Journal of Clinical Lipidology (2025) 000, 1–10

Journal of Clinical Lipidology

Original Research

# Health outcomes and survival among patients with severe hypertriglyceridemia after acute pancreatitis

**Michael S. Broder, MD, MSHS*; Eunice Chang, PhD; Kathleen F. Villa, MS; Nathan D. Wong, PhD, MPH**

*ADVI Health, Washington, DC, USA (Drs Broder and Chang); Ionis Pharmaceuticals, Carlsbad, CA, USA (Ms Villa); School of Medicine, University of California, Irvine, CA, USA (Dr Wong)*

**KEYWORDS**
Severe hypertriglyceridemia;
Acute pancreatitis;
Healthcare claims analysis;
Burden of disease;
Diabetes mellitus;
Primary hypertriglyceridemia

**BACKGROUND:** Severe hypertriglyceridemia (sHTG) can lead to complications, the most serious being acute pancreatitis (AP). Risk of sHTG-induced AP increases with higher triglyceride (TG) levels, resulting in worse clinical outcomes compared to AP due to other etiologies.

**OBJECTIVE:** Characterize health outcomes of patients with combined sHTG and AP (sHTG-AP) compared to patients with sHTG without AP.

**METHODS:** Our retrospective cohort study estimated clinical outcomes and mortality of patients with sHTG-AP (triglycerides 500-15,000 mg/dL) compared to propensity score-matched patients with sHTG alone, using a nationally representative de-identified claims database with 2012-2022 enrollees.

**RESULTS:** A total of 1232 patients with sHTG-AP and 96,207 patients with sHTG without AP were identified. After 1:1 propensity score matching (PSM), 1197 patients from each group were included. Mean (SD) follow-up was 2.9 (2.1) years for sHTG-AP and 3.0 (2.2) years for sHTG without AP ($P = .310$). Risks of emergency department (ED) visits (hazard ratio [HR] 1.6; 95% CI, 1.6 1.4-1.7; $P < .001$), hospitalizations (HR 1.7; 95% CI, 1.5-2.0; $P < .001$), and death (HR 1.8; 95% CI, 1.4-2.4; $P < .001$) were statistically significantly higher in patients with sHTG-AP; patients with index triglycerides ≥880 mg/dL were also at greater risk. PSM identified 330 patients without baseline type 2 diabetes (T2DM) in each group; probability of developing T2DM was nearly double in patients with sHTG-AP than sHTG without AP.

**CONCLUSION:** ED visits, hospitalizations, and mortality were more common in patients with sHTG-AP than sHTG without AP, warranting better prevention of initial episodes. Prospective studies are also needed to establish causal links between AP and clinical outcomes.



## Introduction

Approximately 1.5% of adults in the United States (US) have triglyceride (TG) levels ≥500 mg/dL, which is defined as severe hypertriglyceridemia (sHTG).[1,2] Patients with sHTG are at increased risk for complications, the most

* Corresponding author at: ADVI Health, 1000 F Street NW, Suite 650, Washington, DC 20004, USA.
E-mail address: mbroder@ucla.edu (M.S. Broder).
Submitted February 25, 2025. Accepted for publication August 23, 2025.


https://doi.org/10.1016/j.jacl.2025.08.017

Please cite this article as: Broder et al., Health outcomes and survival among patients with severe hypertriglyceridemia after acute pancreatitis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.08.017

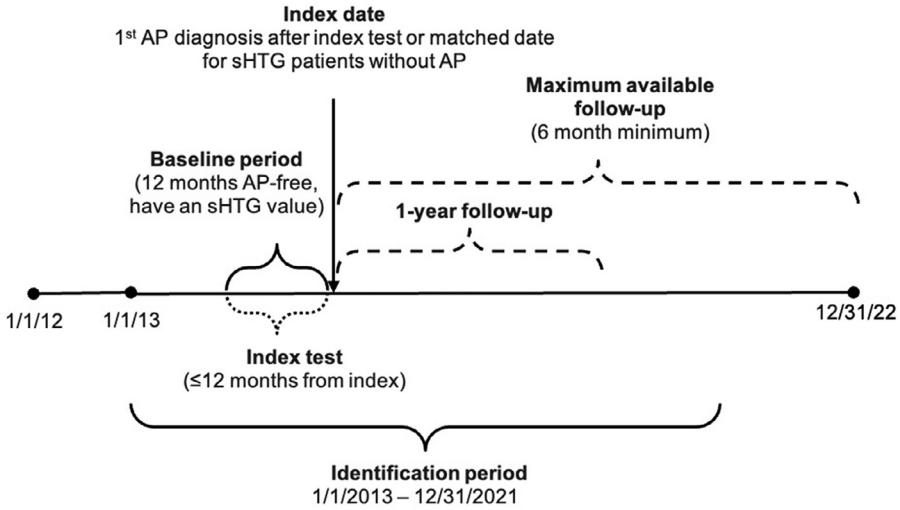


**Figure 1. Patient identification**. Abbreviations: AP, acute pancreatitis; sHTG, severe hypertriglyceridemia.

serious of which is acute pancreatitis (AP).[3-6] The risk of sHTG-induced AP increases with rising TG levels[4] and can result in worse clinical outcomes than pancreatitis due to other etiologies.[3,5,7] It is also associated with significant morbidity, mortality, and healthcare utilization costs.[8-12] Primary hypertriglyceridemia is due to mono- or polygenic defects and is suspected if secondary causes have been ruled out.[13,14] Secondary hypertriglyceridemia can result from a variety of secondary causes, including pregnancy, metabolic syndrome, obesity, and lifestyle factors; addressing lifestyle factors can typically improve TG values.[13,14]

While data on healthcare utilization among patients with sHTG and AP (sHTG-AP) are limited, there is some evidence that patients with sHTG-AP have higher healthcare costs compared to those with sHTG alone.[9,11] The burden of sHTG-AP and its relationship to patient mortality is not well established.[4] We aimed to determine whether patients with severe primary hypertriglyceridemia and history of AP subsequently had differing health outcomes, recurrent AP episodes, death, other acute events, or chronic conditions compared to patients with sHTG who do not have a history of AP.

## Methods

To assess health outcomes in patients with sHTG-AP and patients with sHTG without AP, we conducted a retrospective cohort study using data and laboratory values from a nationally representative, de-identified claims database, which included over 81 million enrollees from January 1, 2012, to December 31, 2022. This database is Health Insurance Portability and Accountability Act-compliant, contains de-identified adjudicated medical claims, and was exempt from institutional review board review. The data include plan enrollment information, medical and pharmacy claims, and laboratory results from multiple payers.

### *Patient identification*

The study included 2 primary hypertriglyceridemia patient cohorts: sHTG with AP and sHTG without AP. We included patients who were continuously enrolled for 12 months pre-index (baseline) and a minimum of 6 months post-index (Fig. 1). The index date was defined as the first AP diagnosis for patients with AP and the date of a randomly selected sHTG value for patients without AP, as further described below. Outcomes were reported across 2 time periods: 1) 12 months post index and 2) maximum patient follow up. Maximum follow-up ended at either the study end date, patient death, or end of a patient's enrollment period, whichever event occurred first.

In both patient cohorts, we identified adult patients (≥18 years) with at least 1 sHTG laboratory value (TG value 500-15,000 mg/dL) between January 1, 2013, and December 31, 2021. We excluded patients with evidence of conditions associated with non-sHTG related pancreatitis, including alcohol-induced diagnoses (ie, alcohol related disorders, alcohol-induced chronic pancreatitis, alcohol-induced AP), drug-induced AP, other chronic pancreatitis, biliary obstruction, gallstones (ie, gallstone ileus, cholelithiasis), hypercalcemia, and acute coronary syndrome, stroke, or transient ischemic attack within 3 months prior to their index date. Corresponding ICD-9-CM and ICD-10-CM codes can be found in the Supplementary Materials.

Patients with a diagnosis of AP (ICD-9-CM: 577.0; ICD-10-CM: K85.xx except for K85.2 and K85.3) during the identification (ID) period (January 1, 2013-December 31, 2021) were classified as sHTG-AP. The first AP diagnosis date during the identification period was defined as the index date. Patients who had a diagnosis of AP prior to the identification period were excluded to ensure that the index AP episode was the first such event. The baseline sHTG value (ie, TG value ≥500 mg/dL) closest in time to the index date was defined as the index test.

Please cite this article as: Broder et al., Health outcomes and survival among patients with severe hypertriglyceridemia after acute pancreatitis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.08.017

For patients without a diagnosis of AP, 1 qualifying sHTG test was randomly selected as the index test. A qualifying sHTG test was defined as one for which there was no evidence of AP in the 12 months before or after the test. An index date was assigned to patients with sHTG without AP, based on the distribution of days between the index test date and the index date (ie, the first AP episode during the ID period) for patients with sHTG-AP, such that the mean length of time between the sHTG test and index date was similar for both groups.

Propensity score matching (PSM) was conducted to match patients with sHTG without AP to those with sHTG-AP in a 1:1 ratio. The propensity for sHTG-AP was estimated using logistic regression containing the following baseline variables as independent variables: age, sex (female/male), region, race/ethnicity, insurance type, index year, Charlson Comorbidity Index, atherosclerotic cardiovascular disease, chronic liver disease, chronic kidney disease, diabetes mellitus (DM), type 2 diabetes mellitus (T2DM), disorders of lipoprotein metabolism and other lipidemias, heart failure, hypertension, obesity, usual care physician, statin use, non-statin lipid-lowering medications use, glucagon-like peptide-1 (GLP-1) use, index TG value, and total cholesterol. In addition, patients were matched exactly on index TG value categories (500-879, 880-999, 1000-1999, 2000-15,000 mg/dL), baseline DM status, and index year. The greedy nearest neighbor method with a caliper width of 0.2 of the SD of the logit of the propensity score was used to identify matched patients with sHTG without AP.

### *Measures and statistical analysis*

Baseline variables, including demographics, comorbidities, physician characteristics, laboratory results, and treatment use, were measured over the 12-month baseline. Emergency department (ED) visits, hospitalizations, and deaths were assessed over a 1-year post-index period. These outcomes, as well as comorbidities (ie, Charlson comorbidity index, Healthcare Cost and Utilization project [HCUP] chronic conditions), healthcare utilization, lipid-lowering treatment, incidence of recurrent AP, ED visits, hospitalizations, overall survival, and laboratory results (ie, number of TG tests, TG levels), were also measured over the maximum available follow up.

Descriptive statistics were conducted to examine patient characteristics and healthcare utilization. Means and SD were used to summarize continuous variables. Frequencies and percentages were used to summarize categorical variables. All time to events (eg, mortality and comorbidity incidence) were examined using Kaplan-Meier estimation and plotting. Analyses were stratified to compare sHTG-AP and sHTG without AP cohorts using Chi-square tests for categorical variables, *t*-tests for continuous variables, and log rank tests for survival outcomes.

Two sensitivity and subgroup analyses were conducted. First, we stratified both sHTG-AP and sHTG without AP cohorts into groups of either TG $\geq$ 880 mg/dL or TG $<$ 880 mg/dL. Second, we excluded patients who had T2DM during the baseline period in order to assess incidence of T2DM during the maximum available follow-up the index date. A new diabetes diagnosis was defined as patients who had either $\geq$1 T2DM claim or $\geq$2 T2DM claims at least 30 days apart. All data transformations and statistical analyses were performed using SAS® version 9.4.

## Results

Prior to PSM, 1232 patients with sHTG-AP and 96,207 patients with sHTG without AP were identified (Table 1). After matching, 1197 patients with sHTG-AP were 1:1 propensity score matched to 1197 patients with sHTG without AP. Across both sHTG-AP and sHTG without AP cohorts, the mean (SD) age was 54.5 (13.4 sHTG-AP, 13.3 sHTG without AP) years, 34.2% were female, and 59% (59.4 sHTG-AP, 58.6% sHTG without AP) were White. The mean (SD) follow-up period was 2.9 (2.1) years for patients with sHTG-AP and 3.0 (2.2) years for patients with sHTG without AP ($P = .310$).

### *Baseline*

At baseline, the mean (median, SD) TG levels for patients with sHTG-AP and sHTG without AP were 1143 (739.0, 1074.7) mg/dL and 1115 (692.0, 1117.6) mg/dL, respectively ($P = .533$) (Table 1). Other risk factors for elevated TG levels were also comparable between the cohorts: total cholesterol (268.6 vs 269.7 mg/dL, $P = .956$), high-density lipoprotein cholesterol (32.5 vs 33.7 mg/dL, $P = .009$), and direct low-density lipoprotein cholesterol (88.0 vs 95.1 mg/dL, $P = .213$). The majority of patients in both cohorts were receiving lipid-lowering therapy, with 78.1% ($n = 935$) of sHTG-AP patients and 78.9% ($n = 945$) of sHTG without AP patients on lipid-lowering treatment, including statins, cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin type 9 inhibitors, small interfering agents, adenosine triphosphate citrate lyase inhibitor, fibrates, bile acid sequestrants, nicotinic acid, omega-3 fatty acids, and angiopoietin-like protein 3 inhibitors. Fibrates were used by nearly half of patients in both groups, 45.2% ($n = 541$) in the sHTG-AP cohort vs 44.5% ($n = 533$) in the sHTG without AP cohort. Additionally, 17.5% ($n = 210$) of patients with sHTG-AP and 16.7% ($n = 200$) of patients with sHTG without AP were on either GLP-1 agonists or sodium-glucose cotransporter 2 inhibitors.

### *Follow-up*

During the year following their initial AP episode, 51.4% ($n = 615$) of patients with sHTG-AP and 35.7% ($n = 427$) of patients with sHTG without AP had either an ED visit, hospitalization, or death ($P < .001$) (Table 2). Patients with sHTG-AP also had a greater risk of death (4.5%, $n = 54$ vs 1.6%, $n = 19$), ED visits (47.4%, $n = 567$ vs 33.2%, $n = 398$), and

Please cite this article as: Broder et al., Health outcomes and survival among patients with severe hypertriglyceridemia after acute pancreatitis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.08.017

**Table 1. Patient characteristics at baseline after matching.**

| | Matched | | | Matched (no baseline T2DM) | | |
|---|---|---|---|---|---|---|
| | sHTG-AP | sHTG without AP | *P*-value | sHTG-AP | sHTG without AP | *P*-value |
| N | 1197 | 1197 | - | 330 | 330 | - |
| Age, mean (SD) years | 54.5 (13.4) | 54.5 (13.3) | .979 | 51.1 (13.0) | 50.1 (12.6) | .294 |
| Female, n (%) | 409 (34.2) | 409 (34.2) | 1.000 | 98 (29.7) | 98 (29.7) | 1.000 |
| Race, n (%) | | | .586 | | | .669 |
| Asian | 46 (3.8) | 34 (2.8) | - | 14 (4.2) | 13 (3.9) | - |
| Black | 121 (10.1) | 131 (10.9) | - | 29 (8.8) | 25 (7.6) | - |
| Hispanic | 263 (22.0) | 267 (22.3) | - | 62 (18.8) | 77 (23.3) | - |
| White | 711 (59.4) | 701 (58.6) | - | 208 (63.0) | 201 (60.9) | - |
| Unknown | 56 (4.7) | 64 (5.3) | - | 17 (5.2) | 14 (4.2) | - |
| Years of follow-up, mean (SD) | 2.9 (2.1) | 3.0 (2.2) | .310 | 3.0 (2.2) | 2.9 (2.1) | .876 |
| CCI, mean (SD) | 2.7 (2.8) | 2.7 (2.7) | .640 | 0.9 (1.9) | 0.9 (1.7) | .748 |
| Comorbidities, n (%) | | | | | | |
| Atherosclerotic cardiovascular disease | 291 (24.3) | 307 (25.6) | .450 | 48 (14.5) | 46 (13.9) | .824 |
| Chronic liver disease | 194 (16.2) | 199 (16.6) | .783 | 47 (14.2) | 42 (12.7) | .569 |
| Chronic kidney disease | 239 (20.0) | 240 (20.1) | .959 | 20 (6.1) | 25 (7.6) | .440 |
| T2DM | 772 (64.5) | 771 (64.4) | .966 | - | - | - |
| Disorders of lipoprotein metabolism and other lipidemias[a] | 1069 (89.3) | 1070 (89.4) | .947 | 259 (78.5) | 268 (81.2) | .382 |
| Heart failure | 92 (7.7) | 96 (8.0) | .761 | 7 (2.1) | 6 (1.8) | .779 |
| Hypertension | 899 (75.1) | 914 (76.4) | .475 | 188 (57.0) | 185 (56.1) | .814 |
| Obesity | 449 (37.5) | 457 (38.2) | .736 | 93 (28.2) | 83 (25.2) | .379 |
| Pancreatic necrosis | 4 (0.3) | 1 (0.1) | .374 | 0 (0) | 0 (0.0) | - |
| Persistent organ failure | 133 (11.1) | 124 (10.4) | .552 | 16 (4.8) | 8 (2.4) | .096 |
| Index TG value (mg/dL), mean (SD), [median] | 1143.1 (1074.7) [739.0] | 1115.2 (1117.6) [692.0] | .533 | 1053.1 (934.4) [703.5] | 994.4 (838.2) [642.5] | .396 |
| Total cholesterol value (mg/dL), mean (SD), [median] | 268.6 (433.3) [228.0] | 269.7 (545.4) [227.0] | .956 | 264.4 (121.9) [233.0] | 255.8 (105.4) [240.0] | .331 |
| HDL-C (mg/dL), mean (SD), [median] | 32.5 (12.1) [31.0] | 33.7 (10.7) [33.0] | .009 | 35.1 (14.8) [33.0] | 35.3 (11.6) [34.0] | .807 |
| LDL-C (mg/dL), mean (SD), [median] | 88.0 (50.8) [81.0] | 95.1 (43.5) [89.5] | .213 | 92.1 (54.0) [81.0] | 102.5 (35.3) [103.0] | .325 |
| Treatments, n (%) | | | | | | |
| Lipid-lowering treatment | 935 (78.1) | 945 (78.9) | .619 | 216 (65.5) | 212 (64.2) | .744 |
| Statins | 692 (57.8) | 697 (58.2) | .836 | 135 (40.9) | 130 (39.4) | .691 |
| Nonstatins | 629 (52.5) | 649 (54.2) | .413 | 137 (41.5) | 151 (45.8) | .272 |
| PCSK9 inhibitors | 6 (0.5) | 1 (0.1) | .124 | 2 (0.6) | 0 (0.0) | .499 |
| Fibric acid derivatives | 541 (45.2) | 533 (44.5) | .742 | 121 (36.7) | 123 (37.3) | .872 |
| GLP-1 agonists or SGLT-2 inhibitors | 210 (17.5) | 200 (16.7) | .587 | 1 (0.3) | 1 (0.3) | 1.000 |

Abbreviations: AP, acute pancreatitis; CCI, Charlson comorbidity index; GLP-1, glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT-2, sodium-glucose cotransporter 2; sHTG, severe hypertriglyceridemia; T2DM, type 2 diabetes mellitus; TG, triglycerides.
[a]Does not include hypertriglyceridemia.

hospitalizations (23.5%, $n = 281$ vs 13.6%, $n = 163$) than patients with sHTG without AP, all measures were statistically significant ($P < .001$).

Considering the maximum available follow-up period, mean follow-up time for patients with sHTG-AP and sHTG without AP was 2.9 and 3.0 years, respectively (Table 1). Over this time, patients with sHTG-AP were more likely to have an ED visit (90.6% vs 54.5%, $P < .001$), be hospitalized (72.0% vs 29.2%, $P < .001$), or die (11.4% vs 6.5%, $P < .001$) compared to patients with sHTG without AP (Table 3). The risk of death (hazard ratio [HR] 1.8; 95% CI, 1.4-2.4; $P < .001$), ED visits (HR 1.6; 95% CI, 1.4-1.7; $P < .001$), and hospitalization (HR 1.7; 95% CI, 1.5-2.0; $P < .001$) were all statistically significantly higher

Please cite this article as: Broder et al., Health outcomes and survival among patients with severe hypertriglyceridemia after acute pancreatitis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.08.017

**Table 2. Emergency visits, inpatient hospitalizations, and mortality during 1-year follow-up.**

| | Matched | | |
|---|---|---|---|
| | sHTG-AP | sHTG without AP | *P*-value |
| N | 1197 | 1197 | - |
| Any ED visit, hospitalization, or death, n (%) | 615 (51.4) | 427 (35.7) | <.001 |
| Any ED visit or hospitalization | 591 (49.4) | 422 (35.3) | <.001 |
| Any hospitalization | 281 (23.5) | 163 (13.6) | <.001 |
| Any ED visit | 567 (47.4) | 398 (33.2) | <.001 |
| Death, n (%) | 54 (4.5) | 19 (1.6) | <.001 |

Abbreviations: AP, acute pancreatitis; ED, emergency department; sHTG, severe hypertriglyceridemia.

**Table 3. Emergency department visits[a], inpatient hospitalizations,[a] and mortality during maximum available follow-up.**

| | Matched | | |
|---|---|---|---|
| | sHTG-AP | sHTG without AP | *P*-value |
| N | 1197 | 1197 | - |
| Any ED visit or hospitalization, n (%) | 1101 (92.0) | 680 (56.8) | <.001 |
| Any hospitalization | 862 (72.0) | 350 (29.2) | <.001 |
| Any ED visit | 1085 (90.6) | 652 (54.5) | <.001 |
| Any specialty visits, n (%) | 1032 (86.2) | 924 (77.2) | <.001 |
| Number of visits per year,[b] mean (SD) | | | |
| Hospitalizations | 1.6 (8.8) | 0.3 (0.9) | <.001 |
| ED | 2.6 (6.6) | 1.1 (2.8) | <.001 |
| Specialist | 5.6 (7.1) | 4.2 (5.7) | <.001 |
| Office visits (overall) | 13.5 (11.4) | 11.2 (10.2) | <.001 |
| Death, n (%) | 136 (11.4) | 78 (6.5) | <.001 |

Abbreviations: AP, acute pancreatitis; ED, emergency department; sHTG, severe hypertriglyceridemia.
[a]Include all claims during the follow-up without skipping the index AP episode. Patients had various lengths of follow-up.
[b]Total number divided by the years of follow-up.

**Table 4. Triglyceride values during follow-up.**

| | Matched | | |
|---|---|---|---|
| | sHTG-AP | sHTG without AP | *P*-value |
| Years of follow-up, mean (SD) | 2.9 (2.1) | 3.0 (2.2) | |
| TG test during follow-up, n (%) | 956 (79.9) | 951 (79.4) | .800 |
| TG value (mg/dL) over follow-up, mean (SD), [median] | 544.9 (524.7) [380.5] | 383.3 (354.6) [292.0] | <.001 |
| Last TG value (mg/dL), mean (SD), [median] | 499.7 (613.4) [310.0] | 363.4 (398.6) [266.0] | <.001 |
| Last TG value, n (%) | | | |
| <500 | 942 (78.7) | 1050 (87.7) | - |
| 500-879 | 147 (12.3) | 102 (8.5) | - |
| 880-999 | 16 (1.3) | 7 (0.6) | - |
| 1000-1999 | 55 (4.6) | 26 (2.2) | - |
| 2000+ | 37 (3.1) | 12 (1.0) | - |

Abbreviations: AP, acute pancreatitis; sHTG, severe hypertriglyceridemia; TG, triglycerides.

in patients with sHTG-AP than sHTG without AP. Death occurred in 11.4% ($n = 136$) of patients with sHTG-AP and 6.5% ($n = 78$) of patients with sHTG without AP ($P < .001$) (Table 3, Fig. 2). Mean TG levels were higher in patients with sHTG-AP than patients with sHTG without AP, 544.9 mg/dL (median 380.5, SD 524.7) and 383.3 mg/dL (median 292.0, SD 354.6) ($P < .001$), respectively (Table 4). Triglyceride values were further assessed across several different strata, <500, 500-879, 880-999, 1000-1999, and ≥2000 mg/dL. At every group ≥500 mg/dL, there were more patients with sHTG-AP, whereas at TG levels <500 mg/dL, there were more patients with sHTG without AP.

### *Sensitivity analyses*

The cohorts were stratified into 2 groups according to their baseline TG values, either <880 mg/dL or ≥880 mg/dL, and assessed over their maximum available follow-up. Among patients in the TG < 880 mg/dL group, the risk of death, ED visits, and hospitalizations were each individually sta-

Please cite this article as: Broder et al., Health outcomes and survival among patients with severe hypertriglyceridemia after acute pancreatitis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.08.017

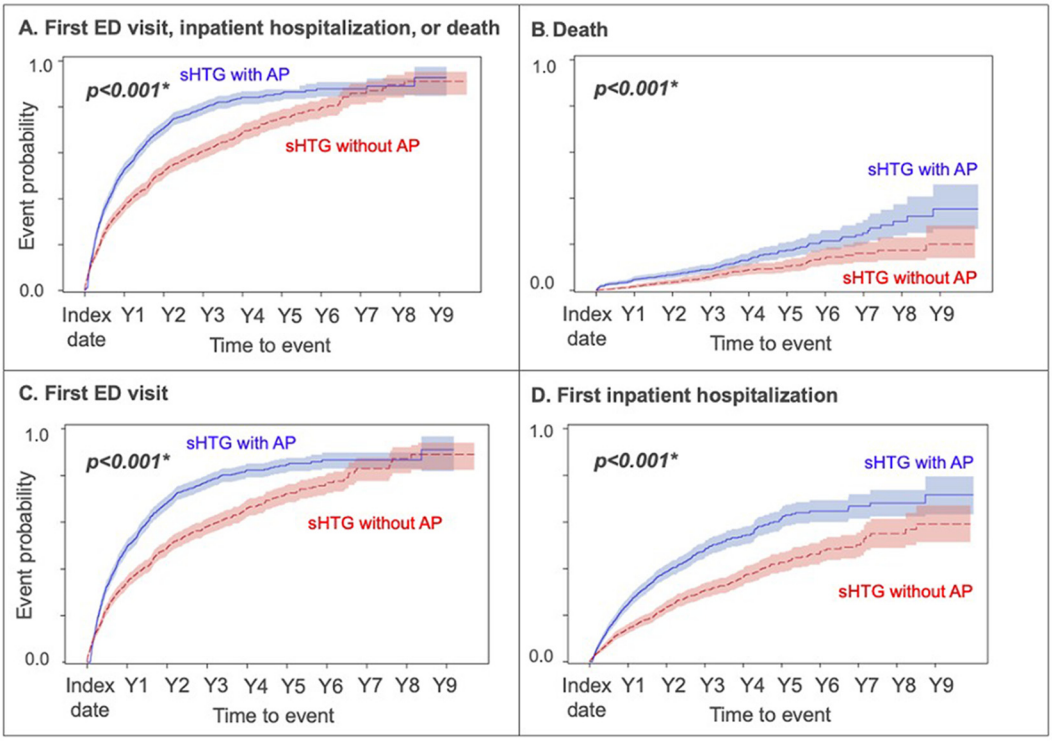


**Figure 2.** **Risk of emergency department visits, hospitalizations, and deaths**. (A) Hazard ratio (HR) 1.5; 95% CI, 1.4 to 1.7; $P < .001$; (B) HR 1.8; 95% CI, 1.4 to 2.4; $P < .001$; (C) HR 1.6; 95% CI, 1.4 to 1.7; $P < .001$; (D) HR 1.7; 95% CI, 1.5 to 2.0; $P < .001$. *By log-rank test. Abbreviations: AP, acute pancreatitis; ED, emergency department; sHTG, severe hypertriglyceridemia; Y, year.

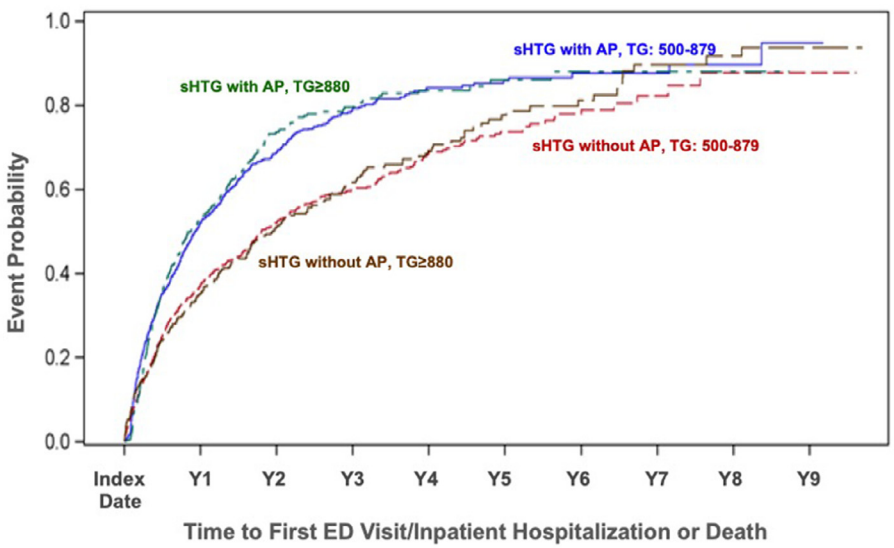


**Figure 3.** **Risk of emergency department visit, hospitalization, or death by triglyceride value**. Log-rank test: sHTG with AP vs sHTG without AP among patients with TG ≥880 mg/dL: $P < .001$; sHTG with AP vs sHTG without AP among patients with TG < 880 mg/dL: $P < .001$; TG ≥ 880 vs TG < 880 mg/dL among sHTG patients with AP: $P = .735$; TG ≥ 880 mg/dL vs TG < 880 mg/dL among sHTG patients without AP: $P = .832$. Abbreviations: AP, acute pancreatitis; ED, emergency department; sHTG, severe hypertriglyceridemia; TG, triglyceride; Y, year.

tistically significantly higher in patients with sHTG-AP (log rank $P < .001$ for all comparisons). Among patients in the TG ≥ 880 mg/dL subgroup, the risks of hospitalization and ED visits were both statistically significantly higher in patients with sHTG-AP than in those with sHTG without AP ($P < .001$) (Fig. 3). Mortality risk was not statistically significantly different between the sHTG-AP and sHTG without AP group with TG ≥ 880 mg/dL ($P = .126$) (Fig. 4).

We conducted a second sensitivity analysis in 330 propensity score matched pairs of patients who did not have T2DM at baseline. Over the maximum available follow-up, there were 37.3% ($n = 123$) patients with sHTG-AP and 16.4%

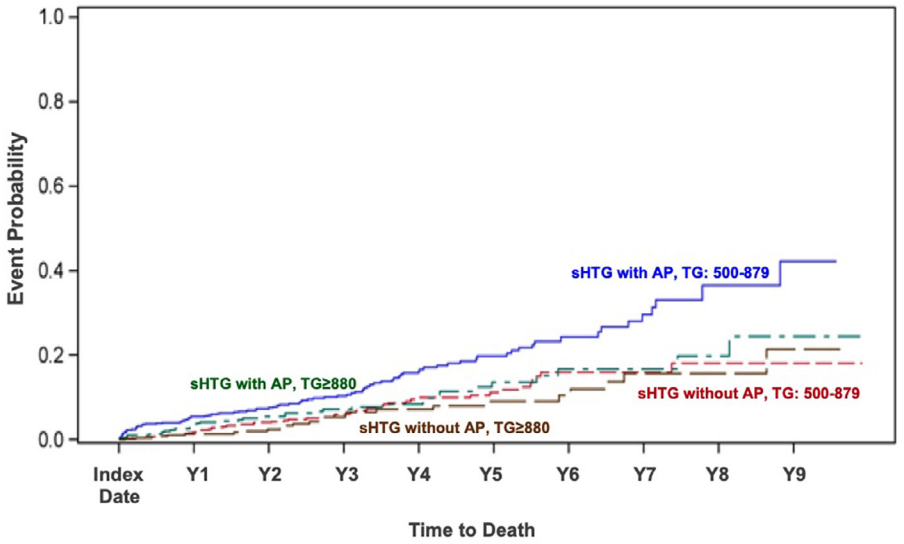


**Figure 4. Risk of death during follow-up**. Log-rank test: sHTG with AP vs sHTG without AP among patients with TG ≥ 880: $P = .126$; sHTG with AP vs sHTG without AP among patients with TG < 880: $P < .001$; TG ≥ 880 vs TG < 880 among sHTG patients with AP: $P = .008$; TG ≥ 880 vs TG < 880 among sHTG patients without AP: $P = .370$. Abbreviations: AP, acute pancreatitis; ED, emergency department; sHTG, severe hypertriglyceridemia; TG, triglyceride; Y, year.

**Table 5. Incidence of type 2 diabetes mellitus during maximum available follow-up.**

| | Matched | | |
|---|---|---|---|
| | sHTG-AP | sHTG without AP | *P*-value |
| N | 330 | 330 | - |
| Years of follow-up, mean (SD) | 3.0 (2.2) | 2.9 (2.1) | .867 |
| Incidence of T2DM, n (%) (≥1 claim with T2DM diagnosis) | 123 (37.3) | 54 (16.4) | <.001 |
| Incidence of T2DM, n (%) (≥2 claims with T2DM diagnosis ≥30 d apart) | 92 (27.9) | 37 (11.2) | <.001 |

Abbreviations: AP, acute pancreatitis; T2DM, type 2 diabetes mellitus; sHTG, severe hypertriglyceridemia.

($n = 54$) patients with sHTG without AP ($P < .001$) who developed T2DM (Table 5). The probability of patients with sHTG-AP developing T2DM was approximately double that of patients who had sHTG without AP (Fig. 5).

## Discussion

Acute pancreatitis is one of the most serious complications of sHTG.[9,10] Both the risk and severity of AP increases progressively with higher levels of hypertriglyceridemia.[15] Patients with sHTG who experience an episode of AP are at a statistically significantly greater risk of ED visits, hospitalization, and death compared to patients with sHTG without AP. Nearly twice as many patients with AP had an ED visit (90.6% vs 54.5%), more than twice as many were hospitalized (72.0% vs 29.2%), and nearly twice as many died (11.4% vs 6.5%) compared to controls with sHTG without AP. The higher risk of ED visits, hospitalizations, and death was more pronounced in patients with sHTG-AP than in the subset of patients with sHTG without AP.

Although the mechanism for development of diabetes after an AP episode is not entirely clear, it is most likely due to pancreatic beta cell damage disrupting insulin secretion.[16] At least 1 study has found that the severity of AP does not seem to affect the risk of diabetes.[17] Several studies have reported on the higher prevalence of diabetes after AP compared to the general population.[17-20] Our study determined that over a third of patients with sHTG-AP developed diabetes over a mean of 3 years follow-up compared to 16% of patients with sHTG without AP. These findings on incident diabetes are similar to those found in Christian et al., who reported that out of 3.4 million Americans with sHTG levels between 200 to 5000 mg/dL, 14% had diabetes mellitus.[21]

Overall, the patient population included in our study had similar age, race, and gender characteristics to those reported in other studies on the prevalence of sHTG.[21]

Other studies using commercial insurance claims have found increased AP episodes in patients with elevated TG levels. Sanchez et al. found that the risk of AP increases with the severity of elevated TG levels, with patients who had a recent history of AP being at an even higher risk of having AP recurrence.[22] Toth et al. found that healthcare costs were approximately 3 times higher in patients with sHTG-AP compared to those with sHTG without AP. Toth et al. also sug-

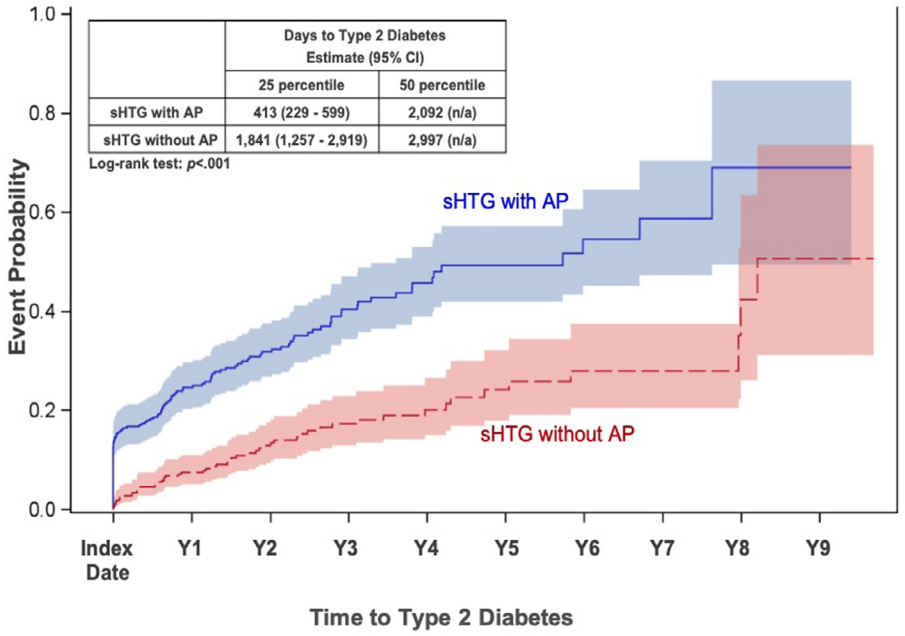


**Figure 5. Risk of type 2 diabetes mellitus in matched severe hypertriglyceridemia cohorts with no baseline type 2 diabetes mellitus**. Abbreviations: AP, acute pancreatitis; sHTG, severe hypertriglyceridemia; Y, year.

gested that healthcare utilization and costs increase with the severity of TG elevation.[9,23] Significantly greater total medical costs have also been reported in patients with chylomicronemia and elevated TG who had a history of AP compared to disease-free controls, $33,587 vs $4,402, $P < .01$, respectively.[12] Our study built on these prior studies and used propensity score-matched controls to reduce the risk of confounding. To our knowledge, ours is the first such study to examine diabetes incidence after an AP episode in patients with sHTG.

Given the high morbidity and mortality of AP and the difficulty of predicting who it will affect, prevention may be the most effective treatment approach. There have been limited standardized treatment guidelines for patients with sHTG-AP, and the few treatment recommendations there are, have not been examined in large, longitudinal studies.[4] However, recent phase III clinical trials of 2 RNA-targeting therapies, olezarsen and plozasiran, have found them to be effective at significantly lowering TG levels and decreasing the incidence of pancreatitis in patients with familial chylomicronemia syndrome and persistent chylomicronemia.[24,25] If the clinical trial results can be replicated in a broader group of patients with sHTG, these new treatments may be quite useful at preventing serious complications, including AP.

### *Limitations*

This study used healthcare claims which are designed for reimbursement purposes, not for research. The presence of a diagnosis code on a medical claim does not guarantee the presence of a disease, nor do all patients with a code necessarily have the condition coded. Specifically, the incidence of diabetes in the sHTG-AP group could have been increased by closer monitoring of patients after AP, although the between-group difference was maintained when a stricter definition of T2DM was used.[17] The claims data we used did not include details such as reasons for intensive care unit admissions or causes of death. Results may not be generalizable to uninsured individuals or to other types of patient populations who use other types of health insurance programs, such as Medicaid and Medicare in the US.

## Conclusion

This retrospective study suggests that preventing initial episodes of AP in patients with sHTG may reduce ED visits, hospitalizations, and mortality. However, establishing a causal link between AP and these outcomes will require prospective studies. Further research on the clinical and economic burden associated with sHTG-AP in larger populations, over longer periods of time, and with different insurance coverage, may help to identify additional benefits of AP prevention. Given the significant disease burden associated with sHTG-AP, continued research should be a public health priority.

## CRediT authorship contribution statement

**Michael S. Broder:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Eunice Chang:** Writing – review & editing, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Kathleen F. Villa:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Nathan D. Wong:** Writing –

review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

## Ethical approval

This study did not involve human subjects as defined by 45 CFR part 46 and therefore did not require institutional review board approval.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This study was sponsored by Ionis Pharmaceuticals.

## Declaration of competing interest

All authors completed ICMJE forms. All authors declare the following: support for the present manuscript (eg, funding, provision of study materials, medical writing, article processing charges): Ionis Pharmaceuticals.

MSB is an employee of PHAR (now a part of ADVI Health), which was paid by Ionis Pharmaceuticals to conduct the research described in this article. PHAR also discloses financial relationships with the following entities outside of the submitted work: AbbVie, Akcea, Amgen, AstraZeneca, BioMarin Pharmaceuticals, Bristol-Myers Squibb, Boston Scientific Corporation, Eisai, Ethicon, Genentech, Gilead, Novartis, Otsuka, Pfizer, Recordati, Regeneron, Sanofi US Services, Sunovion, and Takeda Pharmaceuticals USA.

EC is an employee of PHAR (now a part of ADVI Health), which was paid by Ionis Pharmaceuticals to conduct the research described in this article. PHAR also discloses financial relationships with the following entities outside of the submitted work: AbbVie, Akcea, Amgen, AstraZeneca, BioMarin Pharmaceuticals, Bristol-Myers Squibb, Boston Scientific Corporation, Eisai, Ethicon, Genentech, Gilead, Novartis, Otsuka, Pfizer, Recordati, Regeneron, Sanofi US Services, Sunovion, and Takeda Pharmaceuticals USA.

KFV is an employee and shareholder of Ionis Pharmaceuticals.

NDW reports the following: consulting fees from Ionis Pharmaceuticals. Research support through institution from Regeneron, Novartis, and Novo Nordisk. Consultant for Amgen, Novartis, and HeartLung.

## Acknowledgments

The authors would like to thank Cynthia Campos, MPH, of ADVI Health for providing medical writing support, which was funded by Ionis Pharmaceuticals.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2025.08.017.

## References

1. Ford ES, Li C, Zhao G, Pearson WS, Mokdad AH. Hypertriglyceridemia and its pharmacologic treatment among US adults. *Arch Intern Med*. 2009;169(6):572.
2. Nichols GA, Arondekar B, Garrison LP. Patient characteristics and medical care costs associated with hypertriglyceridemia. *Am J Cardiol*. 2011;107(2):225–229.
3. Garg R, Rustagi T. Management of hypertriglyceridemia induced acute pancreatitis. *Biomed Res Int*. 2018;2018:4721357.
4. Ata F, Yousaf Z, Khan AA. Management of hypertriglyceridemia-induced pancreatitis—a review of updates from the past decade. *Yemen J Med*. 2022;1(1):2–5.
5. Ewald N, Hardt PD, Kloer HU. Severe hypertriglyceridemia and pancreatitis: presentation and management. *Curr Opin Lipidol*. 2009;20(6):497–504.
6. Hassanloo J, Béland-Bonenfant S, Paquette M, Baass A, Bernard S. Prevalence, severity and management of hypertriglyceridemia-associated pancreatitis; A 7-year retrospective cohort study at Canadian quaternary care hospitals. *J Clin Lipidol*. 2022;16(4):455–462.
7. Blom DJ, O'Dea L, Digenio A, et al. Characterizing familial chylomicronemia syndrome: baseline data of the APPROACH study. *J Clin Lipidol*. 2018;12(5):1234–1243 e5.
8. Zafrir B, Saliba W, Jubran A, Hijazi R, Shapira C. Severe hypertriglyceridemia-related pancreatitis: characteristics and predictors of recurrence. *Pancreas*. 2019;48(2):182–186.
9. Toth PP, Grabner M, Ramey N, Higuchi K. Clinical and economic outcomes in a real-world population of patients with elevated triglyceride levels. *Atherosclerosis*. 2014;237(2):790–797.
10. Kichloo A, El-amir Z, Aucar M, et al. Clinical outcomes and predictors of thirty-day readmissions of hypertriglyceridemia-induced acute pancreatitis. *Gastroenterol Res*. 2022;15(1):19–25.
11. Rashid N, Sharma PP, Scott RD, Lin KJ, Toth PP. All-cause and acute pancreatitis health care costs in patients with severe hypertriglyceridemia. *Pancreas*. 2017;46(1):57–63.
12. Gaudet D, Signorovitch J, Swallow E, et al. Medical resource use and costs associated with chylomicronemia. *J Med Econ*. 2013;16(5):657–666.
13. Milne V.L. Practical pearls: primary hypertriglyceridemia—treating triglycerides when it's not the usual suspects | national lipid association online [Internet]. National Lipid Association. Available from: https://www.lipid.org/communications/lipidspin/2012FALL13. [Accessed May 23, 2025].
14. Shah AS, Wilson DP. Primary hypertriglyceridemia in children and adolescents. *J Clin Lipidol*. 2015;9(5):S20–S28.
15. Bashir B, Ferdousi M, Durrington P, Soran H. Pancreatic and cardiometabolic complications of severe hypertriglyceridaemia. *Curr Opin Lipidol*. 2024;35(4):208.
16. Cerf ME. Beta cell dysfunction and insulin resistance. *Front Endocrinol*. 2013;4:37. Available from. http://journal.frontiersin.org/article/10.3389/fendo.2013.00037/abstract . [Accessed May 30, 2025].
17. Das SLM, Singh PP, Phillips ARJ, Murphy R, Windsor JA, Petrov MS. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. *Gut*. 2014;63(5):818–831.
18. Hart PA, Bradley D, Conwell DL, et al. Diabetes following acute pancreatitis. *Lancet Gastroenterol Hepatol*. 2021;6(8):668–675.
19. Zhi M, Zhu X, Lugea A, Waldron RT, Pandol SJ, Li L. Incidence of new onset diabetes mellitus secondary to acute pancreatitis: a systematic review and meta-analysis. *Front Physiol*. 2019;10. Available from. https://www.frontiersin.org/article/10.3389/fphys.2019.00637/full . [Accessed May 23, 2025].

20. Śliwińska-Mossoń M, Bil-Lula I, Marek G. The cause and effect relationship of diabetes after acute pancreatitis. *Biomedicines*. 2023;11(3):667.
21. Christian JB, Bourgeois N, Snipes R, Lowe KA. Prevalence of severe (500 to 2000 mg/dL) hypertriglyceridemia in United States adults. *Am J Cardiology*. 2011;107(6):891–897.
22. Sanchez RJ, Ge W, Wei W, Ponda MP, Rosenson RS. The association of triglyceride levels with the incidence of initial and recurrent acute pancreatitis. *Lipids Health Dis*. 2021;20(1):72.
23. Toth P, Grabner M, Ramey N, Higuchi K. Incidence and characteristics of acute pancreatitis in a real-world sample of patients with severe hypertriglyceridemia. *Atherosclerosis*. 2014;235(2):e285.
24. Watts GF, Rosenson RS, Hegele RA, et al. Plozasiran for managing persistent chylomicronemia and pancreatitis risk. *N Eng J Med*. 2025;392(2):127–137.
25. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al. Olezarsen, acute pancreatitis, and familial chylomicronemia syndrome. *N Eng J Med*. 2024;390(19):1781–1792.

Please cite this article as: Broder et al., Health outcomes and survival among patients with severe hypertriglyceridemia after acute pancreatitis, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2025.08.017