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Subsets associated with developing acute pancreatitis in patients with severe hypertriglyceridemia and the severity of pancreatitis

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ABSTRACT

Background and objectives: Hypertriglyceridemia (HTG) is a rare but well-recognized cause for acute pancreatitis (AP). This study aimed to determine subsets related to development of AP in patients with severe HTG and the severity of HTG-induced AP (HTG-AP).
Methods: Patients who had severe HTG (serum triglyceride level >1,000 mg/dL) more than once between Jan. 2010 and Dec. 2017 in a single institute were evaluated retrospectively. Patients were divided into two groups, with AP or without AP, and were compared. HTG-APs in patients with severe HTG were compared to APs due to other causes during the same period.
Results: Sixty-three patients (19.3%) presented with AP of a total 326 patients with severe HTG. The AP group displayed younger age, more alcohol consumption and diabetes mellitus, and higher initial/maximum serum levels of triglyceride, glucose, HbA1c, total cholesterol, and calculated non-high-density lipoprotein cholesterol ($p < 0.05$). HTG-APs were clinically more severe compared with 277 APs due to other causes in terms of CRP ($p < 0.001$), CT severity index ($p = 0.002$), revised Atlanta classification ($p < 0.001$), and hospital stay ($p = 0.011$). In logistic regression analysis, maximum serum triglyceride level (OR 2.706, $p = 0.015$), alcohol consumption amount (OR 5.292, $p < 0.001$), and age (OR 0.358, $p = 0.017$) were independently associated with development of AP in patients with severe HTG.
Conclusions: Development of AP in patient with severe HTG was independently associated with younger age, higher serum TG level, and more alcohol consumption. HTG-APs are clinically more severe than APs due to other causes.

Introduction

Hypertriglyceridemia (HTG) is rare but well-recognized cause for acute pancreatitis (AP). Studies have shown that APs caused by HTG consist of 1.3–12.3% of all APs, and its incidence has increased during the past 15 years [1–3]. HTG is prevalent in the general population. A recent population-based study demonstrated that triglyceride (TG) more than 500 mg/dL was found in 5.4% of 67,269 people in Scotland [4].

HTG can be a primary cause for AP or an associated epiphenomenon of AP in cases of mild or moderately elevated TG [5]. Generally, AP with a serum TG level of more than 1,000 mg/dL is accepted as HTG induced AP (HTG-AP). There have been few studies regarding the incidence of AP in patients with severe HTG (TG > 1,000 mg/dL), and the reported the AP incidence was 3.3–20.2% [6–8]. The included patients in the studies were all Western, and there have been no data regarding Asian patients.

HTG develops from a primary genetic abnormality of lipid metabolism and/or presence of secondary factors related to overproduction of TG [9]. Since TG levels in genetic abnormalities usually range from 250 to 1,000 mg/dl, severe HTG requires secondary risk factors, such as alcohol abuse, insulin resistance, or visceral obesity [9]. Therefore, development of HTG-AP requires secondary factors related to severe HTG. However, it has not been determined which subsets of HTG patients are subject to development of AP.

In addition, the effect of HTG on the severity of AP is still controversial. A UK study showed no correlation between serum TG

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level and either pancreatic complications or final outcome [10]. However, two studies in China demonstrated that severe APs with TG more than 500 mg/dL were associated with higher 24 h APACHE II score, renal failure, shock, and mortality [11] and that HTG-AP (TG > 1,000 mg/dL) was associated with higher frequency of severe AP, organ dysfunction, and mortality than biliary-induced AP [3].

We thus aimed to determine the incidence of AP, subsets of individuals subject to development of AP in Asian patients with severe HTG, and the severity of HTG-AP.

Patients and methods

Patients

Among patients who had blood chemistries performed for any reason, including evaluation of diseases and general checkup between Jan. 2010 and Dec. 2017 in a single institute, the patients in whom fasting serum TG levels were over 1,000 mg/dL more than once were enrolled retrospectively (Fig. 1.). The date severe HTG was first identified was labeled as the index date. One patient who was younger than 18 years old was excluded. Patients were divided into two groups, those with or without AP, for comparison. We included APs developed pre- and post-index date during the study period. A few APs in the no-AP group can develop after the index date during the follow-up period. Therefore, we excluded patients (n = 112) in the no-AP group who were followed for less than one year in order to lessen the number of patients who developed AP during follow-up as much as possible. To evaluate the severity of HTG-AP, the first APs due to causes other than HTG during the same study period were compared with HTG-APs.

Gathering clinical information and diagnostic criteria

The ages of patients were based on index date. Among serum TG levels obtained during follow-up, initial (on index date) and maximal TG level were utilized for comparison. Other blood chemistries were selected at the time of presenting with AP in the AP group and at the time of maximum serum TG level in the no-AP group. The amount of alcohol consumption was estimated using the alcohol ingredient index determined by the kinds of alcoholic beverages and drinking amount. Both current and past smoking was included for amount of smoking. Regardless of the kinds of cigarettes, total smoking experience was documented. The diagnosis of AP was determined when two of the following three findings were present: typical clinical symptoms, elevated serum amylase or lipase level more than three times the upper normal limit, or consistent imaging. CT severity index included grading of pancreatitis (Balthazar score; normal pancreas (0), enlargement of the pancreas (1), inflammatory changes in the pancreas and peripancreatic fat (2), single peripancreatic fluid collection (3), two or more peripancreatic fluid collections (4)) and pancreatic necrosis (none (0), <30% (2), 30%–50% (4), and >50% (6)) [12]. Severity of AP was classified by revised Atlanta classification, 2012 [13]. Hospital days due to surgery or other major comorbidities to prolong admission were excluded in comparisons of length of hospital stay.

Ethics statement

Patient anonymity was carefully protected, and all study protocols were in complete compliance with the Declaration of Helsinki. This study was approved by our institute research board (No. HC18RESI0101).

Statistical analysis

Categorical and continuous data of clinical characteristics in the two groups were compared by Pearson's chi-square test and Student's t-test. Logistic regression analysis (enter method) was used in multivariate analysis for determination of subsets related to the development of AP in patients with severe HTG and for the degree of association of AP with serum TG level, alcohol consumption, and age. A p value < 0.05 was considered to be significant. All statistical analyses were performed using SPSS version 20 (SPSS, Inc., Chicago, IL, USA).

Results

Basal characteristics

After exclusion, 326 patients with severe HTG were enrolled in

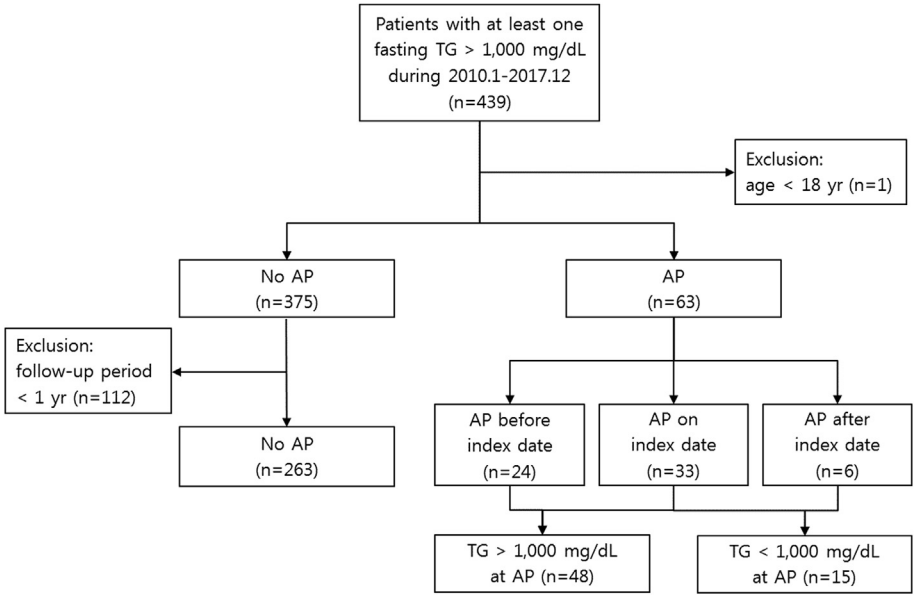

Fig. 1. Diagram of the patients selected in the study.

the study. Patients were followed for an average of 44.3 mo (12.1–103.1 mo), except 30 patients who developed AP and were followed less than one year. Eleven patients died during follow-up due to cardiovascular diseases (5), hepatic failures (2), leukemia (1), ovary cancer (1), AP (1), and pancreatic cancer (1). Sixty-three (19.3%) patients presented with AP. Twenty-four patients had AP prior to the index date (median 22.4 mo), 33 patients were diagnosed with severe HTG and AP simultaneously, and six patients developed AP post-index date (median 42.4 mo). Serum TG levels of more than 1,000 mg/dL at the time of AP diagnosis were documented in 48 (76.2%) patients. Severities of AP were mild in 19 (30.1%), moderately severe in 40 (63.5%), and severe in 4 (6.3%) patients. Organ failure due to AP developed in seven (11.1%) in patients with severe HTG. Three patients had transient organ failure: respiratory, renal, and both renal and cardiovascular. Four patients had persistent organ failure (48 > hrs), and one patient who had persistent renal and cardiovascular failure finally died. Twelve (19.0%) patients were admitted to the ICU, and the median ICU stay was 4.0 days (range 2–14 days). Regarding underlying pancreatic abnormalities, two patients showed parenchymal calcification in the pancreas, and one patient had mild irregularity of the pancreatic duct. AP recurred an average 1.9 ± 1.7 times (maximum 8 times).

Differences in clinical characteristics in patients with severe HTG according to development of AP

Males were more prevalent in both the AP and no-AP groups at 80.9% and 79.5%. Average maximum serum TG levels were significantly higher in the AP group ($2,513 \pm 1,456$ mg/dL) than in the no-AP group ($1,583 \pm 662$ mg/dL) ($p < 0.001$, Fig. 2). BMI was documented in 61 (96.8%) patients with AP and 231 (87.8%) patients with no-AP, and there was no significant difference between the two groups. Alcohol histories were obtained in 237 (90.1%) patients with no-AP, and smoking histories were obtained in 230 (87.5%) patients with no-AP; both were obtained in 100% of patients with AP. Three kinds of medication were used for treatment of HTG, fibric acid, statin, and omega 3. Medication was prescribed in 213 (65.3%) patients, consisting of a single agent (127, 39.0%) or combination of agents (86, 26.4%). Medication did not differ significantly between the two groups.

The AP group displayed younger age ($p < 0.001$), more diabetes ($p = 0.013$), and more alcohol consumption ($p < 0.001$) compared with the no-AP group (Table 1). Sex, smoking, BMI, gallstone, and thyroid function did not significantly differ between the two groups. Blood chemistries indicated higher serum levels of initial TG ($p < 0.001$), maximum TG ($p < 0.001$), total cholesterol level ($p < 0.001$), calculated non-high-density lipoprotein cholesterol ($p < 0.001$), glucose ($p = 0.017$), and HbA1c ($p = 0.037$) in the AP group compared with the no-AP group.

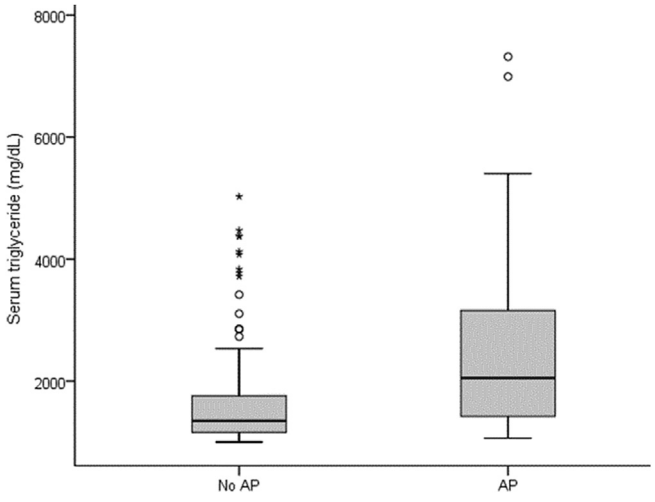

Fig. 2. Maximum serum TG levels in patients with severe HTG according to development of AP.

Comparison of APs due to severe HTG and other causes

Among 63 patients with AP, 48 patients whose TG levels were documented as more than 1,000 mg/dL at the diagnosis of AP were compared with 277 patients with first AP due to other causes during the same study period. The other causes consisted of alcohol 143 (51.6%), gallstone 71 (25.6%), drugs 1 (0.4%), and idiopathic 62 (22.4%). Patients with AP due to severe HTG were younger ($p = 0.005$) and showed more severe clinical findings compared to those with AP due to other causes (Table 2): higher serum levels of CRP ($p < 0.001$), higher CT severity index ($p = 0.002$), more peripancreatic fluid collection ($p < 0.001$) and necrosis ($p = 0.008$), higher severity in revised Atlanta classification ($p < 0.001$), longer hospital stay ($p = 0.011$), and more recurrence of AP ($p = 0.014$). However, serum levels of amylase ($p < 0.001$) and lipase ($p = 0.015$) were lower in HTG-AP.

Multivariate analyses for subsets of severe HTG patients developing AP

In the logistic regression analysis, young age (<40, $p = 0.017$), more alcohol consumption (≥40 g/d, $p < 0.001$), and maximum serum TG level (≥2,000 mg/dL, $p = 0.015$) were independently associated with development of AP in patients with severe HTG (Table 3). Serum TG levels showed a strong positive association with development of AP: patients with TG 2,000–2,999 mg/dL and TG ≥ 3,000 mg/dL developed AP more at 30.6% (odds ratio 3.102, $p = 0.002$) and 60.7% (odds ratio 10.868, $p < 0.001$) compared with 12.4% of AP patients with TG 1,000–1,999 mg/dL (Table 4). Alcohol consumption of more than 40 g/d had a 3.516-fold increased risk of AP compared with alcohol consumption <20 g/day. However, age 40–60 and > 60 had decreased AP incidence at 18.6% and 8.0% compared with age <40 at 39.3%, with corresponding odds ratios of 0.353 ($p = 0.002$) and 0.135 ($p < 0.001$).

Discussion

The present study demonstrated that 19.3% of patients with severe HTG presented with AP. Development of AP in patients with severe HTG was independently associated with higher serum level of TG, younger age, and more alcohol consumption. HTG-AP had a more severe clinical course compared with AP due to other causes. The importance of these results was emphasized by the fact that the incidence of AP in Asian patients with severe HTG was first presented and subsets associated with AP and the severity of HTG-AP was determined.

Although severe HTG is known to be a direct cause of AP, AP does not occur in all patients with severe HTG. The incidence of AP in patients with severe HTG has been little reported, and it included a wide range as 3.3–20.2%. Patients with serum TG level >1,772 mg/dl (mean TG level 3,377 mg/dl) revealed a history of AP prior to referral in 15.8% of 95 patients, and those with TG levels between 886 and 1,771 mg/dl showed a history of AP in 3.3% of 91 patients [7]. Lloret Linares et al. enrolled 129 referred patients for severe HTG (TG level > 1,000 mg/ml), and 26 (20.2%) patients among them had a history of AP prior to referral or presented with AP during follow-up [6]. Another study demonstrated that AP occurred in 4%

Table 1
Comparison between the AP group and no-AP group.

Characteristics	No-AP (n = 263)	N	AP (n = 63)	N	*P* value
Age, yr	54.2 ± 11.7	263	46.7 ± 11.0	63	<0.001
Sex, male/female	209/54	263	51/12	63	0.792
BMI, kg/m^2	25.9 ± 4.1	231	25.2 ± 4.87	61	0.100
Normal (<25)	102 (44.1%)		35 (55.6%)		
Overweight (25–30)	90 (39.0%)		15 (23.8%)		
Obese (>30)	39 (16.9%)		11 (18.0%)		
Underlying diseases					
Diabetes mellitus	101 (39.0%)	259	35 (55.6%)	63	0.017
Gallstone[a]	11 (5.9%)	187	7 (11.1%)	63	0.165
Alcohol consumption, g/d	37.7 ± 42.9	237	65.2 ± 55.1	63	<0.001
Smoking, pack-yr	13.3 ± 17.4	230	15.2 ± 18.2	63	0.465
Treatment for HTG	178 (67.7%)	263	35 (55.6%)	63	0.069
Single					
Fibric acid	40 (15.2%)	40	9 (14.3%)	9	
Statin	67 (25.5%)	67	10 (15.9%)	10	
Omega 3	0 (0)	0	1 (1.6%)	1	
Combination	71 (27.0%)	71	15 (23.8%)	15	
Blood chemistry					
Triglyceride					
Initial, mg/dL	1418.9 ± 465.2	263	2034.1 ± 1194.4	63	<0.001
Maximum, mg/dL	1583.3 ± 662.2	263	2513.9 ± 1456.4	63	<0.001
Total cholesterol, mg/dL	302.3 ± 114.0	263	440.5 ± 238.8	63	<0.001
HDL, mg/dL	32.4 ± 10.9	246	35.4 ± 16.3	62	0.180
LDL, mg/dL	64.2 ± 40.6	93	549.1 ± 2767.3	30	0.345
Non-HDL cholesterol, mg/dL	272.8 ± 111.4	246	408.3 ± 234.0	62	<0.001
Glucose, mg/dL	162.2 ± 118.7	261	209.3 ± 143.8	63	0.017
HbA1c, %	7.3 ± 2.5	172	8.1 ± 2.8	53	0.037
GGT, U/L	224.2 ± 398.5	230	387.0 ± 608.6	62	0.050
Free T4, pg/mL	6.8 ± 6.4	254	6.9 ± 6.4	61	0.900
TSH, mIU/L	1.7 ± 5.2	253	1.8 ± 5.2	61	0.877

Data are expressed as mean ± SD or number.
BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; GGT, gamma-glutamyl transpeptidase; TSH, thyroid stimulating hormone.
[a] In patients who underwent abdominal ultrasonography or magnetic resonance cholangiopancreatography.

Table 2
Comparison between HTG-AP and AP due to other causes.

Characteristics	HTG-AP (N = 48)	AP due to other causes (N = 277)	*P* value
Age, yr	45.4 ± 11.0	50.7 ± 15.9	0.005
TG, mg/dL	2653.6 ± 1566.9	154.6 ± 146.7[a]	<0.001
CRP, mg/L	234.0 ± 144.5	91.9 ± 99.4	<0.001
Amylase, U/L	362.5 ± 328.0	778.7 ± 839.8	<0.001
Lipase, U/L	1090.8 ± 1234.1	1593.2 ± 1602.5	0.015
CT severity index			0.002
0–3	30 (62.5%)	229 (82.7%)	
4–6	15 (31.3%)	45 (16.2%)	
7–10	3 (6.2%)	3 (1.1%)	
Local complication	36 (75.0%)	127 (45.8%)	<0.001
Peripancreatic fluid collection	35 (72.9%)	116 (41.9%)	<0.001
Necrosis	8 (16.7%)	16 (5.8%)	0.008
Pseudocyst	9 (18.8%)	28 (10.1%)	0.082
Severity			<0.001
Mild	13 (27.1%)	149 (53.8%)	
Moderately severe	31 (64.6%)	126 (45.5%)	
Severe	4 (8.3%)	2 (0.7%)	
Length of hospital stay, d	20.0 ± 20.0	12.1 ± 11.9	0.011
Recurrence of pancreatitis	2.0 ± 1.8	1.4 ± 0.9	0.014

Data are expressed as mean ± SD or number.
CRP, C-reactive protein.
[a] Measured in 219 patients.

of 300 patients with TG level >1,000 mg/dl [8]. All these results were from Western countries, and there were no reports regarding Asian patients. Our study showed 19.3% incidence of AP, and this was located in the upper portion of the range of previous results. Therefore, AP in patients with severe HTG is not rare in Asia, and clinical attention is needed for patients with severe HTG.

Alcohol and gallstones are mainly responsible for AP cases, but HTG is another important cause and was found to be responsible for up to 12.3% of AP cases [1]. The pathogenetic mechanism of HTG-AP is not fully elucidated, but it has been proposed that hydrolysis of triglycerides by pancreatic lipase releases a large amount of free fatty acids, which results in toxic injury to the pancreas [14]. Animal models using rats demonstrated that TG causes a dose-dependent elevation of amylase and lipase [15], and that hyperlipidemia

Table 3
Multivariate logistic regression analysis for subsets of severe HTG patients developing AP.

Factors	Odds ratio (95% CI)	*P* value
Age, < 40 *vs.* ≥ 40	0.358 (0.155–0.829)	0.017
HbA1c, < 8 *vs.* ≥ 8%	1.385 (0.623–3.079)	0.424
Alcohol consumption, < 40 *vs.* ≥ 40 g/d	5.292 (2.503–11.188)	<0.001
Serum TG level, max < 2,000 *vs.* ≥ 2,000 mg/dL	2.706 (1.212–6.042)	0.015
Total cholesterol level < 300 *vs.* ≥ 300 mg/dL	1.940 (0.849–4.435)	0.116

Table 4
Multiple logistic regression analyses for development of AP regarding TG, alcohol, and age groups.

Groups	N	N of AP	Odds ratio (95% CI)	*P* value
Maximal TG level, mg/dL				
1,000–1,999	249	31 (12.4%)	1 (reference)	
2,000–2,999	49	15 (30.6%)	3.102 (1.518–6.339)	0.002
≥ 3,000	28	17 (60.7%)	10.868 (4.661–25.341)	<0.001
Alcohol consumption, g/day				
< 20	134	16 (11.9%)	1 (reference)	
20–40	39	6 (15.4%)	1.341 (0.486–3.698)	0.571
≥ 40	127	41 (32.3%)	3.516 (1.852–6.675)	<0.001
Age				
< 40	56	22 (39.3%)	1 (reference)	
40–60	183	34 (18.6%)	0.353 (0.184–0.678)	0.002
≥ 60	87	7 (8.0%)	0.135 (0.053–0.346)	<0.001

intensifies pancreatic injury and aggravates acute necrotizing pancreatitis [16,17]. It is generally accepted that severe HTG (TG level > 1,000 mg/dl) is directly associated with the development of AP. Our study demonstrated proportional increase in AP incidence according to TG level, even among patients with severe HTG. Three previous studies have shown the relevance between TG level and AP. In Scottish people, hazard ratios of AP were 1.50 at TG level 150–499 mg/dl and 3.20 at TG level ≥500 mg/dL, with a reference TG level ≤150 mg/dL [4]. A French study revealed that odds ratios were 0.94 at TG level 1,880–3,500 mg/dL and 3.96 at TG level 3,600–15,050 mg/dl, with a reference of TG level 951–1,800 mg/dl [6]. In Dutch people, AP incidence was 8.7% in patients with TG level 1,151–1,408 mg/dL, 26.1% at TG level 1,408–2,373 mg/dL, and 60.9% at TG level >2,373 mg/dL [8]. The last study showed similar results to our study. Moreover, our study demonstrated increasing and decreasing odds ratios with respect to development of AP according to alcohol consumption amount and age.

Excessive alcohol intake is strongly associated with both HTG and AP [8]. In the present study, alcohol was another independently associated factor with AP in severe HTG patients. Patients with alcohol intake >40 g/d had a 3.5-fold increased risk of AP compared with those with alcohol intake <20 g/d. This risk was similar to a 3.1-fold increase in those with TG level 2,000–2,999 mg/dL and less than a 10.9-fold increase in those of TG level >3,000 mg/dL. Alcohol intake results in decreasing the breakdown of VLDL remnants and chylomicrons via inhibition of lipoprotein lipase activity and an increase in splanchnic extraction of TG from chylomicrons and VLDL remnants [18,19]. Moreover, chronic excessive alcohol intake increases TG by the synthesis of large VLDL particles in the liver [20]. Because alcohol not only induces HTG, but is also an independent risk factor for pancreatitis, it is difficult to differentiate between pancreatitis caused by HTG and alcoholic pancreatitis [8]. Bessembinders et al. showed that 43.1% patients with TG > 2,374 mg/dL had excessive alcohol use compared with 13.9% in patients with TG 1,000–1151 mg/dL [8]. Our study also showed that patients with AP consumed significantly more alcohol compared with patients with no-AP, and alcohol consumption amount was an independent factor related to AP in severe HTG patients.

The age at the diagnosis of HTG was found to be significantly lower in patients with AP compared with patients with no-AP in the present study. Lloret Linares et al. reported that the age at the diagnosis of HTG was significantly lower in the AP group than in the no-AP group, 32.4 vs. 40.2 years in severe HTG patients ($p = 0.0003$). Regarding HTG-AP, a previous study showed that the mean age for diagnosis of HTG-AP was 40.8 years, which was lower than 52.6 years for AP in patients with other etiologies; these were similar to our results [11]. The present study showed that the age was an independent factor associated with AP in severe HTG patients. Therefore, younger HTG patients, particularly less than age 40, need more attention and closer follow-up.

A recent retrospective study showed similar results to our study [21]. They demonstrated that TG levels ≥2,000 mg/dL were associated with HTG-AP in ethnic minorities and that excessive alcohol intake and/or gallstones further accentuated the risk. Except for gallstones, the results were similar to ours. However, our study had some differences and merits. Our study included a large number of pure Asians patients with severe HTG, evaluated the severity of HTG-AP compared with AP due to other causes, quantified the alcohol intake, and utilized detailed subgroup analyses, providing more detailed odds ratios.

The impact of HTG on the clinical course or severity of AP is still uncertain and conflicting. Balachandra et al. showed that TG level did not correlated with APACHE II score, pancreatic complications, and final outcome [10]. Fortson et al. reported that complications, such as pancreatic changes, peripancreatic fluid, necrosis, pseudocysts, and pleural effusion in 70 patients with HTG-AP was similar to historical data on AP complications from other causes [2]. In contrast, Deng et al. reported positive correlation between admission TG level and 24-h APACHE II score [11], and Huang et al. showed that HTG-AP had a higher incidence of severe AP and complications, such as respiratory, renal, or heart failure, compared with gallstone pancreatitis [3]. Two studies from Taiwan and Spain also showed that HTG-AP was more severe and complicated [22,23]. Our study demonstrated that HTG-AP showed clinically severe compared with AP due to other causes. Based on previous studies and our results, it would be reasonable to assume that severe elevations in TG levels (TG > 1,000 mg/dL) affect the severity of AP rather than mild elevation of TG [9].

Our study has some limitations. The main limitations of this study are related to its retrospective design. A few data were missing and further data collection was not possible. Alcohol intake was possibly trivialized because the information was provided by the patient. In addition, some mild local complications of pancreatitis may have been missed if the patients had no symptoms and follow-up imaging studies were not performed. TG levels start decreasing with time and decrease further with administration of intravenous fluids [6]. Delayed measurement of TG levels may have led to falsely low TG levels, which is related to underestimation of the diagnosis of HTG-AP. Because we obtained serum TG levels 3–12 h after admission, the diagnosis of HTG as the cause of AP could have been missed. Furthermore, the diagnosis of AP could have been missed in patients with HTG because HTG, usually >500 mg/ml, is likely to interfere with the assay of serum pancreatic enzyme, leading to determination of falsely low serum amylase and lipase level, as our results showed [9].

In conclusion, the incidence of AP was 19.3% in Asian patients with severe HTG. Higher serum levels of TG, younger age, and more alcohol consumption were independently associated with development of AP in patients with severe HTG. HTG-AP was more severe and recurred more frequently compared with AP due to other

causes. Because of prevalence, severity, and recurrence of HTG-AP, young, alcoholic, and more severe HTG patients should receive close follow-up and careful attention.

Disclosure

The authors report no conflicts of interest in this work.

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