who meet the diagnostic criteria for AP. AP was diagnosed based on 2 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 was ≥ 11.3 mmol/L at the onset of the disease. Or TG is between 5.65 and 11.3 mmol/L, excluding AP caused by other causes such as cholelithiasis and alcoholism. iii) Patients who underwent abdominal enhanced computed tomography (CT) imaging within 72 h 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 accompanied by organ failure and local or systemic complications; ii) MSAP: accompanied by transient organ failure (recovery within 48 hours), or accompanied by local or systemic complications; iii) SAP: with persistent organ failure (> 48h), modified Marshall score ≥ 2.

Initially, all enrolled patients received targeted lipidemia-lowering and general therapy, including fasting, low molecular weight heparin and insulin reducing blood lipid, gastrointestinal decompression, fluid resuscitation, nutritional therapy, organ function maintenance, preventive usage of antibiotics against gram-negative bacilli and Traditional Chinese Medicine approaches, taking raw rhubarb, in order to restore gastrointestinal tract dynamics and treat the pancreatitis. Blood purification therapy include plasma exchange and hemofiltration were carried out for patients with severe tendency after admission evaluation. According to the final clinical outcome, HTGP patients were divided into MAP group and MSAP-SAP group. Demographic and clinical data were collected, and ultra-early indicators (serum calcium, TG, IL-6, D-dimer, HbAc1, arterial lactate) levels were measured within 6 h of admission. A multivariate logistic regression analysis model and receiver operating characteristic curve were adopted to evaluate the value of ultra-early indicators for identifying high-risk patients. The chi-square test method was used to estimate the time of hospitalization and complications in MSAP-SAP group after plasma exchange within or more than 24 hours.

Data collection

For each patient, age, sex, body mass index (BMI), medical history, admission data, and length of stay were collected as baseline demographic data. Moreover, we collected vital signs of all patients on admission and important laboratory tests, radiological data, and clinical outcomes after hospitalization. Within 6h of admission, the following laboratory parameters were determined: TG, IL-6, D-dimer, HbAc1, and arterial lactate levels. Enhanced CT was performed to determine the necrotic tissue extent 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 analyses. The results are presented as percentages (%) or means ± SD. Comparisons were performed using Student's t test and Mann-Whitney U test for two groups of independent samples. Categorical data are presented as n (%) prevalence, and between-group differences were assessed using χ^2-test, or Fisher's exact test, as appropriate. Logistic regression analyses were 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. The AUC ranged from 0-1, and a variable with an AUC of >0.7 was considered useful, while an AUC between 0.8 and 0.9 was considered to indicate excellent diagnostic accuracy.

Results

Demographic and clinical characteristics of the study population

Of the 110 patients with HTGP, 56 patients were classified with mild AP, and 54 patients were classified with moderately severe and severe AP (MSAP-SAP). Age of onset in the mild AP group was higher (44.3±4.1 versus 33.6±4.9 years) but the incidence of type 2 diabetes mellitus disease was lower (32 versus 43 patients) compared with the MSAP-SAP group ($P < 0.05$). There was no statistical difference between the sex of the patients ($P > 0.05$). Patients in MAP group had lower BMI than patients in SAP group ($P < 0.05$). As shown in **Table 1.**

The following were significantly higher in the MSAP-SAP group versus MAP group (**Table 2**): 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). Serum calcium was significantly lower in MSAP-SAP group versus MAP group (2.01±0.13 versus 2.29±0.21 mmol/l). No statistically significant difference was found between patients with MAP or MSAP-SAP patients in terms of C-reactive protein.

Summary of indictors for predicting severity in HTGP

We summarized the sensitivity, specificity, and AUC results in predicting severity in HTGP in **Figure 1**. Some parameters were highly accurate in predicting severity in HTGP. For predicting MSAP-SAP, IL-6≥27.4 pg/ml had the highest accuracy, with a relatively highest sensitivity of 87% and had the high specificity of 73%, the area under the curve for IL-6 levels was 0.86. D-dimer ≥2.65 mg/l had the sensitivity of 63% and had the highest specificity of 94% in predicting severity, the area under the curve for serum D-dimer levels was 0.82. Arterial lactate≥1.69 mmol/L had the lower sensitivity of 57% and had the specificity of 79% in predicting severity, with an AUC of 0.73. And serum calcium < 2.14 mmol/l had the sensitivity of 72% and specificity of 70%, with an AUC of 0.77 (**Table 3**).

Admission IL-6, D-dimer, Serum calcium level as independent prognostic factors for MSAP-SAP

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 6h of admission. In the multivariate logistic regression model, IL-6, D-dimer, and Serum calcium were independent risk factors for AP. Odds ratio (OR) respectively listed in **Table 4.** When D-dimer ≥2.65 mg/l, IL-6≥27.4 pg/ml, or serum calcium < 2.14 mmol/l, the risk of HTGP transforming to severe state was greatly increased.

Therefore, we combined the three independent risk factors to predict the severity of HTGP and found that the combination of the three indicators could further improve the prediction accuracy, with an AUC of 0.88 (**Figure 2**).

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

For HTGP patients with severe tendency, early blood purification therapy within 24 hours after admission could shorten the hospitalization time. We observed 50 patients of SAP with higher level clinical indicators (D-dimer ≥2.35 mg/L or IL-6≥27.4 pg/ml) at admission and found that 28 patients received early blood purification therapy within 24h. The other 22 patients delayed blood purification therapy. The results in **Table 5** show that patients received early blood purification therapy had shorter time of hospitalization and fewer complications than delayed treatment. However, for MAP patients, the traditional lipidemia-lowering treatment scheme could obtain better therapeutic effect, while blood purification treatment could not shorten hospitalization time, but greatly increased medical expenses.

Discussion

The incidence of HTGP has been on the rise in recent years and often leads to more serious clinical processes. HTGP mostly occurs in young people, especially obese, alcoholic, and diabetic patients. 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 caused by other causes. Therefore, it is necessary to reduce the serum triglyceride to below 5.65 mmol/L as soon as possible at the initial stage of the disease, interrupting the vicious circle between triglyceride and inflammation, so as to reduce the severity of the disease and improve the prognosis. Heparin and insulin have synergistic effect of reducing serum triglyceride. The combined effect of heparin and insulin on HTGP has been clinically recognized and can be used for first-line treatment of severe HTGP[20, 21]. Blood purification, including plasma exchange and hemofiltration, can be used to treat HTGP. A recent systematic review shows that the serum triglyceride of most HTGP patients decreases significantly after plasma exchange, accompanied by improvement of clinical symptoms or laboratory indicators, but cannot reduce the mortality of patients[22]. Moreover, it is not superior in terms of clinical outcomes and costs. There are some research deviations in these conclusions. For example, the patients in the 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, better result may be predicted[23].

Our research has two main findings. First, we found that in the ultra-early stage of HTGP, we can still find indicators that can better predict the severity of pancreatitis. This will help to evaluate the progress of the disease as soon as possible and actively take targeted treatment measures. Effective intervention can be carried out 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 for assessing AP severity in patients with HTGP, so that patients with HTGP with severe tendency can be identified earlier using these indicators. Then early intervention can be given, which is conducive to the rehabilitation of patients. Second, we found that in patients finally diagnosed with MSAP-SAP, blood purification therapy within 24 hours of admission can shorten the 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 to the recovery of the disease. Considering the high medical cost of blood purification therapy and the potential risk of blood-borne infection, our research found that for patients finally diagnosed with MAP, the conventional treatment scheme can still obtain good therapeutic effect, while the blood purification method will prolong the hospitalization time. Therefore, early assessment after admission is especially important, and we can preliminarily judge the outcome of the disease through indicative indicators. For patients with severe manifestations, blood purification therapy should be implemented as soon as possible, while for patients without obvious severe manifestations, traditional treatment schemes can be implemented, thus reducing medical expenses and hospitalization time.

Our study is clearly limited in several aspects. this is a retrospective study, which is potentially prone to

selection bias. To minimize the possibility of selection bias, we adopted strict inclusion criteria and expanded the sample size as much as possible. Despite these limitations, this retrospective study can provide effective information on treatment strategies. 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, thus different effective treatment schemes can be implemented in the early stage, which can not only accelerate the recovery of pancreatitis, but also reduce medical expenses.

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Not applicable.

Authors' contributions

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

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Availability of data and materials

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

Ethical 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).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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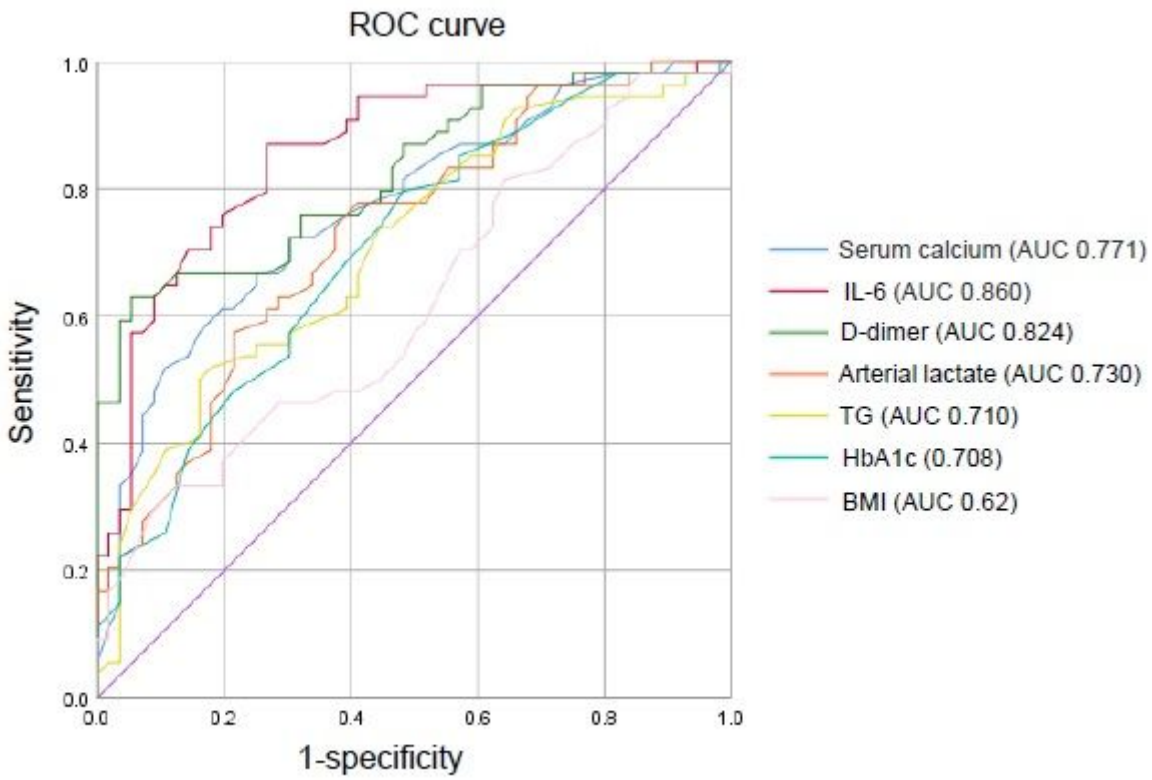
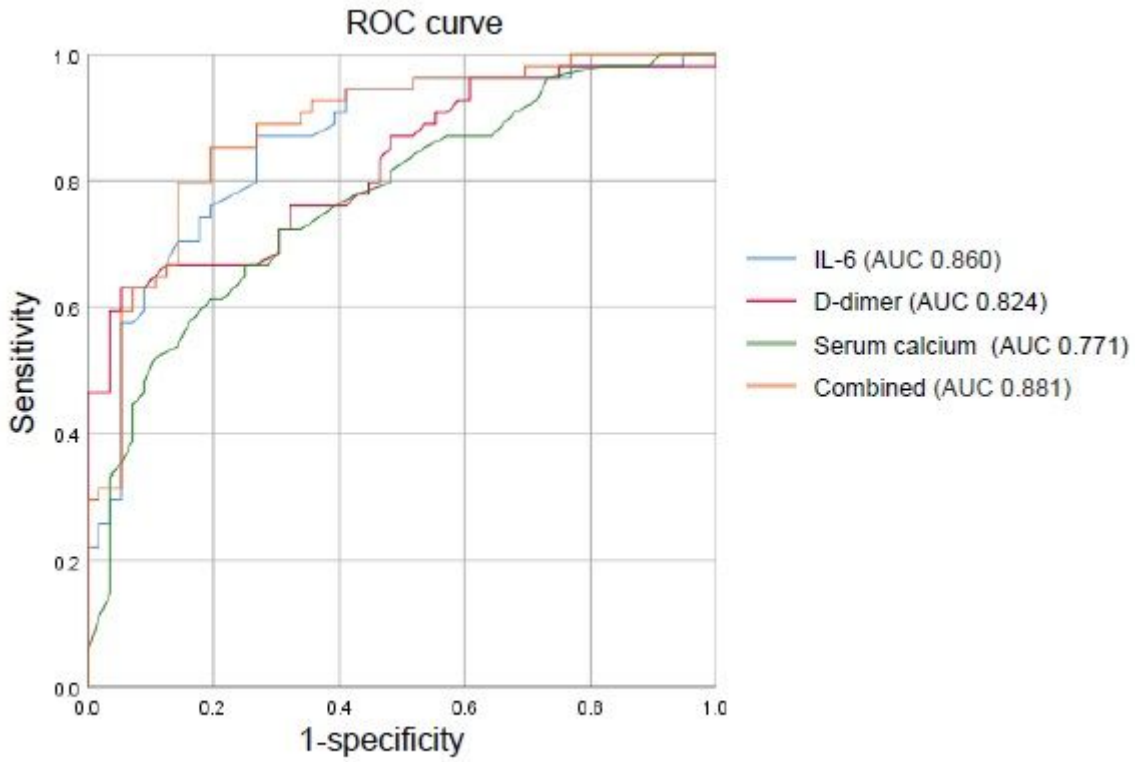
Figures



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 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

Figure 2. ROC curve for combined diagnosis to predict the MSAP SAP in HTGP within 6h after admission.

Supplementary Files

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