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LESS IS MORE: classified management of hypertriglyceridemia-induced acute pancreatitis on the basis of a propensity score matching cohort study

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Abstract

Background Effective management of hypertriglyceridemia is crucial in the treatment of hypertriglyceridemia-induced acute pancreatitis (HTG-AP). The prognosis of HTG-AP may vary with different serum triglyceride levels, suggesting the need for stratified treatment approaches. In this study, we investigated hypertriglyceridemia management in HTG-AP patients and the optimal strategy.

Methods Patients with HTG-AP from October 2020 to October 2022 were included in the study. Propensity score matching was used to balance the bias and confounding variables. A mixed-effects model was used to analyse the decreasing tendency of triglycerides.

Results A total of 171 patients who were diagnosed with HTG-AP were enrolled in this cohort. Patients with very severe serum triglycerides (> 22.6mmol/L) had a higher proportion of severe acute pancreatitis ($p < 0.05$) than patients with severe hypertriglyceridemia (11.3–22.6 mmol/L). For the very severe hypertriglyceridemia group, no significant differences in prognosis were noted between the insulin and heparin group and the plasma exchange group. The cost of the insulin and heparin group was significantly lower than that of the plasma exchange group ($p < 0.01$). In patients with severe hypertriglyceridemia, no significant differences in prognosis were noted between the nothing-by-mouth (NPO) group and the insulin and heparin group. Compared with the insulin and heparin group, the NPO group had lower hospital costs ($p < 0.05$).

Conclusion HTG-AP patients with very severe hypertriglyceridemia may be treated safely and effectively with insulin and heparin, potentially offering a more cost-effective treatment approach. Similarly, patients with severe hypertriglyceridemia might benefit from treatment involving NPO, which may be associated with lower costs. Further studies are needed to validate these findings in diverse populations and through long-term follow-up.

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Keywords Acute pancreatitis, Hypertriglyceridemia, Propensity score matching, Insulin and heparin, Nothing by mouth, Plasma exchange

Introduction

Acute pancreatitis (AP) is a potentially fatal disease requiring prompt hospitalization. Hypertriglyceridemia (HTG) has become the third most common cause of AP [1], resulting in considerable economic and health burdens [2]. HTG is an independent risk factor for the prognosis of HTG-AP patients [3–5], and early lipid lowering is helpful for improving the prognosis [6, 7].

Acute triglyceride lowering measures are divided into noninvasive treatments, including nothing by mouth (NPO, also known as cessation of oral intake), intravenous insulin and heparin, and invasive treatments, such as plasma exchange [8]. Many studies have compared insulin and heparin with respect to plasma exchange, and most believe that the two treatments are comparable [9–11]. Studies have suggested that NPO can efficiently lower serum triglyceride levels [12]; however, the application of triglyceride-lowering measures in HTG-AP patients has not become standardized.

At present, the confusion regarding HTG management in AP involves whether the triglyceride-lowering strategy needs to be classified according to HTG levels. The European Endocrine Society distinguished severe HTG (triglyceride 11.3–22.6 mmol/L) from very severe HTG (triglyceride > 22.6 mmol/L) and proposed standard long-term management [13]. However, standard acute HTG management in AP patients has not been investigated. Studies have reported that patients with very severe hypertriglyceridemia (> 22.6 mmol/L) are at a significantly greater risk of developing complications such as pancreatic necrosis, systemic inflammation, and persistent organ failure, as shown in studies by Mosztbacher et al. [5] and Zhang et al. [4]. Therefore, it is questionable whether patients with severe HTG can benefit from relatively aggressive acute triglyceride-lowering treatments such as plasma exchange. Notably, Berberich et al. reported a 22-case series that showed that NPO-only management can safely and effectively reduce triglyceride levels without the need for plasma exchange. The evaluation of NPO efficacy in HTG-AP patients with severe HTG warrants further investigation.

Accordingly, we performed this retrospective cohort study with propensity score matching (PSM) to explore acute triglyceride-lowering strategies. First, we proposed the standard strategy and divided patients into very severe HTG (triglyceride > 22.6 mmol/L) and severe HTG (triglyceride 11.3–22.6 mmol/L) subgroups [13]. Second, we investigated the effects of insulin, heparin and plasma exchange in the very severe HTG group and investigated the effects of NPO, insulin and heparin in the severe HTG group.

Materials and methods

Study subjects

Patients with HTG-AP admitted to a hospital from October 2020 to October 2022 were retrospectively and consecutively included in the study.

The diagnosis of AP requires 2 of the following 3 criteria: (1) abdominal pain consistent with acute pancreatitis (acute onset of persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) above three times the upper limit of normal; and (3) characteristic findings of AP on imaging [14]. The HTG-AP diagnosis criteria were as follows: (1) met the diagnostic criteria for AP; (2) the serum triglyceride level exceeded 11.3 mmol/L or ranged from 5.6 to 11.3 mmol/L with chylous serum; and (3) other causes of induced AP were excluded [15].

The Endocrine Society classified HTG as mild (1.7–2.3 mmol/L), moderate (2.3–11.3 mmol/L), severe (11.3–22.6 mmol/L), or very severe (> 22.6 mmol/L) on the basis of the degree of serum triglyceride elevation [13]. In this study, patients were categorized into two groups on the basis of their serum triglyceride levels measured within the first 48 h of admission (very severe HTG group > 22.6 mmol/L; severe HTG group 11.3–22.6 mmol/L).

This study adhered to the STROBE guidelines for observational studies. The checklist was used throughout the preparation of the manuscript to ensure comprehensive reporting of the study design, methods, results, and limitations. (Supplement file STROBE-checklist)

As this was a retrospective study, obtaining individual informed consent was waived by the Clinical Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University, owing to the use of anonymized data and the minimal risk to participants. The waiver aligns with ethical guidelines for retrospective research, including those outlined by the Declaration of Helsinki.

Data collection

Patient demographic and clinical characteristics, including sex, age, body mass index (BMI), presence of diabetes mellitus (DM), daily triglyceride level, local complications, and Acute Physiology and Chronic Health Evaluation II (APACHE II, a scoring system used to assess the severity of disease in critically ill patients on the basis of physiological and laboratory data), were collected during hospitalization. The severity of AP was based on the

following criteria: (1) mild acute pancreatitis (MAP): without organ failure or systemic or local complications; (2) moderate severe acute pancreatitis (MSAP): with transient (< 48 h) organ failure or/and systemic or local complications; and (3) severe acute pancreatitis (SAP): acute pancreatitis characterized by persistent organ failure lasting more than 48 h. The diagnosis of organ failure was based on the modified Marshall Organ Failure Score. The APACHE II score was used to assess patient condition.

Study procedures

This study is a retrospective cohort study. Patients who met the diagnostic criteria for HTG-AP were treated initially with intravenous therapy (IV) fluids/hydration and symptomatic care, including pain management together with modalities after admission. Acute triglyceride-lowering treatments such as NPO, heparin combined with insulin or invasive plasma exchange were used to manage HTG [16–18]. The choice of triglyceride-lowering therapy was at the discretion of the treating physicians.

NPO protocol: (1) Duration: patients were placed on complete NPO for 72 h or until significant clinical improvement was observed. Daily reassessments were performed determine whether to extend the NPO period. (2) Fluid type: intravenous fluids included isotonic saline or balanced crystalloids (e.g., Ringer's lactate). For patients at risk of hypoglycaemia, 5% dextrose was added. Electrolyte levels were monitored and supplemented as needed. (3) Nutritional support: For patients requiring prolonged NPO (> 72 h), enteral nutrition was initiated with careful monitoring of triglyceride levels to avoid exacerbating hyperlipidaemia. (4) Risk monitoring: (a) Electrolyte imbalances: frequent monitoring and supplementation with potassium, magnesium, and calcium are necessary. (b) Patient compliance: hunger and weakness were managed through clear communication and supportive care. (c) Hypoglycaemia risk: blood glucose levels were monitored closely, and IV dextrose concentrations were adjusted accordingly. (d) Transition to oral intake: oral intake was gradually reintroduced, starting with clear liquids and advancing to low-fat diets, minimizing the risk of recurrence.

The empirical dosing regimen for low-molecular-weight heparin is as follows [15]: (1) For HTG-AP patients without bleeding tendency, low-molecular-weight heparin 100 U/kg (a single dose not more than 5000 U) is recommended at admission, at 12-h intervals. (2) Subcutaneous injection is the preferred method of administration. (3) Coagulation function should be monitored during the treatment of HTG-AP patients with low-molecular-weight heparin [15]. A continuous infusion of unfractionated heparin (12 500 U/2 mL) was administered at a rate of 10–15 U/kg/h, and the infusion rate was then adjusted to maintain an activated partial thromboplastic time of 46 to 70 s [19].

The insulin application scheme was based on the blood glucose concentration [15]: (1) Intravenous pumping of insulin 0.1 ~ 0.3 $U{\cdot}kg^{-1}{\cdot}H^{-1}$. (2) Blood glucose was monitored every hour to adjust the insulin pumping dose. (3) It is necessary to be alert to the occurrence of hypoglycaemia, and 5% glucose can be administered in a timely manner to prevent hypoglycaemia. (4) Control blood glucose to 6.1 ~ 8.3 mmol/L, and stop insulin when the serum triglyceride level is lower than 5.6 mmol/L [15].

Plasma exchange was selected in this study because of its ability to rapidly and effectively reduce triglyceride levels, particularly in patients with very severe HTG (> 22.6 mmol/L). The plasma exchange protocol for HTG-AP patients is as follows: (1) It can be implemented using a dual lumen central venous catheter. (2) Citrate can be a beneficial replacement for heparin as an anticoagulant. (3) Liquid substitutes can be plasma or 5% albumin. (4) The plasma volume was calculated using the Kaplan formula, and the plasma volume = [0.065 × mass (kg)] × (1-haematocrit), which is 1.2–1.5 times the plasma volume per exchange. (5) The frequency of plasma exchange was determined according to the specific serum triglyceride control target [15]. Risk monitoring of plasma exchange: (1) Coagulation parameters were routinely monitored, and patients with significant bleeding risk were excluded. (2) Vital signs and haemodynamic parameters were continuously monitored during and after the procedure, with fluid and electrolyte management as needed. (3) A standardized protocol was followed to minimize procedural variability, including the use of citrate as an anticoagulant to reduce bleeding risk.

Statistical analysis

The statistical analysis of the data was performed using R4.3.0 software. The qualitative data are presented as percentages and were tested with the chi-square test. The quantitative data are presented as the means ± standard deviations (SDs). T tests were used for normally distributed variables or as medians (IQRs), and nonparametric tests were used for nonnormally distributed variables.

Propensity score matching (PSM) is a statistical technique used in observational studies to balance baseline characteristics between treatment groups, thereby reducing confounding. The propensity score is the probability that the patient will receive the treatment of interest, which is inferred from the patient's baseline and clinical data. Cases from different groups are matched according to similar or identical PSs. After PSM, the reliability of the studies was practically comparable to that of randomized controlled trials. In this study, a 1:3 matching ratio was chosen to balance the statistical efficiency and the availability of matched pairs. Research shows

that increasing the ratio beyond 1:3 provides diminishing returns in efficiency and may introduce bias due to less similar matches [20]. The calliper width was set at 0.2 times the standard deviation of the logit of the propensity score, as recommended by Austin [21]. This threshold minimizes bias and ensures sufficient similarity between matched pairs. Specifically, we included the following variables in the matching process:

- Age.
- Gender.
- Body mass index (BMI).
- Diabetes mellitus (DM) status.
- Serum triglyceride (TG) levels at admission.
- Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Given that triglyceride levels are a critical confounding factor influencing both the choice of treatment and clinical outcomes in HTG-AP patients, we explicitly included serum triglyceride levels at admission as a matching variable. By accounting for triglyceride severity, our analysis aimed to ensure balance between treatment groups and minimize bias related to baseline differences in disease severity.

Mixed-effects regression models were used to analyse the effects of different TG-lowering strategies over time. Mixed-effects models offer a robust statistical framework for analysing complex data structures, particularly those involving repeated measures, and provide a powerful tool for understanding the dynamics of data within a hierarchical structure. Given that TG was measured repeatedly, we applied a multilevel model.

To verify the robustness of our results, we conducted a series of sensitivity analyses as follows: (1) Matching ratio: Different matching ratios (1:1, 1:2) were tested to determine whether the number of controls matched to each case affected the balance of covariates or the results. (2) Calliper width: The calliper width for propensity score matching varied (0.1, 0.15, and 0.25 times the standard deviation of the logit of propensity scores) to assess its influence on sample size and covariate balance. (3) A second statistical approach for lowering the TG efficiency was performed after PSM. Briefly, the decline rate of triglycerides for the first 48 h of enrolment was obtained from linear regression, and the regression coefficient was the slope of the triglyceride decline. Comparisons of differences between groups in the slope of the triglyceride decline were performed using the Wilcoxon rank-sum test.

Results

Analysis of serum triglyceride levels

A total of 171 patients meeting the inclusion criteria were ultimately enrolled in the study (Fig. 1). Among them, 100 (58.5%) were assigned to the very severe HTG group (triglyceride > 22.6 mmol/L), and 71 (41.5%) were assigned to the severe HTG group (triglyceride 11.3–22.6 mmol/L). Compared with patients with severe HTG, patients with very severe HTG had a greater APACHE II score ($p < 0.05$) and a greater incidence of severe acute pancreatitis (SAP) ($p < 0.05$, Table 1). Consistent with the above findings, patients with very severe HTG were more likely to spend more on hospitalization expenses ($p < 0.05$, Table 1).

Analysis of patients with very severe HTG

Among patients with very severe HTG, 66 (66%) patients were assigned to the insulin and heparin group, and 34 (34%) patients were assigned to the plasma exchange group. Patients' age, sex, BMI, previous DM history, serum triglyceride level at admission and APACHE II

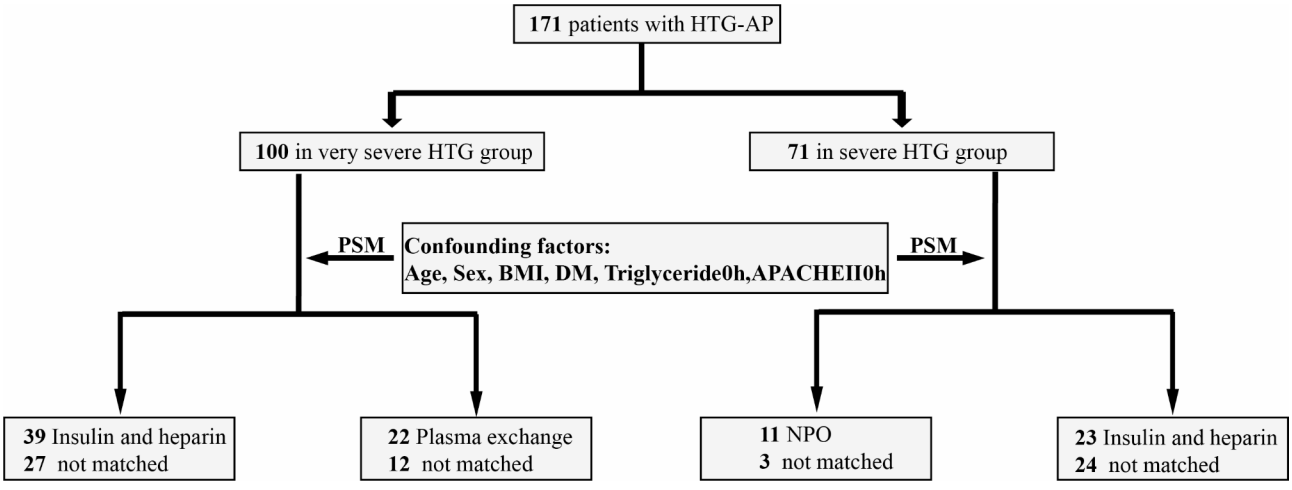

Fig. 1 Flow chart of participants enrolled in the study

Table 1 Comparison between the very severe HTG group and the severe HTG group

Variables	Very severe HTG group ($n=100$)	Severe HTG group ($n=71$)	p
Baseline characteristics			
Age, median (IQR), years	39.0 (31.0–45.0)	35.0 (31.0-44.5)	0.665
BMI, mean (SD), kg/m^2	26.99 (3.75)	26.99 (3.96)	1
Male (%)	75 (75.0)	56 (78.9)	0.685
DM (%)	38 (38.0)	25 (35.2)	0.832
Clinical outcomes			
Triglyceride, 0 h, median (IQR), mmol/L	44.7 (31.9–66.0)	15.8 (13.7–18.7)	**< 0.01**
APACHE II, 0 h, median (IQR)	5.0 (4.0–9.0)	4.0 (2.0–7.0)	**< 0.01**
SAP (%)	30 (30.0)	11 (15.5)	**< 0.05**
Local complication (%)	50 (80.6)	50 (79.4)	1
APFC (%)	38 (61.3)	46 (73.0)	0.288
Pseudocyst (%)	4 (6.5)	9 (14.3)	0.254
APNC (%)	16 (25.8)	10 (15.9)	0.251
WON (%)	13 (21.0)	7 (11.1)	0.208
Secondary infection (%)	7 (11.3)	5 (7.9)	0.739
Hospitalization expenses			
Hospital LOS, median (IQR), day	10.0 (7.0–15.0)	9.0 (6.0–12.0)	**< 0.05**
Total cost, median (IQR), thousand CNY	21.6 (14.7–39.0)	13.6 (10.3–24.5)	**< 0.01**
Hospital daily cost, median (IQR), thousand CNY/day	2.1 (1.6–3.4)	1.8 (1.5–2.1)	**< 0.01**

BMI, body mass index; DM, diabetes mellitus; APACHE, Acute Physiology and Chronic Health Evaluation; HTG, hypertriglyceridemia; SAP, severe acute pancreatitis; APFC, acute peripancreatic fluid collection; APNC, acute peripancreatic necrosis collection; WON, wall-off pancreatic necrosis; LOS, length of stay; CNY, Chinese Yuan; IQR, interquartile range; NA, not available

#Data description method, median with interquartile range

* p values were calculated using the Wilcoxon rank-sum test

score at admission were included in the PSM. After PSM, confounding factors were equally distributed into two groups (Fig. 2), and 39 patients in the insulin and heparin group were matched with 22 patients in the plasma exchange group.

To explore the effects of different triglyceride-lowering treatments on the rate of decrease in plasma triglyceride levels, daily serum triglyceride levels were analysed using repeated measures analysis of variance. In the matched cohort, no difference was found in the decreasing trend in daily serum triglyceride levels between the insulin and heparin group and the plasma exchange group ($p=0.532$) (Fig. 3).

In the matched cohort, the total cost and hospital daily cost of the insulin and heparin group were significantly lower than those of the plasma exchange group ($p<0.01$) (Table 2). No significant difference in clinical outcomes was observed (Table 2).

Analysis of patients with severe HTG

Among patients with severe HTG, 14 (23%) patients were included in the NPO group, and 47 (77%) patients were included in the heparin and insulin group. After PSM, confounding factors were balanced (Fig. 4). In total, 11 patients were included in the NPO group, and 23 patients were included in the insulin and heparin group.

In patients with severe HTG, there was no significant difference in the decreasing trend of serum triglycerides between the NPO group and the insulin and heparin group ($p=0.282$) (Fig. 5).

After PSM, no significant differences in clinical outcomes were detected ($p>0.05$) (Table 3). The total cost of the NPO group was significantly lower than that of the insulin and heparin group ($p=0.02$) (Table 3).

Sensitivity analysis

The sensitivity analyses demonstrated that the findings of the study remained consistent across different matching ratios (1:1 and 1:2) and different calliper widths (0.1 SD and 0.2 SD). The balance of baseline covariates, including triglyceride levels, diabetes status, and APACHE II scores, was adequately achieved in all matched cohorts. Key outcomes, including the rate of triglyceride reduction and clinical outcomes, showed no significant variation across the different matching ratios and different calliper widths. The results of the cost-effectiveness comparisons between the subgroups remained robust ($p<0.01$). The detailed results of the sensitivity analyses are provided in the Supplementary Material (Supplemental Tables 1–8).

A second statistical approach for lowering the TG efficiency was performed after PSM as a sensitivity analysis. Briefly, the rate of reduction in triglyceride levels for the first 48 h of enrolment was obtained using linear regression, and the regression coefficient was the slope of the triglyceride decline. Comparisons of differences between

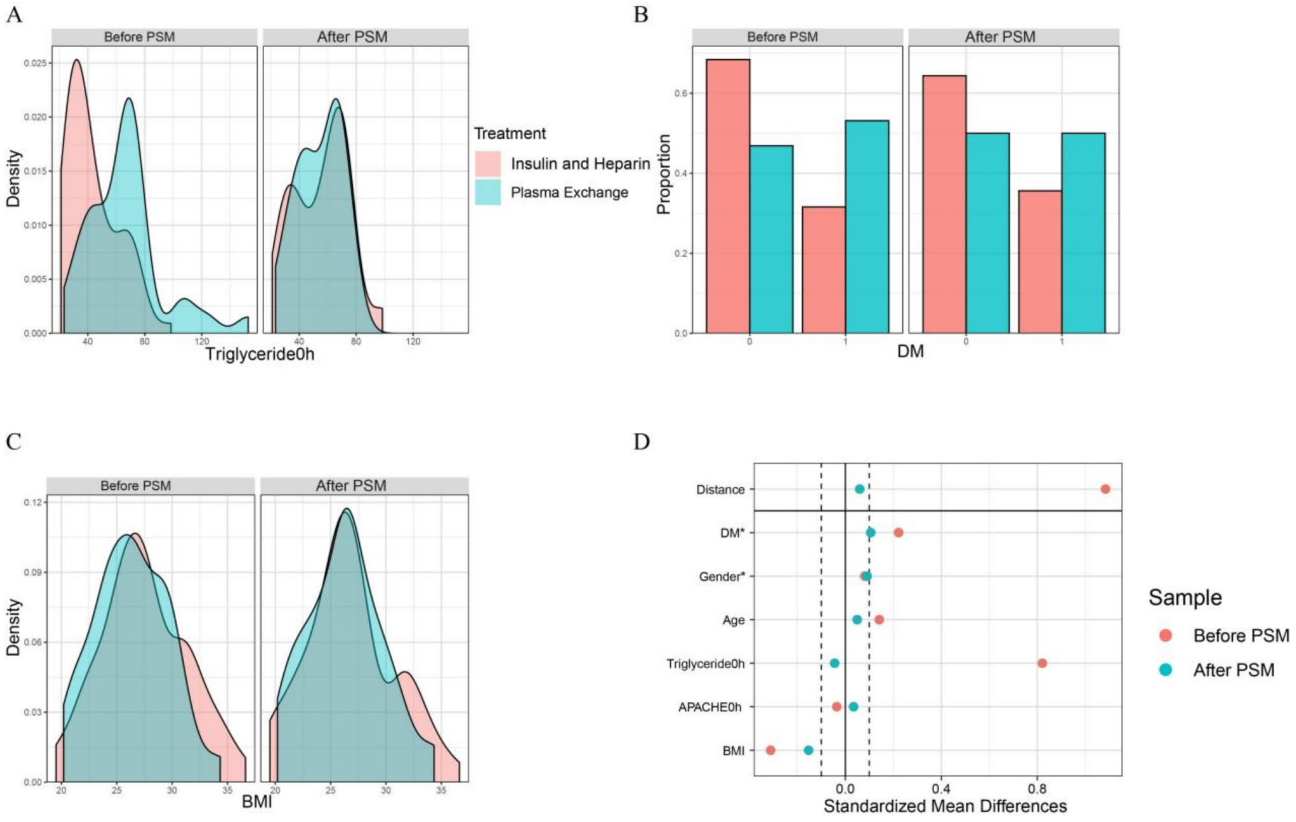

Fig. 2 Equilibrium analysis of the baseline data distributions in the insulin and heparin group and the plasma exchange group. (**A**) Distribution balance for triglyceride levels at 0 h before and after PSM. (**B**) Distribution balance for DM before and after PSM. (**C**) Distribution balance for BMI before and after PSM. (**D**) Standardized mean differences (SMDs) before and after PSM. The SMDs of BMI and triglyceride levels at 0 h were less than 0.25 after PSM. BMI, body mass index; PSM, propensity score matching; APACHE II, acute physiology and chronic health evaluation II; DM, diabetes mellitus

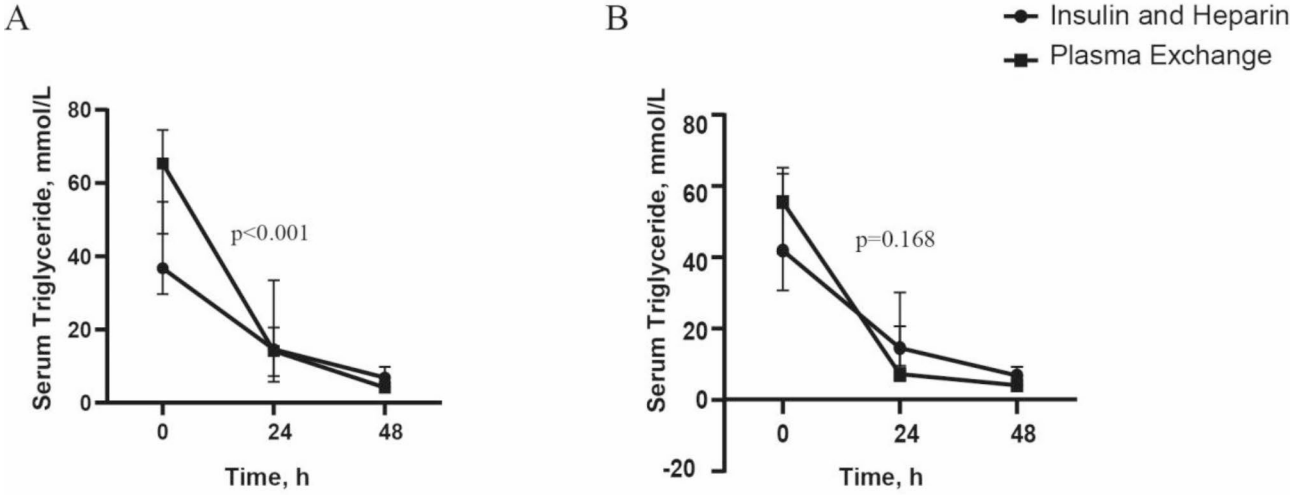

Fig. 3 Daily serum triglyceride levels during the first 48 h in the insulin and heparin group and the plasma exchange group. (**A**) Daily serum triglyceride levels during the first 48 h in the insulin and heparin group and the plasma exchange group before PSM. Triglyceride levels decreased differently between the two groups over 48 h ($p < 0.001$, mixed-effects models). (**B**) Daily serum triglyceride levels during the first 48 h in the insulin and heparin group and the plasma exchange group after PSM. Triglyceride levels decreased similarly in both groups over 48 h ($p = 0.168$, mixed-effects models)

Table 2 Outcome variables for patients with very severe HTG after PSM

Outcome variables	Insulin and heparin ($n=39$)	Plasma Exchange ($n=22$)	p
Clinical outcomes			
SAP (%)	9 (23.1)	10 (45.5)	0.127
Local complication (%)	30 (76.9)	20 (90.9)	0.309
APFC (%)	25 (64.1)	16 (72.7)	0.685
Pseudocyst (%)	1 (2.6)	2 (9.1)	0.606
APNC (%)	6 (15.4)	7 (31.8)	0.238
WON (%)	6 (15.4)	5 (22.7)	0.712
Secondary infection (%)	5 (12.8)	2 (9.1)	0.984
Hospitalization expenses			
Hospital LOS, median (IQR), day	9.0 (7.0-12.5)	11.0 (8.3–15.8)	0.219
Total cost, median (IQR), thousand CNY	15.3 (11.8–18.4)	39.3 (29.5–51.2)	**<0.01**
Hospital daily cost, median (IQR), thousand CNY/day	1.7 (15.6–20.4)	34.5 (32.2–39.3)	**<0.01**

APACHE, Acute Physiology and Chronic Health Evaluation; HTG, hypertriglyceridemia; SAP, severe acute pancreatitis; APFC, acute peripancreatic fluid collection; APNC, acute peripancreatic necrosis collection; WON, walled-off pancreatic necrosis; LOS, length of stay; CNY, Chinese Yuan; IQR, interquartile range; NA, not available

#Data description method, median with interquartile range

* p values were calculated using the Wilcoxon rank-sum test

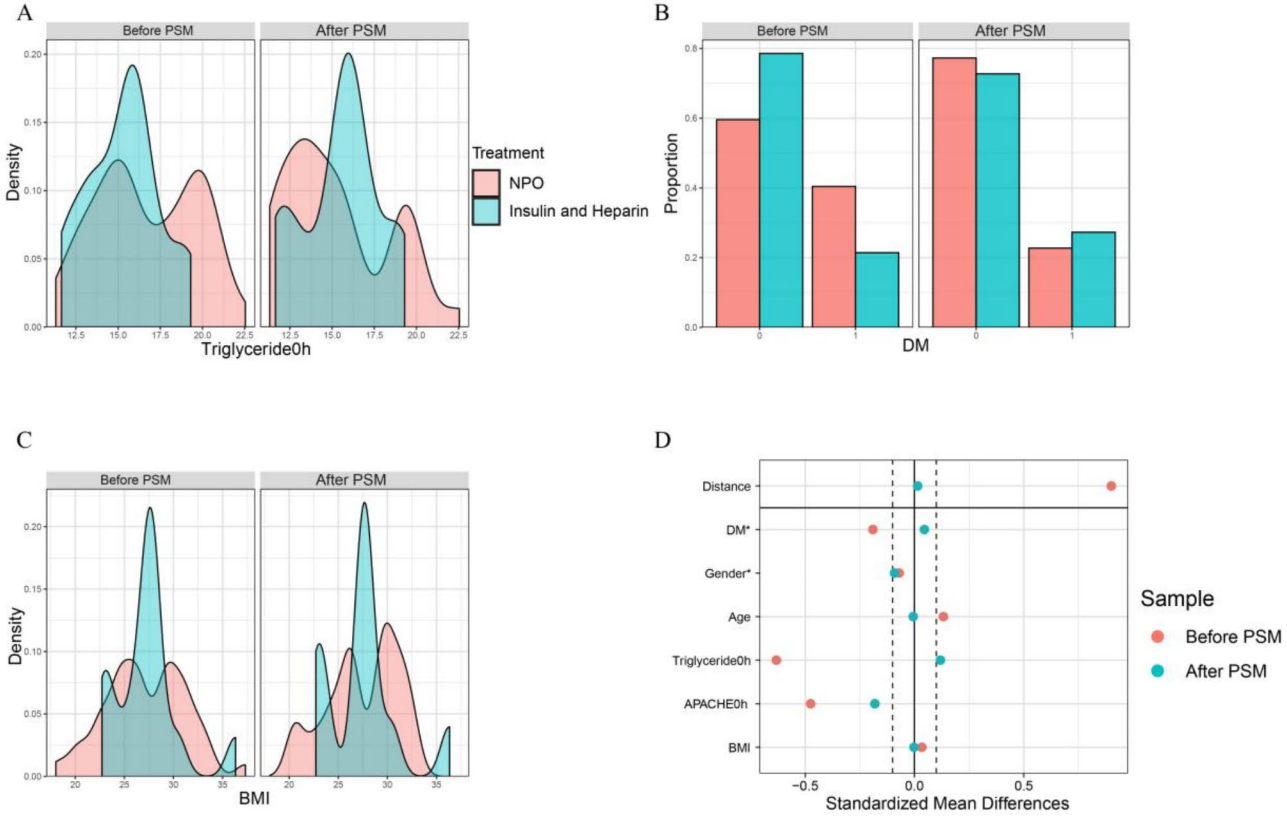

Fig. 4 Equilibrium analysis of the baseline data distributions in the NPO group and the insulin and heparin group. (**A**) Distribution balance for triglyceride levels at 0 h before and after PSM. (**B**) Distribution balance for DM before and after PSM. (**C**) Distribution balance for BMI before and after PSM. (**D**) Standardized mean differences (SMDs) before and after PSM. The SMDs of the APACHE II score at 0 h and the triglyceride level at 0 h decreased to lower than 0.25 after PSM. NPO, Cession of oral intake; BMI, body mass index; PSM, propensity score matching; APACHE II, 0 h acute physiology and chronic health evaluation II; DM, diabetes mellitus

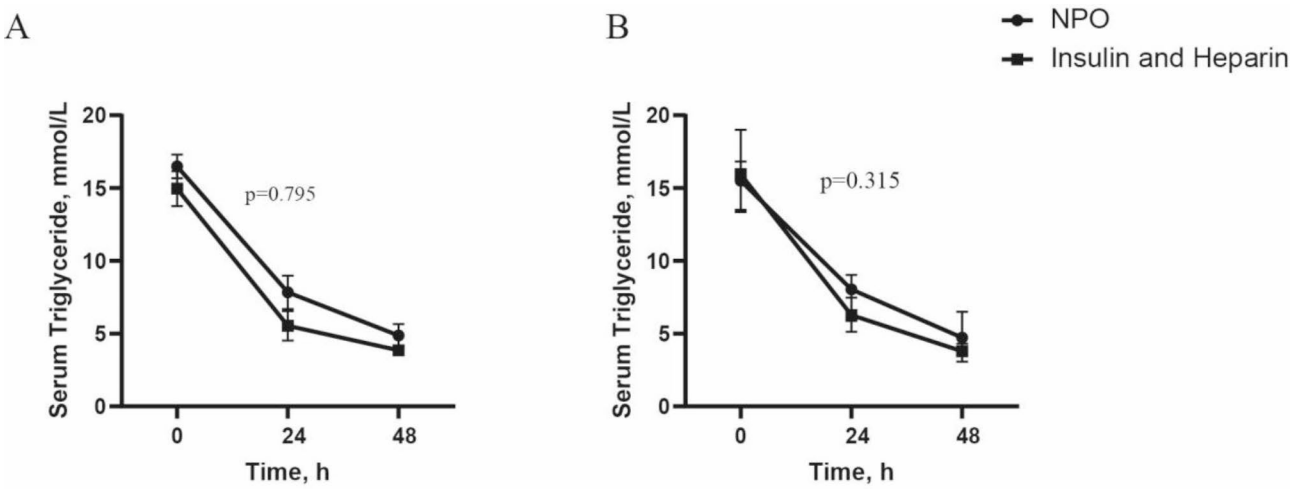

Fig. 5 Daily serum triglyceride levels during the first 48 h in the NPO group and the insulin and heparin group. (**A**) Daily serum triglyceride levels during the first 48 h in the NPO group and the insulin and heparin group before PSM. Triglyceride levels decreased similarly in both groups over 48 h ($p = 0.795$, mixed-effects models). (**B**) Daily serum triglyceride levels during the first 48 h in the NPO group and the insulin and heparin group after PSM. Triglyceride levels decreased similarly in both groups over 48 h ($p = 0.315$, mixed-effects models). NPO, Nothing of mouth

Table 3 Outcome variables for patients with severe HTG after PSM

Outcome variables	NPO ($n = 11$)	Insulin and Heparin ($n = 23$)	p
Clinical outcomes			
SAP (%)	0 (0.0)	3 (13.0)	0.548
Local complication (%)	7 (63.6)	19 (82.6)	0.431
APFC (%)	7 (63.6)	17 (73.9)	0.831
Pseudocyst (%)	0 (0.0)	3 (13.0)	0.543
APNC (%)	0 (0.0)	3 (13.0)	0.543
WON (%)	0 (0.0)	2 (8.7)	0.819
Secondary infection (%)	0 (0.0)	3 (13.0)	0.543
Hospitalization expenses			
Hospital LOS, median (IQR), day	7.0 (6.0-8.5)	10.0 (6.5–12.5)	
Total cost, median (IQR), thousand CNY	10.3 (9.2–12.2)	15.9 (11.1–24.5)	**< 0.05**
Hospital daily cost, median (IQR), thousand CNY/day	15.5 (14.8–17.5)	18.2 (15.4–19.5)	0.090

APACHE, Acute Physiology and Chronic Health Evaluation; HTG, hypertriglyceridemia; SAP, severe acute pancreatitis; APFC, acute peripancreatic fluid collection; APNC, acute peripancreatic necrosis collection; WON, walled-off pancreatic necrosis; LOS, length of stay; CNY, Chinese Yuan; IQR, interquartile range; NA, not available

#Data description method, median with interquartile range

* p values were calculated using the Wilcoxon rank-sum test

groups in the slope of the triglyceride decline were performed using the Wilcoxon rank-sum test. The results remain robust across different subgroups.

Discussion

In this PSM retrospective cohort study, we first found that patients with higher serum triglyceride levels might have worse prognoses; in accordance with this finding, we next explored the management of HTG on the basis of classified serum triglyceride levels. We found that the choice between insulin and heparin or plasma exchange in patients with very severe HTG may not significantly influence the rate of daily serum triglyceride reduction or HTG-AP prognosis. Moreover, the insulin and heparin group tended to incur lower hospital expenses. In patients with severe HTG, there was no significant difference in the rate of daily serum triglyceride reduction or the prognosis of HTG-AP between the NPO group and the insulin and heparin group. Patients treated with NPO also tended to have lower hospital expenses.

Consistent with our study, previous clinical studies revealed that higher serum triglycerides (> 22.6 mmol/L) significantly increased the risk of pancreatic necrosis [22]. Another prospective, multicentre, international cohort analysis of 716 acute pancreatitis patients revealed that patients with higher serum triglyceride levels (> 22.6 mmol/L) have a worse prognosis than those with lower serum triglyceride levels (11.3–22.6 mmol/L) [7]. In our analysis, patients with very severe HTG had significantly higher rates of SAP and hospital costs than did those with

severe HTG. These findings align with prior observations that higher triglyceride levels are associated with worse clinical outcomes. Accordingly, for patients with severe HTG (11.3–22.6 mmol/L), less invasive interventions, such as NPO, may be able to lower TG levels effectively, as observed in our study. However, for patients with very severe HTG, aggressive measures such as insulin/heparin or plasma exchange may be necessary to rapidly reduce TG levels and mitigate complications. Classifying patients on the basis of TG levels allows for cost-effective treatment by avoiding overtreatment in less severe cases.

In this study, we aimed to evaluate the relative effectiveness and cost-effectiveness of insulin and heparin versus plasma exchange as primary triglyceride-lowering strategies for HTG-AP patients with very severe HTG. Although we acknowledge that these two treatment modalities are not strictly mutually exclusive in clinical practice, our design sought to compare their dominant roles in managing HTG-AP on the basis of the literature. For example, Wang et al. reported that blood purification (including plasma exchange) therapy for HTG-AP is now widely used [23]. Plasma exchange is believed to not only remove plasma triglycerides but also reduce the levels of chylomicrons and inflammatory cytokines [20]. However, despite its benefits, plasma exchange has inherent risks and limitations, such as bleeding, haemodynamic instability and high cost. Recently, Cao et al. conducted a large multicentre cohort study of patients with HTG-AP. Their results showed that, compared with noninvasive measures such as insulin and heparin, plasmapheresis was associated with increased ICU requirements [24, 25]. Similarly, Gubensek et al. conducted a randomized trial to compare the efficacy of insulin and PE in HTG-AP patients, revealing comparable clinical course between these two groups [10]. Drawing on this evidence, we grouped patients on the basis of their primary triglyceride-lowering therapy to enable a clinically relevant comparison of their outcomes. Our study specifically focused on AP patients with very severe HTG and revealed that insulin/heparin therapy may achieve comparable clinical outcomes to plasma exchange while being associated with a significantly lower cost. This finding underscores the importance of considering cost-effective alternatives to invasive procedures, particularly in resource-limited settings.

For patients with severe HTG, our results suggest that NPO may be effective in lowering triglyceride levels while being associated with lower costs. The effectiveness of a strict diet and lifestyle modification has been well demonstrated in long-term HTG management [26]. However, the application of NPO in HTG-AP was limited. Berberich et al. first proposed the feasibility of NPO in patients with HTG-AP, which can achieve triglyceride lowering without the use of acute triglyceride-lowering medicine [12]. Several studies have also shown that NPO can lower serum triglycerides efficiently among patients with HTG-AP [26, 27]. In this PSM study, it is noteworthy that NPO may be as effective as insulin/heparin therapy in lowering triglyceride levels while being associated with reduced hospital expenses. These findings support the use of nonpharmacological approaches in this subgroup, particularly for patients with mild symptoms or contraindications to insulin therapy. The efficacy of NPO in HTG-AP treatment should be further explored in a larger multicentre randomized control study.

These findings advocate for a stratified approach to managing HTG-AP, integrating cost-effective and patient-specific treatment strategies into clinical practice. For example, the proposed classification system, which is based on TG levels, can help clinicians prioritize interventions that balance efficacy, safety, and cost, thereby optimizing resource allocation and patient outcomes. However, the cost differences observed are based on short-term outcomes and may not capture all clinical decision-making factors. Further studies with long-term clinical data such as recurrence rates, chronic complications, or quality-of-life measures are needed to better address this issue.

There are certain limitations in our study. First, as a retrospective cohort study, our research is inherently limited in its ability to establish causality. Although PSM was used to minimize confounding, residual confounding from unmeasured variables cannot be excluded. For example, factors such as genetic predispositions or lifestyle differences may have influenced the outcomes. Second, the study was conducted at a single institution with a relatively small sample size, which may restrict the generalizability of our findings to other health care settings or populations with varying demographic and clinical characteristics. Third, the absence of long-term follow-up limits our understanding of important outcomes, such as the recurrence of HTG or chronic pancreatitis and the sustainability of the observed cost-effectiveness. Future research, such as multicentre trials and randomized controlled trials, is essential to validate our findings across diverse populations, minimize bias and provide more definitive evidence regarding the efficacy of classified management strategies for HTG-AP. Future studies should include long-term follow-up to evaluate outcomes such as recurrence and chronic complications. Fourth, this classification provides a clinically relevant starting point for stratified analyses, and further prospective studies are needed to refine and validate these thresholds in the context of HTG-AP treatment. Moreover, investigating subgroups with specific risk factors or comorbidities could help refine treatment strategies and provide personalized recommendations.

Conclusions

In conclusion, our study suggests that a classified management approach for HTG in HTG-AP patients may help avoid overtreatment and reduce the economic burden. For patients with very severe HTG, plasma exchange may not improve the prognosis of HTG-AP patients and could increase hospital expenses. In such cases, insulin and heparin therapy may represent a more cost-effective alternative to plasma exchange in the very severe HTG subgroup. For patients with severe HTG, no significant difference in HTG-AP prognosis was noted between the NPO group and the insulin and heparin group. Moreover, NPO could reduce total hospital costs and may be a preferable option in the severe HTG subgroup.

Abbreviations

AP	Acute pancreatitis
HTG-AP	Hypertiglyceridemia induced acute pancreatitis
HTG	Hypertriglyceridemia
NPO	Nothing by mouth
CECT	Contrast-enhanced computed tomography
MRI	Magnetic resonance imaging
IV	Intravenous therapy
BMI	Body mass index
DM	Diabetes mellitus
SD	Standard deviation
IQR	Interquartile range
PSM	Propensity score matching
APFC	Acute peripancreatic fluid collection
APNC	Acute peripancreatic necrosis collection
WON	Walled-off pancreatic necrosis
APACHE II	Acute Physiology and Chronic Health Evaluation II
Hospital LOS	Hospital length of stay
CNY	Chinese yuan
NA	Not available

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

TP, JM, YCH, LSS and CQX contributed to conceptualization. TP, JM, LSS and CQX provided the methodology. TP, JM, LSS, CQX, MHJ, KW and HXW performed the investigation. TP, LSS and CQX carried out the formal analysis. TP performed visualization. JM and YCH contributed to funding acquisition. JM and YCH supervised the study. TP, LSS and CQX wrote the original draft. JM performed writing—review and editing.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The corresponding author will oversee execution of data management and sharing.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhejiang University (IIT20230022C-R1).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Use of AI and AI-assisted technologies statement

AI has not been used.

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