Reviewer 1

The authors reported a retrospective single-center study on the incidence, clinical characteristics, and treatment of hypertriglyceridemic acute pancreatitis. The authors evaluated the effect of intravenous insulin and hemoperfusion in hypertriglyceridemic acute pancreatitis using propensity-score matching. However, I have some concerns which need to be addressed.

1. What was the reason that hemoperfusion was used instead of plasmapheresis or continuous renal replacement therapy? How was hemoperfusion started and stopped? Please describe in detail how hemoperfusion was performed.

Dear reviewer, thank you very much for your valuable comments. Hemoperfusion (HP) is another blood purification modality which can absorb large pathogenic molecules from the circulation by adsorbent materials installed in the HP cartridge and didn't need to transfuse plasma. HP is more effective in removing middle and large molecules and toxins bonded with proteins than CVVH. Studies had shown that both hemoperfusion and plasma exchange were effective in reducing triglyceride in the blood. Hemoperfusion is easy to use, low cost, good tolerance, safe, reliable, effective, small side effects, easy for patients to accept, it is worth further promotion. Therefore, combined with the will, financial capacity and severity of patient, could choose HP treatment. Two hours of HP was carried out every 24 hours when the patients with hypertriglyceridemic acute pancreatitis agreed, then check the serum triglyceride to determined whether to treated with HP again until the triglyceride drops to the target. We have supplemented the procedure of HP in the 'Grouping Methods'.

2.All patients included in this study received proton-pump inhibitor and low molecular weight heparin. Why?

Dear reviewer, thank you very much for your valuable comments. Patients with acute pancreatitis often need to fast early in the disease, and PPI treatment is given to prevent stress ulcers. At the same time, in patients with hypertriglyceridemic acute pancreatitis, we found a general increase in D-dimer, given low molecular weight Heparin anticoagulation to prevent thrombosis.

3.Did all patients receive somatostatin/octreotide inhibitor? Or somatostatin/octreotide? Why?

Dear reviewer, thank you very much for your valuable comments. Yes, all patients received somatostatin/octreotide inhibitor. It is well known that abdominal pain was the most common symptom of acute pancreatitis, and it was demonstrated that somatostatin/octreotide significantly alleviated pain in many patients, so we used somatostatin/octreotide to relieve the pain.

4. Was serum lipase level checked in the patients of this study?

Dear reviewer, thank you very much for your valuable comments. No, serum lipase was not checked. Because acute pancreatitis is not easily missed in the absence of serum lipase, and the cost of serum lipase testing was higher than that of serum amylase testing, so our hospital had cancelled the serum lipase testing program from 2015.

5. Was there any difference in the severity of patients with DM or fatty liver?

Thank you. We have supplemented the comparison of the severity of patients with DM or fatty liver in the Table 2.

Reviewer 2

Excellent work with important message for clinical practice. Only one comment - I miss a comment that it is hard to tell sometimes if the AP is alcoholic or primarily caused only by TG, since alcoholics have high TG quite ofter. And people lie about alcohol consumption. How did you exclude alcohol as a cause of AP?

Dear reviewer, thank you very much for your valuable comments. Acute alcoholic pancreatitis was diagnosed in patients who had a history of chronic and recent alcohol abuse. Alternatively, diagnostic criteria of alcohol abuse for acute alcoholic pancreatitis are not standardized. However, the amount of alcohol required to induce pancreatitis in different populations is unknown. Few epidemiologic studies suggested that the alcohol consumption threshold should be exceeded to induce pancreatitis, and this threshold seemed to be approximately more than or equal to 4 to 5 alcoholic drinks per day (⩾48-60g/d), and over 5 years. So, we excluded patients with a history of chronic and recent alcohol abuse. Then, some biochemical parameters which can be potential predictors of alcoholic acute pancreatitis (greater ratio of aspartate aminotransferase/alanine aminotransferase, enhanced triglycerides and values of mean corpuscular volume) may assist in the diagnosis of alcoholic pancreatitis when people lie about alcohol consumption.

Reviewer 3

The authors have conducted an interesting study to determine the incidence and clinical characteristics of patients with acute pancreatitis due to hyper triglyceridemia. I have following comments regarding the manuscript:

1. The first paragraph of the Methods section describing the number of patients should be mentioned in the Results section.

Dear reviewer, thank you very much for your valuable comments. We have supplemented the number of patients in the Results section.

2. Some of the patients have multiple etiologies for acute pancreatitis such as gallstones with hypertriglyceridemia. Were such patients included in this study?

Dear reviewer, thank you very much for your valuable comments. We included patients with acute pancreatitis only induced by hypertriglyceridemia.

3. All patients were not given intravenous insulin therapy or hemoperfusion. So what were the indications of giving intravenous insulin therapy or hemoperfusion or CRRT in the study patients?

Dear reviewer, thank you very much for your valuable comments. We supplied two treatments included intravenous insulin and HP to reduce serum triglyceride rapidly, and other therapies would be guided by guidelines. The final choice depended on the patient's willingness of invasive procedures and economic affordability. To compare with HP, CRRT can not only reduce

TG rapidly but also remove inflammatory mediators and is more accurate for SIRS control. As a result, patients with SAP were more likely to choose CRRT which created an artificial bias, so we did not compare the efficacy of intravenous insulin with CRRT.

4. The role of intravenous insulin and hemoperfusion for hypertriglyceridemia is still evolving. So inorder to determine their effectiveness, the authors should add a control group in the propensity score matching and compare the three groups.

Dear reviewer, thank you very much for your valuable comments. Of 219 patients, 84 and 32 patients were treated with intravenous insulin and HP. The remnant 103 patients treat with anti-lipemic drugs (43 patients) and CRRT/HP+CRRT (60 patients). Because of the high safety and accessibility of anti-lipemic drugs, all patients were treated with anti-lipemic drugs without contraindication. To compare with HP, CRRT can not only reduce TG rapidly but also remove inflammatory mediators and is more accurate for SIRS control. As a result, patients with SAP were more likely to choose CRRT which created an artificial bias, so we did not add a control group.

5. Diet and drinking have been mentioned as the causes of hyper triglyceridemia. However, further details such as the type of diet and drinking should be mentioned. Also, if alcohol drinking causes hypertriglyceridemia, then it also causes acute pancreatitis. So, how was it determined whether acute pancreatitis was due to hypertriglyceridemia or alcohol? Whether such cases with dual etiologies included in this study?

Dear reviewer, thank you very much for your valuable comments. We have supplemented the type of diet and drinking in Table 1. Acute alcoholic pancreatitis was diagnosed in patients who had a history of chronic and recent alcohol abuse. Alternatively, diagnostic criteria of alcohol abuse for acute alcoholic pancreatitis are not standardized. However, the amount of alcohol required to induce pancreatitis in different populations is unknown. Few epidemiologic studies suggested that the alcohol consumption threshold should be exceeded to induce pancreatitis, and this threshold seemed to be approximately more than or equal to 4 to 5 alcoholic drinks per day (≥48-60g/d), and over 5 years. So, we excluded patients with a history of chronic and recent alcohol abuse. We included patients with acute pancreatitis only induced by hypertriglyceridemia.

Reviewer 4

Aggressive initial fluid replacement is important for hypertriglyceridemic acute pancreatitis.

1. Please investigate the initial fluid volume in this study.

Dear reviewer, thank you very much for your valuable comments. The importance of fluid replacement in the initial stages has been accepted as standard of treatment. But the exact amount and composition of fluid resuscitation that is required has not been extensively studied. We used goal-directed fluid therapy. The fluid requirements were frequently re-evaluated 6 h after admission and 24-48 h after admission. The rate of fluid resuscitation is adjusted according to clinical evaluation (urine output, etc.), vital sign (heart rate, etc.),

hematocrit and BUN. So, there were a lot of individual variation in the volume of fluid replacement, and we did not have investigate the initial fluid volume.

2. You should also state body mass index (BMI) in the patient background.
Thank you. We have supplemented the BMI in the patient background in Table 1 and Table 2.

Reviewer 5
Reviewer's comments, Thank you for giving me the opportunity to review this interesting article. Lin XY et al. conducted a retrospective study regarding the clinical characteristics of HTG-AP. Because the treatment strategy for HTG-AP remains controversial, this study shows potentially significant results. However, there are several major issues to be addressed in this study. I attach the Reviewer's comments and recommend the authors to reconsider following issues.
Major issues:
1. Why was the incidence of HTG-AP increased recently, not only in your institution but also in other countries? For example, was it due to the improvement of disease recognition or availability of the detection of serum TG?
Dear reviewer, thank you very much for your valuable comments. We have supplemented the points in the Discussion section.

2. In this study, how did you decide or select lipid-lowering treatment such as intravenous insulin, HP or only anti-lipemic drugs? Please clarify the basic treatment strategy for HTG-AP in your institution.
Dear reviewer, thank you very much for your valuable comments. Because of the high safety and accessibility of anti-lipemic drugs, all patients were treated with anti-lipemic drugs without contraindication. We supplied two treatments included intravenous insulin and HP to reduce serum triglyceride rapidly, and other therapies would be guided by guidelines. The final choice depended on the patient's willingness of invasive procedures and economic affordability.

3. In the 'Results section', the descriptions of 'Trends in Incidence of HTG-AP' are redundant. Each data is easily available in Figure 2, therefore please show and summarize important data in the main text.
Thank you. We have deleted the descriptions of 'Trends in Incidence of HTG-AP' and summarize important data in the main text.

4. In the section of 'Clinical Characteristics of HTG-AP', the descriptions of the symptoms of HTG-AP are also redundant.
Thank you. We have deleted the symptoms of HTG-AP.

5. The authors described that 54.7% of patients with HTG-AP were related to diet and/or drinking. I think identification of etiology in those patients is sometimes difficult. How did you distinguish between alcoholic AP and HTG-AP in patients with both drinking and high-level of TG?

Dear reviewer, thank you very much for your valuable comments. Acute alcoholic pancreatitis was diagnosed in patients who had a history of chronic and recent alcohol abuse. Alternatively, diagnostic criteria of alcohol abuse for acute alcoholic pancreatitis are not standardized. However, the amount of alcohol required to induce pancreatitis in different populations is unknown. Few epidemiologic studies suggested that the alcohol consumption threshold should be exceeded to induce pancreatitis, and this threshold seemed to be approximately more than or equal to 4 to 5 alcoholic drinks per day (⩾48-60g/d), and over 5 years. So, we excluded patients with a history of chronic and recent alcohol abuse. HTG-AP was considered in patients with AP when the level of serum TG was over 11.3 mmol/L or between 5.65 and 11.3 mmol/L with lactescent serum on admission.

6. Were eleven patients who died during hospitalization all categorized into SAP? I recommend clarifying the mortality rate according to disease severity.

Thank you. Yes, the eleven patients who died during hospitalization all categorized into SAP. We have supplemented the mortality rate according to disease severity in the Table 2.

7. The authors described that 90.6% of patients with HTG-AP had comorbidity with fatty liver disease. I recommend adding the body weight and/or body mass index to table 1.

Thank you. We have supplemented the BMI in the patient background in Table 1 and Table 2.

8. What was the dose of insulin in ING group? Were there any adverse events such as hypoglycemia?

Dear reviewer, thank you very much for your valuable comments. We usually start the intravenous infusion of regular insulin at a rate of 0.1-0.3 U/ (kg h) and monitor blood glucose levels per 1-2 h. For patients with a blood glucose level of 150-200 mg/dl, an additional infusion of 5-10% glucose solution is given to prevent hypoglycemia caused by insulin infusion. We did not foud any adverse events such as hypoglycemia.

9. Was there any difference in fluid resuscitation among MAP, MSAP, and SAP group?

Dear reviewer, thank you very much for your valuable comments. The importance of fluid replacement in the initial stages has been accepted as standard of treatment. But the exact amount and composition of fluid resuscitation that is required has not been extensively studied. We used goal-directed fluid therapy. The fluid requirements were frequently re-evaluated 6 h after admission and 24-48 h after admission. The rate of fluid resuscitation is adjusted according to clinical evaluation (urine output, etc.), vital sign (heart rate, etc.), hematocrit and BUN. So, there were a lot of individual variation in the volume of fluid replacement, and we did not have investigate the initial fluid volume.

10. In table 2, Why was the proportion of 'Intravenous insulin' extremely low (only 1.3%) in patients with SAP?

Dear reviewer, thank you very much for your valuable comments. To compare with intravenous insulin and HP, CRRT can not only reduce TG rapidly but also remove inflammatory mediators

and is more accurate for SIRS control. As a result, patients with SAP were more likely to choose CRRT or CRRT+HP. Table 2 showed the proportion of 'CRRT/HP+CRRT' extremely high (77.6%) in patients with SAP. So, we did not compare the efficacy of intravenous insulin with CRRT.

11. Of 219 patients, 84 and 32 patients were treated with intravenous insulin and HP, respectively. How did you treat HTG-AP in remnant 103 patients? Were there any patients treated with the combination of heparin and insulin? Some previous reports recommended the combination therapy as first-line therapy for severe HTG-AP.

Dear reviewer, thank you very much for your valuable comments. The remnant 103 patients treat with anti-lipemic drugs (43 patients) and CRRT/HP+CRRT (60 patients). Because the use of heparin requires close monitoring of APTT which is difficult to administer in general wards. However, the patients with SAP in intensive care unit mostly selected blood purification which effect was also remarkable.

12. Although the details of Table 2 and Table 3 were described in the discussion section of 'Comparisons of Different Grades of Severity of HTG-AP', these contents should be described in the 'Results' section. Also, I agreed high CRP, low calcium, and low albumin were risk factors of severe HTG-AP, as concluded from this study. However, these factors seemed not to be specific for HTG-AP. High CRP and low calcium are well known predictive factors for severe AP, caused by not only HTG-AP but also other etiologies including alcoholic and biliary AP. Therefore, these results only confirmed the usefulness of the revised Atlanta classification and did not indicate the novelty or strength of this study. I recommend changing 'Conclusion' and modifying the contents of 'Discussion'.

Dear reviewer, thank you very much for your valuable comments. We couldn't agree with you more. We have changed 'Conclusion' and modified the contents of 'Discussion'.

13. The 'Aim' of this study is confusing. Did the authors intent to clarify clinical characteristics of HTG-AP or to compare the treatment efficacy between ING and HP? I think the main finding in this study was the efficacy of intravenous insulin as a non-invasive and low-cost treatment for patients with mild or moderately severe HTG-AP. Therefore, I recommend describing the aim of this study more clearly.

Dear reviewer, thank you very much for your valuable comments. We couldn't agree with you more. We have changed the Aim.

Minor issues

1. I think 'mg/dL' is more appropriate rather than 'mmol/L' as the unit of TG.

Thank you. We have modified the units.

2. There are several misspellings in the section of 'ARTICLE HIGHLIGHTS', such as 'To compared', 'diffident' and 'sued'. Please check them carefully throughout

the manuscript.

Thank you. We have modified the mistakes.