SYSTEMATIC REVIEW



A systematic review of the epidemiology and risk factors for severity and recurrence of hypertriglyceridemia-induced acute pancreatitis

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Abstract

This systematic review aims to comprehensively assess the epidemiology and identify risk factors associated with the severity and recurrence of hypertriglyceridemia-induced acute pancreatitis (HTG-AP). A search of PubMed, Web of Science, and Cochrane databases was conducted to identify all relevant randomized controlled trials (RCTs), prospective, or retrospective cohort studies on HTG-AP. Data related to epidemiology and risk factors for severity and recurrence of HTG-AP were extracted and analyzed. Seventy-seven studies met the inclusion criteria, comprising 1 RCT, 21 prospective studies, and 55 retrospective studies. A total of 56,617 acute pancreatitis (AP) patients were included, of which 19.99% were diagnosed with HTG-AP (n = 11,315). Compared to non-HTG-AP patients, HTG-AP patients were more likely to be male (68.7% vs. 57.3%) and younger (mean age 41.47 ± 4.32 vs. 50.25 ± 7.70 years). HTG-AP patients exhibited higher mortality rates (up to 20% vs. 15.2%), increased severity (8.3% to 100% vs. 3.8% to 47.2%), and higher recurrence rates (up to 64.8% vs. 23.3%). Analysis of temporal trends from 2002 to 2023 showed a range of HTG-AP prevalence in overall AP patients from 1.6% to 47.6%, with a slight upward trend that was not statistically significant (P = 0.1081). Regional analysis indicated relatively stable prevalence in North America (P = 0.5787), Europe (P = 0.0881), other regions (P = 0.738), while prevalence in China showed a significant increase (P = 0.0119). Thirteen studies investigated risk factors affecting HTG-AP severity, with elevated serum triglyceride (TG) levels associated with increased risk of complications such as pancreatic necrosis, systemic inflammatory response syndrome (SIRS), shock, and multi-organ failure. Additional factors including high neutrophil-to-lymphocyte ratio (NLR), elevated levels of amylase and C-reactive protein (CRP), hypocalcemia, and hypoalbuminemia were also implicated in HTG-AP severity. Smoking history, poor lipid control (TG>3.1 mmol/L), or recurrent hypertriglyceridemia during follow-up

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were identified as potential predictors of HTG-AP recurrence. Our findings indicate a stable global prevalence of HTG-AP within AP patients, but a notable increase in China, possibly attributed to socio-economic and dietary factors. **Keywords** Hypertriglyceridemia-induced Acute pancreatitis, Incidence, Severity, Recurrence

Introduction

Acute pancreatitis (AP), a common condition of the digestive system, has been exhibiting a rising trend of incidence globally at a rate of 3.07% per year, posing a significant burden on individuals and society [1]. Although 80% of AP patients have mild self-limited disease, 20% of patients develop pancreatic necrosis and infected pancreatic necrosis (IPN), which have significantly increased mortality [2]. In addition, approximately 20% AP patients have a risk of recurrence, and as the frequency of AP attacks increases, the risk of pancreatic ductal adenocarcinoma (PDAC) also rises [3, 4]. Common causes of AP include biliary, alcoholic, and hypertriglyceridemia (HTG) [5]. Compared to other etiologies, HTG can not only cause AP, but also modify its severity [6–8].

A recent meta-analysis encompassing 127 studies on the etiology of AP revealed that patients with hypertriglyceridemia acute pancreatitis (HTG-AP) have higher rates of severe pancreatitis, mortality, and recurrence compared to those with other etiologies [such as biliary, alcoholic, and post- endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis] [1]. Additionally, multiple domestic and international studies have found that HTG-AP patients tend to be younger, with the age of onset fluctuating between 30 and 50 years, and have a higher proportion of male patients, ranging from 60 to 80% [6, 9–12]. This trend further suggests that HTG-AP is a highly morbid condition that deserves sufficient attention.

In China, with changes in lifestyle and dietary structure, multiple multicenter studies from different regions have confirmed an increasing trend in the proportion of HTG-AP patients among AP patients, ranging from 10.4% to 23.9% [13-15]. However, globally, despite AP remaining a global gastrointestinal emergency, the temporal trends in the etiological distribution of AP, particularly the proportion of HTG-AP, are poorly characterized, and no systematic synthesis has evaluated whether HTG-AP prevalence has increased over time or identified consistent risk factors for its severity and recurrence. This systematic review hypothesizes that: the proportion of HTG-AP among all AP cases has significantly increased globally over the past two decades, and serum TG levels may affect the severity and recurrence of HTG-AP. Clarifying these hypotheses will prioritize the treatment strategy for HTG-AP.

Methods

Search strategy

A comprehensive search was conducted on PubMed, Web of Science, and Cochrane databases, The search terms were designed as follows ("acute pancreatitis" OR "pancreatitis") AND ("hypertriglyceridemia" OR "hyperlipidemia" OR "hyperlipidemia pancreatitis" OR "hypertriglyceridemia pancreatitis" OR "hyperlipidemic acute pancreatitis" OR "hypertriglyceridemia-induced acute pancreatitis"). Studies involving HTG-AP patients were included up to July 31, 2023.

Inclusion criteria

Randomized controlled trials (RCTs), prospective, or retrospective cohort studies focusing on HTG-AP patients were included. Studies were eligible if published up to July 31, 2023. The definition of HTG-AP complied with international guidelines for AP and HTG-AP definition [16]. The definition of AP as follows: fulfillment of two of the following three criteria: 1) acute onset of epigastric pain radiating to the lower back; 2) blood amylase and/or lipase levels > 3 times higher than normal; and 3) imaging examination (e.g., abdominal ultrasound, enhanced CT, and MRI) revealing typical findings of acute pancreatitis. Patients diagnosed with HTG-AP met any of the following criteria: serum TG \geq 11.3 mmol/L (1000 mg/dL) or TG \geq 5.65 mmol/L (500 mg/dL) with chylemia and excluded other etiology (e.g., cholelithiasis, alcoholic AP).

Exclusion criteria

Reviews, commentary, letters to the editor, conference abstracts (without complete patient data), review articles, meta-analyses, case reports (< 10), and animal experiments were excluded from this study. Articles without sufficient data were excluded.

Article screening and bias risk assessment

After excluding duplicate literature, 1670 articles were screened, and relevant studies were independently assessed by two reviewers (LJD and MWT) based on their title and abstract for relevance to this review. Discrepancies in abstract interpretation were resolved by a third senior reviewer (WZ). The risk of bias in the studies was evaluated independently by two reviewers using the Cochrane collaboration tool, with any discrepancies resolved through discussion with a third reviewer. Adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was maintained to assess bias in all included studies [17].

A total of 77 articles were included in this research. included 1 RCT and 21 cohort studies, and significant differences among the studies in the following three aspects: first, the diagnostic criteria for HTG-AP varied among different studies (TG > 1000 mg/dL, TG > 602 mg/ dL, TG > 500 mg/dL, etc.) due to the large time span of the included studies; second, the selection of observation indicators was diverse (treatment measures, different etiologies, potential markers, etc.); and finally, the outcome evaluation systems were not uniform (such as severity, recurrence risk, prognosis differences, etc.), which failed to meet the requirement of homogeneity of data for meta-analysis. Therefore, this study only conducted a systematic review, aiming to systematically summarize the changing trends of the proportion of HTG-AP patients in the AP population in different regions and time periods, as well as the risk factors for severe and recurrent HTG-AP.

Data extraction, collection, and synthesis

Upon thorough examination of the literature, research data were extracted using a predetermined table.

Research data included study basic information (author, publication year, country, study design, duration, etc.), Patient characteristics (age, gender, baseline TG level, underlying disease, AP severity, etc.), intervention measures (lipid-lowering therapy, plasma exchange, insulin injection, etc.), outcome indicators (mortality, recurrence rate, severe disease rate, complications, etc.). along with identified risk factors influencing HTG-AP severity or recurrence. The data extraction work was completed by two researchers (LJD and MWT), and the data extraction was completed in October 2023.

Results

Study characteristics

Seventy-seven studies meeting the inclusion criteria were included in this analysis, comprising 1 RCT study, 21 prospective studies, and 55 retrospective studies. The literature screening process is illustrated in Fig. 1, while the results of bias risk assessment are depicted in Supplementary Fig. 1. A total of 56,617 AP patients were included in the analysis, of which 19.99% were diagnosed with HTG-AP (n = 11,315). Compared to non-HTG-AP patients, those with HTG-AP tended to be male (68.7% vs. 57.3%) and younger (41.47 ± 4.32 vs. 50.25 ± 7.70 years



Fig. 1 PRISMA flow diagram

old). Additionally, compared to non-HTG-AP patients, HTG-AP patients exhibited higher mortality rates (0%-20% vs. 0.7%-15.2%), greater severity (8.3%-100% vs. 3.8%-47.2%), and higher recurrence rates (0%-64.8% vs. 6.4%-23.3%) (Supplementary Table 1 and Table 2.

Trend of HTG-AP proportion

Our analysis evaluated the temporal and regional trends in the proportion of HTG-AP patients among AP cases. From 2002 to 2023, the proportion of HTG-AP patients ranged from 1.6% to 47.6% (P = 0.1081), Specifically, from 2002 to 2010, HTG-AP accounted for 6.3% to 32.6% of AP cases (P = 0.3297), while from 2011 to 2019 and from 2020 to 2023, it constituted 2.3% to 47.6% (P = 0.2131) and 1.6% to 40.8% (P = 0.1723), respectively (Fig. 2). Although the proportion of HTG-AP showed an upward trend, there was no statistical difference. This might be related to the relatively high proportion of HTG-AP patients in some small-sample studies (n = 43, n = 36, n =21), which were 32.6%, 38.9%, and 47.6%, respectively. [18–20]. though statistically nonsignificant. Regionally, the proportion of HTG-AP varied, with North America (2.6%-17.0%, P= 0.5787), Europe (1.6%-32.6%,





Fig. 2 Time trend of the proportion of HTG-AP patients

P= 0.0881), and other regions (4.0%-12.6%, P= 0.738). Notably, the proportion in China exhibited a significant increase (6.3%-47.6%, P= 0.0119) (Fig. 3).

Risk factors associated with HTG-AP severity

Thirteen studies analyzed risk factors influencing the severity of HTG-AP. Elevated serum TG levels in AP patients were consistently associated with increased risk of complications, such as pancreatic necrosis, systemic inflammatory response syndrome (SIRS), shock, and multi-organ failure. Additionally, factors including high neutrophil-to-lymphocyte ratio (NLR), admission amylase levels exceeding three times the upper limit of normal, SIRS, low apoA-I levels (< 1.1 g/L), CRP levels > 90 mg/L, hypocalcemia, and hypoalbuminemia were identified as potential predictors of HTG-AP severity (Table 1). TG level on the severity of HTGAP in supplementary Fig. 2.

Risk factors for HTG-AP recurrence

Five studies reported on risk factors influencing HTG-AP recurrence, including smoking history, poor lipid control (TG > 3.1 mmol/L) or recurrent hypertriglyceridemia



Trends in the incidence of HTGAP (2020-2023)





: :

Year

R²=0.28, *P*=0.0881

2010

2015

2020

2025

Trends in the incidence of HTGAP - North America



2016

Trends in the incidence of HTGAP - Other country

Year

2018

2020

2024

2022



Fig. 3 Regional trends in the proportion of HTG-AP patients

2005

10

0+

2000

Table 1	Risk	factors	for Seve	re HTG-AP

Reference	Year	Risk factors for Severe HTG-A	P		
Chen et al. [21]	2006	Male	TG 🗲 170mg/dL		
Nakhoda et al. [22]	2017	Alcohol abuse	Family history of familial HTG	HbA1c>8%	
Wang et al. [23]	2017	NLR [P=0.019, 6.71(1.36,33.07)]			
Pascual et al. [24]	2019	TG ≻ 100 mg/dl			
Kim et al. [25]	2020	On admission SIRS On admission amylase levels <3 times [2.311(1.013-5.274), P=0.046] (4.141(1.806-9.498), P=0.001)		046]	
Chen et al. [26]	2021	Albumin< 35 g/L [3.362 (1.492–8.823), <i>P</i> =0.004]	apoA-I< 1.1 g/L [5.126(2.348– 11.195), <i>P</i> <0.001]	CRP> 90mg/L [3.061(1.407- 6.659), <i>P</i> =0.005]	Hyperlipase [2.283(1.070-4.873), <i>P=</i> 0.033]
Pothoulakis et al. [27]	2021	HTG: 150–199 mg/dL [2.3(1.3- 4.0), <i>P</i> =0.004]	HTG:200–999 mg/dl [3.0 (1.9- 5.0), P<0.001]	HTG≥1.000 mg/dl [9.6(1.8- 52.6), <i>P</i> =0.009]	
Yang et al. [12]	2021	Abdominal obesity [(3.205(1.570–6.544), <i>P</i> < 0.05]	HTG < 5.65 mmol/L [2.746 (1.125–6.701), <i>P</i> < 0.05]	HTG≥ 5.65mmol/L [3.649(1.403–9.493), <i>P</i> < 0.05]	
Dancu et al. [28]	2022	HT 48h: 38 (27–46) [0.85 (0.66–0.96), <i>P</i> = 0.002]			
Dong et al. [29]	2022	24h serum TG >500mg/dl (r=0.407, <i>P</i> <0.001)	48h serum TG >500mg/dl (<i>r</i> =0.209, <i>P</i> =0.007)	3-4 days serum TG>500mg/dL (r=0.200, P=0.010)	
Lin et al. [30]	2022	High CRP [1.011(1.003-1.019), P = 0.005]	Low calcium [0.016(0.001- 0.239), <i>P</i> = 0.003]	Hypoalbumin [0.821(0.693- 0.973), <i>P</i> = 0.023]	
Song et al. [31]	2022	Male [1.699(1.541–1.902), P=0.006]	HTG [2.534 (2.021–3.176), <i>P</i> <0.001]	DM [1.838(1.385–2.439), P<0.001]	
Song et al. [32]	2023	HTG [3.911 (1.772–8.630), P= 0.0	001]		

TG Triglycerides, HTG Hypertriglyceridemia, NLR Neutrophil-to-lymphocyte ratio, SIRS Systemic inflammatory response syndrome, CRP C-reactive protein, HT Haematocrit, DM Diabetes mellitus

during follow-up, previous history of diabetes, Chalson score ≥ 2 , non-high-density lipoprotein levels >4.90 mmol/L, apoA1 levels ≥ 0.76 g/L, and blood glucose levels \geq 7.0 mmol/L (Table 2). TG level on the recurrence of HTGAP in supplementary Fig. 3.

Discussion

Our study examined the changing trends in the proportion of HTG-AP patients among AP cases, considering both temporal and regional factors. We found that although the proportion of HTG-AP patients in AP cases did not exhibit a statistically significant increase (P > 0.05), HTG-AP patients tended to be younger, predominantly male, and experienced more severe symptoms compared to other types of AP, thereby posing an increased burden on healthcare systems [8, 38]. According to the guidelines of the American College of Gastroenterology (ACG) (2024), serum triglycerides can represent a cause for AP, only when their levels are higher than 1000 mg/dL (> 11.3 mmol/L) [16]. However, the Chinese Guidelines for Acute pancreatitis (2021) indicate that a lower threshold (TG \geq 5.65 mmol/L or 500 mg/dL) can be used as diagnostic criteria for AP patients with chylomicronemia [39]. The reasons may be as follows: 1) the incidence of HTG-AP in China is significantly higher than that in the West, which may be related to genetics (such as lipoprotein lipase gene mutations) and dietary structure, leading to a preference for a lower threshold in the guidelines. 2) some medical centers may lack the ability to rapidly detect TG and need to rely on clinical manifestations for a comprehensive judgment. 3) some studies have shown that TG \geq 5.65 mmol/L can trigger AP, especially when there is chylomicronemia or secondary factors (such as diabetes, pregnancy) [29, 30, 35]. 4) the mechanism by which HTG leads to AP, (such as free fatty acid toxicity, pancreatic microcirculation disorders) may have threshold differences among different individuals [40, 41].

While 71.4% of the studies reported an increasing trend in the proportion of HTG-AP among AP cases over time, this trend lacked statistical significance (P >0.05). Several factors may contribute to this observation. Firstly, the diagnostic criteria for AP and HTG-AP have evolved over time, and discrepancies exist among researchers regarding the definition of HTG-AP, with varying thresholds for serum TG levels [11, 34, 42, 43]. Additionally, the majority of included studies were retrospective, introducing potential lag time between publication and data inclusion, which could affect the accuracy of trend analysis. Moreover, the prevalence of HTG-AP is influenced by various factors such as gender, alcohol consumption, family history of hyperlipoproteinemia, and metabolic diseases like obesity and diabetes, which may differ across regions and contribute to the observed variation in HTG-AP proportions, particularly in China [15, 37, 44, 45].

Existing literature, including meta-analyses by Jordan et al., have indicated a global increase in AP incidence, primarily driven by gallstone-associated and alcoholinduced AP cases in North America and Europe [5]. However, the incidence of HTG-AP and AP in Asia has remained relatively stable. Notably, the rising incidence of dyslipidemia in China, particularly HTG, may explain the observed increase in HTG-AP cases in this region compared to Western countries [46, 47]. Factors such as improved living standards, dietary changes (e.g., highfat, high-protein diets), climate variations, holiday influences, sedentary lifestyles, and demographic transitions may further contribute to the rising prevalence of HTG-AP in China [29, 48–50].

Studies have demonstrated a positive correlation between serum TG levels and AP incidence, with higher TG levels associated with increased severity, mortality, and prolonged hospital stays [48, 51]. Elevated TG levels lead to the release of free fatty acids (FFAs), triggering an inflammatory response and systemic complications such as systemic inflammatory response syndrome (SIRS) [52]. Therefore, early lipid-lowering interventions, alongside standard supportive care, are essential for managing HTG-AP. Although the efficacy of various lipid-lowering

Table 2 histractors for recurrence of higher					
Author	Year	Risk factors for recurrence of HTG-AP			
Xiang et al. [33]	2017	Smoke [5.1(1.7-15.2), <i>P</i> = 0.003]			
Liao et al. [<mark>34</mark>]	2021	HTG (5.411±1.91, P=0.017)	Previous DM (5.127±1.91, <i>P</i> =0.019)		
Ding et al. [35]	2023	TG≥5.65 mmol/L[2.00(1.05-3.80), <i>P</i> =0.034]	Blood glucose≥7.0 mmol/L[3.31(1.56-7	7.03), <i>P</i> =0.002]	
Guan et al. [36]	2023	TG > 3.1 mmol/L [10.3(2.5–34.1)]	Charson score ≥2 [9.0(1.1-96.9)]		
Tang et al. [37]	2023	Serum TG[2.421(1.152–5.076), <i>P</i> =0.020]	Non-high-density lipopro- tein[4.630(1.692–12.658), <i>P=</i> 0.003]	Apolipoprotein A1[1.735(1.093–2.754) <i>P</i> =0.019]	

 Table 2 Risk factors for recurrence of HTG-AP

HTG Hypertriglyceridemia, TG Triglycerides, DM Diabetes mellitus

treatments remains debated, some studies suggest potential benefits of interventions like plasma exchange therapy or early lipid-lowering drugs administration in improving outcomes for HTG-AP patients [45, 53].

HTG-AP can stem from both primary and secondary lipid metabolism abnormalities, with primary hyperlipoproteinemia types I, IV, and V being implicated [54]. Secondary HTG is associated with metabolic disorders, pregnancy, and obesity [42]. While the specific etiology of HTG may vary, studies have emphasized the importance of lipid control in preventing HTG-AP recurrence, underscoring the need for post-discharge health promotion measures including dietary modifications, regular lipid-lowering drug use, exercise, and routine monitoring.

This study found that the recurrence of HTG-AP may be the result of multiple factors (such as smoking, diabetes, poor lipid control, and recurrent hyperlipidemia, etc.). Multiple studies have confirmed that as the TG level of patients increases, the risk of AP recurrence also increases [7, 54, 55]. A meta-analysis showed that the risk of AP in diabetic patients is 1.74 (1.33-2.29) times that of non-diabetic patients [56], which may be due to diabetes causing structural changes in the pancreas and increasing the risk of AP [57]. Therefore, clinicians should attach importance to health education for HTG-AP patients (such as low-fat diet, increased aerobic exercise, smoking cessation, and blood sugar control, etc.), regularly (every 3-6 months) test lipid levels, and take lipid-lowering drugs (such as fibrates, statins, niacin, and omega-3 fatty acids, etc.) regularly to reduce the recurrence risk of HTG-AP patients.

However, several limitations of our study should be noted. First, this study only one RCT included in the analysis, and the study design, population characteristics, and diagnostic criteria were different in most studies, therefore there is some possibility of unintentional bias. Second, Subgroup analysis was not conducted in this study, because the sample size of the study was small after grouping according to regional and time differences, and the reliability of the analysis results was poor. Additionally, most included studies focused on short-term clinical outcomes, with limited data available on longterm follow-up of HTG-AP patients.

Conclusions

Our findings indicate a stable global prevalence of HTG-AP within AP patients, but a notable increase in China, possibly attributed to socio-economic and dietary factors, regular oral lipid-lowering drug administration and regular monitoring of blood lipid levels can help reduce the severe illness rate and recurrence rate of HTGAP patients. Future research should prioritize large-scale prospective cohort studies to further elucidate the epidemiology and risk factors associated with HTG-AP, informing the development of targeted clinical strategies for its management and prevention of recurrence.

Abbreviations

HTG-AP	Hypertriglyceridemia-induced acute pancreatitis;
RCTs	Randomized controlled trials
AP	Acute pancreatitis
TG	Triglyceride
SIRS	Systemic inflammatory response syndrome
NLR	Neutrophil-to-lymphocyte ratio
CRP	C-reactive protein
HTG	Hypertriglyceridemia
ERCP	Endoscopic retrograde cholangiopancreatography
PRISMA	Preferred reporting items for systematic reviews and meta-Analyses
SAP	Severe acute pancreatitis
FFAs	Free fatty acids

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

As the co-first author, J.L. and Z.W. wrote the manuscript; W.M., K.P., L.Z. and K.X. produced figure artworks; G.W., Z.W., Y.P., Z.L., X.S., and G.L. critically reviewed and revised the manuscript. L.W and F. C conceived the study concept and revised the manuscript. All authors read and approved the final manuscript.

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Data availability

All data analyzed in this systematic review are derived from previously published studies. The search strategy and inclusion/exclusion criteria are described in detail in the Methods section. The full list of included studies is provided in (supplementary Table 1 Study characteristics).

Declarations

Ethics approval and consent to participate

All data used for the secondary analysis in our manuscript are from published, ethically reviewed studies that have ensured patient privacy protection and data anonymization. Therefore, ethical statements are not applicable in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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