INPLASY

The association between the magnitude of triglyceride reduction and clinical hard outcomes in patients with hypertriglyceridemia-associated acute pancreatitis: a protocol for systematic review and dose-response meta-analysis

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ADMINISTRATIVE INFORMATION

Support - This review received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Review stage at the time of initial registration - Preliminary searches.

Conflicts of interest - No other potential conflicts of interest to declare for this review.

INPLASY registration number: INPLASY2026110080

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 November 2026 and was last updated on 23 November 2026.

INTRODUCTION

Review question / Objective The primary objective of this systematic review and dose-response meta-analysis is to quantitatively evaluate the dose-response relationship between the magnitude of serum triglyceride (TG) reduction (modeled as a continuous exposure) and clinical hard outcomes (in-hospital/30-day mortality and persistent organ failure) in adult patients with hypertriglyceridemia-associated acute pancreatitis (HTG-AP).
The secondary objectives are:
1. To assess whether the association between the TG reduction magnitude and hard outcomes differs systematically across pre-specified subgroups, including intervention modalities (e.g., insulin-based vs. apheresis-based) and comparator types (conventional care vs. active comparators).
2. To critically evaluate the clinical validity of TG reduction as a surrogate endpoint in the acute management of HTG-AP, thereby providing evidence-based guidance for future clinical trials and practice.

Rationale Hypertriglyceridemia-associated acute pancreatitis (HTG-AP) is a severe condition associated with a high risk of persistent organ failure. Rapid triglyceride (TG) reduction, utilizing interventions such as insulin, therapeutic plasma exchange, or hemoperfusion, is widely considered the cornerstone of acute management. However, whether the magnitude of TG reduction itself translates into improved hard clinical outcomes remains highly controversial.
Recent network meta-analyses have compared different TG-lowering modalities, indirectly suggesting that faster TG reduction may not consistently improve mortality or organ failure. Nevertheless, existing evidence primarily focuses on categorical comparisons between treatments (e.g., Modality A vs. Modality B) or uses TG reduction merely as a surrogate endpoint. The

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dose-response relationship between the exact magnitude of TG reduction and clinical hard outcomes has not been quantitatively established. This systematic review and dose-response meta-analysis aim to address this critical evidence gap. By modeling TG reduction as a continuous exposure via meta-regression, we intend to directly quantify its association with mortality and organ failure, thereby challenging the current clinical inertia and clarifying the true prognostic value of rapid TG reduction in HTG-AP.

Condition being studied Hypertriglyceridemia-associated acute pancreatitis (HTG-AP), defined as acute pancreatitis with serum TG ≥5.65 mmol/L (or the threshold used by original investigators) as the primary or major contributing etiology.

METHODS

Search strategy The detailed search strategy for PubMed is as follows:
(("Hypertriglyceridemia"[Mesh] OR "Hyperlipidemias"[Mesh] OR hypertriglyceridemi*[tiab] OR hyperlipidemi*[tiab] OR hyperlipidaemi*[tiab] OR "hypertriglyceridemic pancreatitis"[tiab] OR "hypertriglyceridaemic pancreatitis"[tiab] OR "hypertriglyceridemia-induced pancreatitis"[tiab] OR "hypertriglyceridaemia-induced pancreatitis"[tiab] OR "hypertriglyceridemia-associated pancreatitis"[tiab] OR "hypertriglyceridaemia-associated pancreatitis"[tiab] OR "hyperlipidemic pancreatitis"[tiab] OR "hyperlipidaemic pancreatitis"[tiab] OR "HTG-AP"[tiab] OR "HTGAP"[tiab] OR "HLAP"[tiab] OR "HTGP"[tiab] OR "HLP"[tiab]) AND ("Pancreatitis"[Mesh] OR "Pancreatitis, Acute Necrotizing"[Mesh] OR pancreatit*[tiab])) AND ("Insulin"[Mesh] OR insulin[tiab] OR "Heparin"[Mesh] OR heparin[tiab] OR "low molecular weight heparin"[tiab] OR LMWH[tiab] OR "Plasma Exchange"[Mesh] OR "Plasma Exchange"[tiab] OR plasmapheresis[tiab] OR "double filtration plasmapheresis"[tiab] OR DFPP[tiab] OR "Hemoperfusion"[Mesh] OR hemoperfusion[tiab] OR "Hemofiltration"[Mesh] OR hemofiltration[tiab] OR "Continuous Renal Replacement Therapy"[Mesh] OR "continuous renal replacement therapy"[tiab] OR CRRT[tiab] OR "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] OR statin*[tiab] OR "Fibric Acids"[Mesh] OR fibrate*[tiab] OR fibric acid*[tiab] OR fenofibrate[tiab] OR "Niacin"[Mesh] OR niacin[tiab] OR "Fatty Acids, Omega-3"[Mesh] OR "omega-3"[tiab] OR "fish oil"[tiab] OR "PCSK9"[tiab] OR evolocumab[tiab] OR alirocumab[tiab] OR "Apolipoprotein C-III"[Mesh] OR "Apolipoprotein C-III"[tiab] OR APOC-III[tiab] OR volanesorsen[tiab] OR olezarsen[tiab] OR plozasiran[tiab])

Note for other databases:
The search strings will be appropriately adapted for other databases (Embase, Web of Science/SCIE, Scopus, Cochrane Library including CDSR and CENTRAL, MEDLINE, CINAHL, CNKI, WanFang Data, SinoMed, and Google Scholar) using their specific syntax and controlled vocabulary (e.g., Emtree for Embase).

Participant or population Inclusion: Adults (≥18 years) with acute pancreatitis and hypertriglyceridemia (serum TG ≥ 5.65 mmol/L, or the threshold used by original investigators) during the acute hospitalization phase.
Exclusion: Chronic pancreatitis; pancreatitis due to other etiologies (e.g., gallstones, alcohol, post-ERCP); pregnancy-associated pancreatitis; patients receiving long-term lipid-lowering therapy without an acute intervention.

Intervention Included: The primary exposure of interest is the magnitude of TG reduction, operationalized as: (1) Percentage reduction from baseline (including reported clearance rates); (2) Absolute reduction (mmol/L); (3) Proportion achieving target TG; or (4) Time (days) to achieve target TG. The specific TG-lowering modalities include, but are not limited to: insulin (with or without heparin), plasma exchange, hemoperfusion, hemofiltration, CRRT, DFPP, oral agents (e.g., statins, fibrates, PCSK9 inhibitors), and combination therapies (e.g., insulin plus plasma exchange). These modalities are recorded as pre-specified covariates, not as the primary exposure.
Excluded: Studies evaluating lifestyle modifications alone, dietary supplements (e.g., red yeast rice, plant sterols), or interventions without the explicit goal of acute serum TG reduction (e.g., long-term oral lipid-lowering therapy without acute intervention).

Comparator Included:
Two comparator categories will be analyzed separately, not pooled:
Comparator A: Conventional supportive care without a dedicated TG-lowering intervention.
Comparator B: Another active TG-lowering strategy (e.g., insulin alone vs. insulin + heparin; plasma exchange vs. insulin; or combination therapies vs. other combination therapies).
Excluded:
Studies without a concurrent control group (e.g., single-arm trials, case series); studies using historical controls; or studies where the

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comparator group received a non-pharmacological intervention without an explicit goal of TG reduction.

Study designs to be included Both randomized and nonrandomized study types will be included.Included: Randomized controlled trials (RCTs) and prospective or retrospective cohort studies provided that the study (1) compares a TG-lowering strategy with conventional care or another active TG-lowering strategy, and (2) reports at least one hard outcome (mortality or persistent organ failure) and at least one TG-reduction metric.Excluded: Case reports, case series, cross-sectional studies, conference abstracts, animal studies, single-arm studies.

Eligibility criteria This review focuses on studies conducted in acute inpatient hospital settings (including general wards, high-dependency units, and intensive care units). Both single-center and multicenter studies from any geographic region will be included, provided they evaluate acute TG-lowering interventions during the index hospitalization for HTG-AP. Studies focused exclusively on outpatient or primary care settings for chronic lipid management will be excluded.

Information sources We will search for published studies with no search language or date restrictions.

The main electronic databases to be searched are CDSR (Cochrane Database of Systematic Reviews), CENTRAL (Cochrane Central Register of Controlled Trials), CINAHL, CNKI, Embase, MEDLINE (PubMed), SCIE (Science Citation Index Expanded), WanFang Data, SinoMed, and Scopus. Google Scholar will be used as a supplementary source.

Other methods of identifying studies will include:
- Contacting authors or experts.
- Hand-searching the reference lists of included studies and relevant systematic reviews (backward citation searching).
- Forward citation searching (snowballing) to identify articles that cite the included studies.

Main outcome(s) 1. In-hospital or 30-day all-cause mortality (dichotomous)
2. Persistent organ failure (>48 hours) (dichotomous)
3. Composite hard outcome (new-onset organ failure and/or death): If an original study reports only a composite outcome without disaggregated data, it will be analyzed as a separate outcome in a distinct model,not mixed into single-outcome analyses.

Additional outcome(s) 1. Proportion achieving target TG (<5.65 mmol/L) within 72 hours (or the closest reported time point).
2. ICU length of stay (days).
3. Total hospital length of stay (days).
4. Local complications (pancreatic necrosis, infection).

Data management References will be imported into EndNote for deduplication. Screening will be performed using Rayyan, following a two-step process: title/abstract screening followed by full-text review. Two reviewers will independently screen and extract data using a standardized Excel form; any disagreements will be resolved by discussion or a third reviewer. Duplicate publications from the same cohort will be collated, and the most comprehensive report will be used. Reasons for exclusion after full-text review will be recorded. If data are missing, study authors will be contacted; otherwise, the limitations will be discussed and sensitivity analyses performed. Data manipulation (e.g., converting mg/dL to mmol/L by dividing by 88.5, or median to mean using Wan et al. method) will be conducted in Excel. Data synthesis will be performed using RevMan or Stata. All extracted data will be securely stored, and no personally identifiable patient data will be collected.

Quality assessment / Risk of bias analysis Risk of bias will be assessed independently by two reviewers. Randomized controlled trials (RCTs) will be evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool. Observational studies will be evaluated using the ROBINS-I tool, with a specific focus on confounding by indication (e.g., baseline disease severity). Any disagreements will be resolved through discussion or by consulting a third reviewer. If required information is unclear or unavailable, study investigators will be contacted.

For reporting bias (missing results), if at least 10 studies are included for a specific outcome, a funnel plot and Egger's test will be performed to assess publication bias. If fewer than 10 studies are available, reporting bias will be assessed qualitatively. The overall certainty of evidence will be assessed using the GRADE approach.

Strategy of data synthesis Data synthesis will be performed in a stepwise manner.

Step 1 — Pairwise meta-analysis and Data Handling: For each hard outcome, a random-

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effects meta-analysis will be conducted separately for RCTs and observational studies. For dichotomous outcomes (e.g., mortality, proportion achieving target TG), risk ratios (RR) with 95% confidence intervals (CIs) will be calculated. For studies with zero events in both arms, a continuity correction of 0.5 will be applied, or the Peto odds ratio (OR) method will be used. For continuous outcomes (e.g., TG reduction, length of stay), mean differences (MD) will be calculated. For studies reporting only median and interquartile range (IQR), we will first attempt to contact the authors for original data; if unsuccessful, the median will be converted to mean using the Wan et al. method, using a pre-specified pre-post correlation coefficient of 0.5 (sensitivity analyses will use 0.3 and 0.7). For studies reporting only the time to target TG, it will be analyzed as a continuous variable (days). Heterogeneity will be assessed using the I^2 statistic and Cochran's Q test.Different forms of triglyceride reduction metrics may be reported across studies. For the dose-response meta-regression, only studies providing uniform comparable TG-reduction measures will contribute to the main model; other studies will still be included for pairwise meta-analysis, subgroup and narrative synthesis.

Step 2 — Dose-response meta-regression (Primary analysis): If at least 10 independent study-level contrasts provide both a TG-reduction metric and a hard-outcome estimate, a random-effects meta-regression will be performed with TG reduction as the continuous explanatory variable and the log RR as the dependent variable. Comparator type, intervention modality, and measurement time point will be included as pre-specified covariates. Restricted cubic splines will be used to test for non-linear dose-response relationship.

Step 3 — Pre-specified fallback: If fewer than 10 contrasts are available, the meta-regression will be reported as exploratory only. The primary synthesis will be a subgroup analysis by TG-reduction magnitude (≥50% vs. <50%). If the 50% threshold is not applicable due to the actual data distribution, a median split will be used as an alternative. If data remain insufficient for subgroup pooling, the findings will be synthesized narratively.

Subgroup analysis Pre-specified subgroup analyses will be conducted to explore potential sources of heterogeneity:
1. Comparator type: conventional supportive care vs. another active TG-lowering strategy.
2. Intervention modality: insulin-based vs. apheresis-based vs. combination therapies.
3. Study design: RCT vs. prospective cohort vs. retrospective cohort.
4. Baseline TG severity: ≥11.3 mmol/L vs. 5.65–11.3 mmol/L.
5. TG-reduction magnitude: ≥50% vs. <50%.

Sensitivity analysis Sensitivity analyses will be performed to test the robustness of the primary results, including:
1. Excluding studies with a high risk of bias.
2. Excluding studies reporting only composite outcomes.
3. Using different pre-post correlation coefficients (0.3 and 0.7) for the conversion of TG change SDs.
4. Excluding studies reporting only median and IQR for TG reduction.
5. Restricting the analysis to RCTs only.

Language restriction None.

Country(ies) involved China.

Other relevant information Several potentially similar records were identified during the initial scoping phase. This review is methodologically distinct from the following registered/published reviews:

1. CRD420261471222 (Evidence Map): The previous review only identifies research gaps. Our review quantitatively synthesizes the dose-response relationship between the magnitude of TG reduction and hard outcomes using meta-regression, which represents a significant methodological advancement.

2. CRD420261425015 (NMA): Although this review also targets HTG-AP, it is a Network Meta-Analysis focusing on ranking specific blood-purification and pharmacological strategies. Our review does not aim to rank treatment categories. Instead, we model the magnitude of TG reduction as a continuous exposure to quantify its dose-response relationship with hard outcomes using meta-regression.

3. CRD420261372291 (NMA): This registered review aims to establish a hierarchy of different early lipid-lowering and blood purification modalities. Our review does not rank treatment categories, but models TG reduction as a continuous exposure to quantitatively evaluate its dose-response relationship with clinical hard outcomes via meta-regression.

4. CRD420261464606 (Systematic Review): This registered review compares early lipid-lowering therapy strictly vs. conventional care alone and

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excludes active-comparator studies. The present review includes both comparator types. More importantly, we model the magnitude of TG reduction as a continuous exposure to quantitatively evaluate its dose-response relationship with hard outcomes via meta-regression, which is not addressed in their study.

Note: This protocol is also registered in parallel on PROSPERO (CRD submission pending). Any updates to the review status will be reflected in both records.
Current review status: Ongoing.

Keywords Hypertriglyceridemia-associated acute pancreatitis; Triglyceride reduction; Persistent organ failure; Mortality; Dose-response meta-analysis; Meta-regression.

Dissemination plans The findings of this systematic review and dose-response meta-analysis will be published in a peer-reviewed scientific journal and presented at relevant national or international medical conferences. We will also share the results through academic social networks to ensure wide dissemination among clinicians and researchers.

Contributions of each author

Author 1 - Jianqiong Rao. Conceptualized the study, designed the methodology, performed the literature search, independently screened and extracted data, performed the data analysis, and drafted the manuscript.
Email: 2136545657@qq.com
Author 2 - Wei Xu. Supervised the study, provided critical methodological advice, and served as the corresponding author for consensus and arbitration.
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