Original Article

ACUTE PANCREATITIS IN PATIENTS WITH SEVERE HYPERTRIGLYCERIDEMIA IN A MULTI-ETHNIC MINORITY POPULATION

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ABSTRACT

Objective: To investigate the prevalence and predictors of hypertriglyceridemic acute pancreatitis (HTG-AP) in a multi-ethnic minority population.

Methods: A retrospective, cross-sectional study from 2003 to 2013 of 1,157 adults with a serum triglyceride (TG) level ≥1,000 mg/dL comparing baseline characteristics and risk factors between those with and without HTG-AP.

Results: Mean study population age was 49.2 ± 11.5 years; 75.6% were male, 31.6% African American, 38.4% Hispanic, 22.7% Caucasian, 5.7% Asian, and 1.6% Pacific Islander. Prevalence of HTG-AP was 9.2%. Patients with HTG-AP were significantly younger (41.3 years vs. 50.0 years; *P*<.001) than those without HTG-AP. Excessive alcohol intake (odds ratio [OR], 3.9; 95% confidence interval [CI], 2.5 to 6.0; *P*<.001), gallstone disease (OR, 3.9; 95% CI, 1.4 to 10.8; *P* = .008), and TG >2,000 mg/dL (OR, 4.8; 95% CI, 3.1 to 7.4; *P*<.001) remained significant independent risk factors. TG levels for patients with HTG-AP were higher (median TG, 2,394 mg/dL; interquartile range [IQR], 1,152 to 4,339 mg/dL vs. median TG, 1,406 mg/dL; IQR, 1,180.7 to 1,876.5 mg/dL). TG levels >2,000 mg/dL were associated with higher incidence of AP (22% vs. 5%). Patients with TG levels <2,000 mg/dL and no risk factors had prevalence of 2% compared to 33.6% with one risk factor and TG >2,000 mg/dL. Patients with HTG-AP had higher incidence of diabetic ketoacidosis at admission (7.5% vs. 2.5%; *P* = .004).

Conclusion: TG level ≥2,000 mg/dL is associated with higher HTG-AP prevalence in ethnic minorities. Presence of excessive alcohol intake and/or gallstones further accentuates risk. **(Endocr Pract. 2018;24:429-436)**

Abbreviations:
AP = acute pancreatitis; **CT** = computed tomography; **DM** = diabetes mellitus; **HbA1c** = hemoglobin A1c; **HIV** = human immunodeficiency virus; **HTG** = hypertriglyceridemia; **HTG-AP** = hypertriglyceridemic acute pancreatitis; **ROC** = receiver operating characteristic; **TG** = triglyceride

INTRODUCTION

Acute pancreatitis (AP) is an inflammatory condition of the pancreas, accounting for more than 220,000 annual hospital admissions (1) and associated with a mortality ranging from 3 to 30% (1-3). Hypertriglyceridemia (HTG) as an underlying etiology is present in 1.3 to 3.8% of patients with AP, making it one of the most common etiologies for AP after gallstone disease and excessive alcohol intake (4). Several pathophysiologic mechanisms have been suggested for AP in the presence of HTG (HTG-AP), with the most commonly accepted theory being that excess TGs are hydrolyzed by pancreatic lipase, resulting in free fatty acids (FFAs). These excess FFAs consequently overwhelm the binding capacity of albumin and cause acinar and pancreatic capillary injury. In addition, hyperviscosity

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resulting from chylomicronemia causes impaired pancreatic blood flow, leading to ischemia and acidosis, ultimately resulting in further pancreatic injury (5-7).

The Endocrine Society clinical practice guidelines (2012) define severe HTG as TG levels between 1,000 and 1,999 mg/dL and very severe HTG as TG levels ≥2,000 mg/dL (8). While a threshold TG value of ≥1,000 mg/dL is often cited as the cut-off for developing pancreatitis, not all patients with severe HTG develop AP (8). At present, there is little information about the risk of AP in relation to TG levels. Some studies have reported cut-off TG values as high as 1,772 mg/dL, while other studies stratified patients based on TG levels >500 mg/dL (9-12). Not only is there ambiguity in the level of HTG causative of pancreatitis, literature is also lacking on the correlation of increased TG levels and the risk of developing AP. Furthermore, the existing literature on HTG-AP has limited data on the prevalence in ethnic minority populations (10,12-14). Given the above-mentioned gaps in the literature, we conducted a retrospective study in a large medical center with high rates of ethnic minorities with the aim of determining the prevalence of HTG-AP in patients with severe HTG (TG ≥1,000 mg/dL) and to study other risk factors of HTG-AP.

METHODS

Patients

In this retrospective study, patients found to have severe HTG in Cook County Health & Hospitals System, an urban safety-net hospital system in Chicago, Illinois, catering to a diverse racial community, were analyzed. The patient population of this system is approximately 53% African American and 29% Hispanic. Inclusion criteria for this study were adult patients (≥18 years) who were found to have a fasting TG ≥1,000 mg/dL whether in inpatient or outpatient settings at any point of time during the collection period from 2003 to 2013. Exclusion criteria included age <18 years or TG <1,000 mg/dL. A diagnosis of HTG-AP was made when any two of the following three criteria were present: abdominal pain characteristic of pancreatitis, computed tomography (CT) evidence of pancreatitis, or serum lipase levels three times the upper level of normal (15) and documented TG >1,000 mg/dL at time of presentation. In cases where multiple episodes of pancreatitis occurred in the same patient, the first episode of AP was included in the analysis.

Based on detailed chart review, spanning from January 2003 to March 2013, we obtained demographic data including self-identified race or ethnicity, presenting symptoms, and presence of risk factors such as excessive alcohol intake, family history of pancreatitis, smoking, recent trauma, preceding endoscopic retrograde cholagiopancreatography (ERCP), infections, and human immunodeficiency virus (HIV) status. Gallstone disease was considered present if documented in admission history or in previous or current imaging investigations (ultrasound or CT). Excessive alcohol intake was defined using the Centers for Disease Control definition stating that it includes binge and heavy drinking (16).

Laboratory values collected included TG levels, lipase levels, calcium, parathyroid hormone levels, hemoglobin A1c (HbA1c), thyroid-stimulating hormone (TSH), and free tetraiodothyronine (FT4). Our lab utilized the Olympus Beckman® assay for lipase, TGs, and calcium. The Access Immunoassay System® was used for TSH and FT4.

Statistical Analysis

Descriptive statistics are reported as percentages for binary and categorical variables as mean and standard deviation if normally distributed and as median (interquartile range) if nonnormally distributed for variables measured on a continuous scale. The significance of association between categorical variables was measured by the χ^2 test. Variables measured on continuous scale were compared between two groups by the independent-samples *t* test, or alternatively, by the nonparametric Mann-Whitney test.

Univariate analysis was used to test the association of age, race, excessive alcohol use, gallstone disease, smoking, TG levels, and diabetes mellitus (DM) with AP (Table 1). We included all risk factors with $P<.10$ in the univariate model into our multivariable risk-adjusted model (Table 2).

Receiver operating characteristic (ROC) curves were used to describe the best predictors for AP development. Based on multivariable analysis, a predictive model for HTG-AP was developed (17) based on variables which were significantly associated with AP. We used 3-fold cross-validation for internal validation of our model in which the patients were divided into three groups of equal sizes; two of the groups were used as training sets based on which probability of AP development was predicted for the remaining validation group. This process was repeated three times. These cross-validated predictions were plotted against the actual data of AP occurrence in a cross-validated ROC curve. A 2-tailed $P<.05$ was considered statistically significant. SPSS version 24 software (IBM Corp) was used for all statistical analyses. The study was approved by the Institutional Review Board of Cook County Health & Hospitals System.

RESULTS

Based on the inclusion criteria, a total of 1,157 patients with TGs ≥1,000 mg/dL were included in the study; 871 patients had TGs 1,000 to 1,999 mg/dL, and 286 patients had TGs ≥2,000 mg/dL. The clinical and laboratory characteristics are shown in Table 1. Mean age was 49.2 ± 11.5 years, and males accounted for 75.6% of the study population. The majority (77.3%) consisted of ethnic minority

Table 1
Baseline Characteristics for all Patients With Severe HTG and in Patients With and Without Pancreatitis[a]

Variable	Total study population with TGs ≥1,000 mg/dL	Patients who developed AP	Patients who did not develop AP	*P*-value (with AP vs. without AP)
Demographics				
Patients, no.	1,157	107	1,050	
Age, years, mean (SD)	49.2 (11.5)	41.3 (9.9)	50.0 (11.3)	<.001
Male sex, no. (%)	875 (76)	79 (74)	796 (76)	.65
Race, no. (%)				
African American	366 (32)	30 (28)	336 (32)	
Hispanic	444 (39)	47 (44)	397 (38)	
Caucasian	242 (21)	19 (18)	223 (21)	.401
Asian	66 (6)	7 (7)	59 (6)	
Pacific Islander	18 (2)	2 (2)	16 (2)	
Unknown	21 (2)	2 (2)	19 (2)	
Clinical presentation (%)				
Abdominal pain	-	97	4	
Positive CT findings	-	94.5	0	<.001
Lipase >3× ULN	-	84.5	0	
Risk factors and comorbid conditions, no. (%)				
Alcohol use	348 (30)	62 (58)	286 (27)	<.001
Smoking	375 (32)	40 (37)	335 (32)	.249
Family history of pancreatitis	4 (0)	1 (1)	3 (1)	.276
Pregnancy	1 (0)	0 (0)	1 (0)	1
Recent trauma	15 (1)	0 (0)	15 (1)	.213
Endoscopic retrograde cholangio-pancreatography	2 (0)	0 (0)	2 (0)	.651
Gallstone disease (either history or imaging evidence)	24 (2)	7 (7)	17 (2)	.001
HIV	103 (9)	2 (2)	101 (10)	.004
Diabetes	820 (71)	76 (71)	744 (71)	.53
Hypothyroidism	15 (1)	1 (1)	14 (1)	.953
Laboratory (normal values)				
HbA1c (4.4-6.7%), mean (SD)	9.6 (2.8)	9.6 (3.2)	9.5 (2.8)	.954
TGs (30-150 mg/dL), median (IQR)	1,444 (1,196.5-1,991.5)	2,394 (1,552-4,339)	1,406 (1,180.7-1,876.5)	<.001
Lipase (5-55 IU/L), median (IQR)	151 (55-440.2)	413 (218.5-1,224.7)	56.5 (38-98.2)	<.001
Ca (8.5-10.5 mg/dL), mean (SD)	9.2 (0.8)	8.48 (1.2)	9.31 (0.7)	<.001
TSH (0.34-5.6 μIU/L), median (IQR)	1.8 (1.1-2.7)	1.3 (0.9-2.1)	1.8 (1.2-2.7)	.833

Abbreviations: AP = acute pancreatitis; Ca = calcium; CT = computed tomography; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; HTG hypertriglyceridemia; IQR = interquartile range; TG = triglyceride; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.
[a]Comparisons between groups were made using *t* tests and for nonparametric data, the Mann-Whitney test was used. Chi-square was used for analysis of categorical variables.

Table 2
Risk-Adjusted Multivariable Model for Factors Associated With Acute Pancreatitis in Patients With Severe Hypertriglyceridemia

	Patients with pancreatitis	Patients without pancreatitis	Unadjusted OR (95% CI)	Unadjusted *P*-value	Final model adjusted OR (95% CI)[a]	Adjusted *P*-value[b]
Gallstone disease	7%	2%	4.3 (1.7-10.5)	.002	3.9 (1.4-10.8)	.008
Excessive alcohol use	58%	27%	3.7 (2.5-5.5)	<.001	3.9 (2.5-6.0)	<.001
Age in years, mean (SD)	41.3 (9.9)	50.0 (11.3)	0.93 (0.92-0.95)	<.001	0.93 (0.91-0.95)	<.001
Triglycerides >2,000 mg/dL	59%	21%	5.3 (3.5-8.0)	<.001	4.8 (3.1-7.4)	<.001

Abbreviations: CI = confidence interval; OR = odds ratio.
[a]Only variables with *P*-value <.1 in the univariate analysis were entered into the multivariable model.
[b]Model adjusted for gallstone disease, excessive alcohol use, age (years), and triglycerides >2,000 mg/dL.

populations: African American (31.6%), Hispanic (38.4%), Asian (5.7%), and Pacific Islander (1.6%). Excessive alcohol intake and history of smoking were found in 30 and 32.4%, respectively. A previous diagnosis of DM and HIV infection were found in 70.9 and 8.9%, respectively. Only 2% (24 patients) had history of gallstones.

The prevalence of AP in patients with severe HTG in this study was 9.2% (107 patients). Among patients who had AP, abdominal pain as the presenting symptom was found in 97.1%; 84.5% had a lipase level three times above the upper limit of normal, and 94.5% had CT evidence of AP. AP complicated by phlegmon formation occurred only in 2 patients, and both were HIV positive. The rate of AP was significantly less in HIV patients compared to patients without HIV (1.8% vs. 10.0%; $P = .004$).

Patients with AP were significantly younger than those without AP (41.3 years vs. 50.0 years; $P<.001$). AP was present in 13.7% of patients younger than 50 years, compared to 4.8% for those above 50 years of age ($P<.001$). Although men clearly outnumbered women in both groups, there was no significant difference in prevalence of AP between male and female patients (9.0% vs. 9.9%).

A history of excessive alcohol intake was found in 57.9% (90.3% males) of patients with AP, compared with 27.2% (86.7% males) of patients without AP ($P<.001$). In the AP group, excessive alcohol intake was found in 78.9% of Caucasians, 66.7% of African Americans, 42.9% of Asians, 48.9% of Hispanics, and 0.0% of Pacific Islanders. Excessive alcohol intake was significantly associated with HTG-AP in univariate analyses for all racial subgroups except Asians and Pacific Islanders.

History of gallstones was present in 6.5% of patients with AP and 1.62% of patients without AP ($P = .004$). Women were more likely to have gallstone disease than men (62.5% vs. 37.5%; $P<.001$). Smoking was equally prevalent in patients with and without AP (37.4% vs. 31.9%; $P = .249$). The DM prevalence and mean HbA1c values were comparable in patients with and without AP. Nine percent of the group had a diagnosis of HIV infection at the time of presentation. HIV patients were older than those without (54.5 ± 2.1 years vs. 41.1 ± 9.8 years; $P = .05$). The two patients with HIV and AP were African American males with TG levels of 1,785 and 2,265 mg/dL. Both HIV-positive patients had pseudocyst formation seen on imaging.

Patients with HTG-AP had higher incidence of diabetic ketoacidosis at admission (7.5% vs. 2.5%; $P = .004$); 88% were men and 12% were women in both cohorts. No one in our cohort had history of trauma, ERCP, pancreas divisum, autoimmune pancreatitis, or pregnancy.

In multivariable logistic regression analysis (Table 2), younger age, excessive alcohol intake, gallstone disease, and TGs >2,000 mg/dL remained significant independent risk factors for the development of HTG-AP.

The median TG level for patients with AP was higher than in those without AP (2,394 mg/dL vs. 1,406 mg/dL; $P<.001$). When patients were divided into two groups based on Endocrine Society guidelines for the classification of HTG (group 1, TGs between 1,000 and 1,999 mg/dL; group 2, TGs ≥2,000 mg/dL), the prevalence of AP was significantly higher in group 2, with 5.1% in group 1 and 22% in group 2 (Fig. 1 *A*). When patients were divided into four equal progressive TG level range groups, there was a significant and incremental increase in prevalence of AP from 6.6% in the lowest group to 66.6% in the highest TG group (Fig. 1 *B*).

TG level association with AP was further stratified by the presence or absence of excessive alcohol intake and/or gallstones. Presence of one or two risk factors in each TG range group increased further the association with AP (Fig. 1 *C* and *D*). It showed that patients in lower TG range groups (both in two or four range group analyses) and without any other risk factors have low association with AP

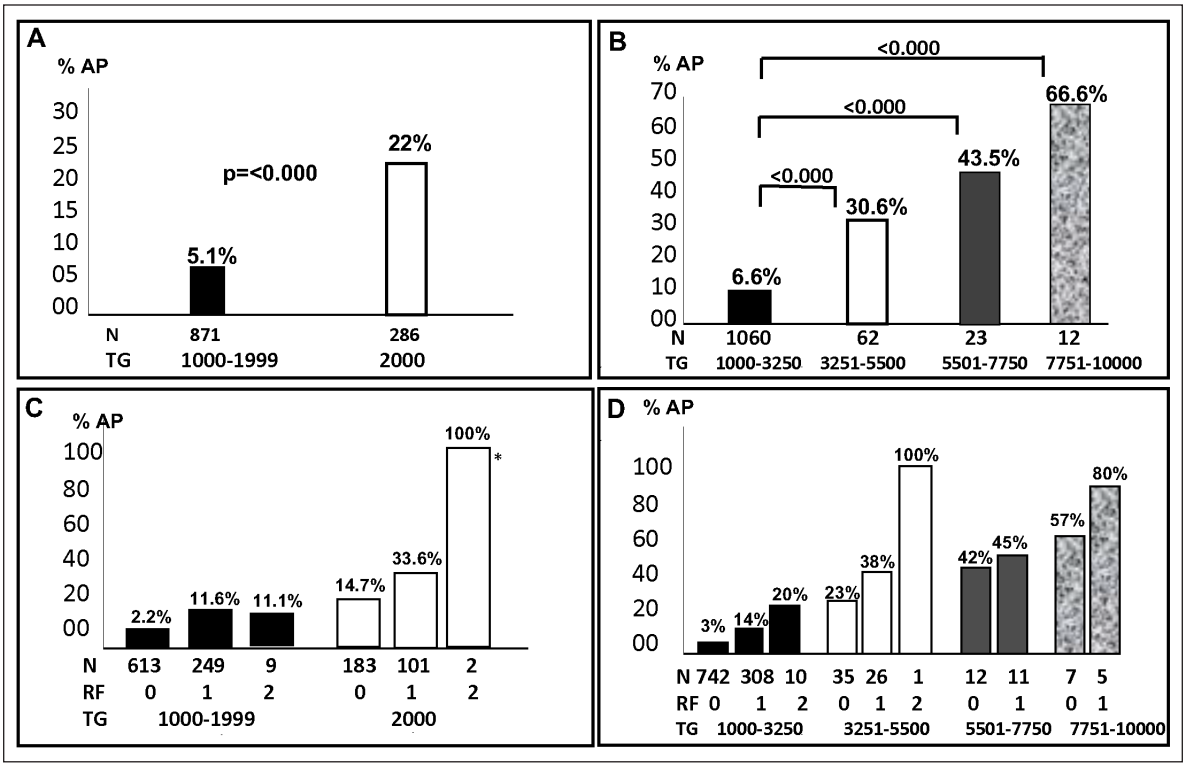

Fig. 1. Prevalence of acute pancreatitis (AP) with and without presence of lifestyle risk factors. (*A*) Prevalence of AP in the two triglyceride (TG) groups. (*B*) Prevalence of AP in the four TG groups. (*C*) Prevalence of AP in the two TG groups with presence of 0, 1, or 2 risk factors (RF). *n is only 2, and hence, have to be cautious with this result. (*D*) Prevalence of AP in the four TG groups with presence of 0, 1, or 2 risk factors (rounded to the nearest decimal).

(prevalence of 2.2% and 3.0%, respectively), and addition of even one risk factor raises the association significantly.

ROC Curve Analysis and Predictive Model

The ROC curve, using predicted values from a model with the four independent risk factors of age, TGs, presence or absence of excessive alcohol intake, and gallstones, yielded an area under the curve of 0.834 (95% CI, 0.80 to 0.87; *P*<.001) (Fig. 2). The cross-validated ROC curve, using 3-fold cross-validated predictions, yielded a comparable area under the curve of 0.813 (95% CI, 0.77 to 0.85; *P*<.001).

A predictive model using the four independent risk factors was developed to calculate the probability of developing AP. Based on this model, we calculated several different scenarios of risk for two hypothetical patients: a younger 30 years old and an older 60 years old (Fig. 3). The risk in the younger patient ranged from 1.7% and progressed as high as 57.0% as the number of risk factors increased. In the older patient, the risk range for AP was much lower (0.2% to 14.1%) as the same risk factors were accumulating. To access an interactive version of this model, visit http://www.cookcountyhhs.org/medical-clinicalservices/department-medicine/diabetes-endocrinology/.

Based on our ROC curve, we suggest three cut-offs to determine the probability of developing AP (%): low risk as <4.4%, intermediate risk as 4.4% to <12.0%, and high risk as ≥12.0%. The sensitivity and specificity for the ≥4.4% cut-off were 94.4% and 52.9%, respectively, while for the ≥12.0% cut-off, they were 71.0% and 81.7%, respectively.

DISCUSSION

The prevalence of HTG-AP in our cohort was 9.2%, which is slightly lower than the weighted mean prevalence of 14.0% with a wide range of prevalence estimates (8 to 31%) reported by a recent systematic review of observational studies (13). However, the size of our cohort was larger than the entire pooled patient population from that review. Plus, this is the first HTG-AP report in a multiethnic minority population.

This study clearly shows that the AP risk increases with higher levels of TGs, especially >2,000 mg/dL. This study validates the Endocrine Society's suggested cut-off of TGs >2,000 mg/dL as a risk factor to develop HTG-AP and shows a 4.3-fold increase in the prevalence of AP at this level compared to the group with TGs 1,000 to 1,999 mg/dL (22.0% vs, 5.1%). This trend was further noted when the TG values were divided into four incremental groups, with the risk of AP increasing 11-fold in the highest group.

Alcohol is a well-known independent risk factor for AP (15,18,19). Our study shows that patients with a history of alcohol intake have 4 times the odds of developing

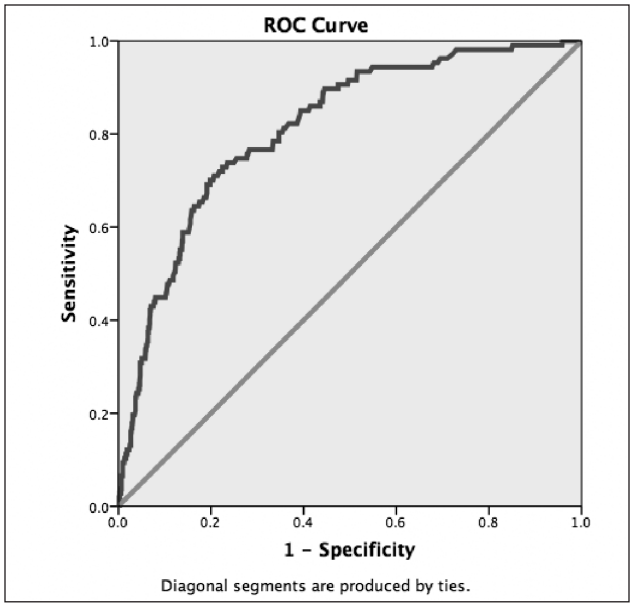

Fig. 2. Receiver operating characteristic (ROC) curve analysis for the predictive model for hypertriglyceridemia-induced acute pancreatitis using the four independent risk factors of age, presence or absence of excessive alcohol intake, gallstones, and triglyceride level. Area under the curve: 0.834 (95% confidence interval, 0.80-0.87; *P*<.001).

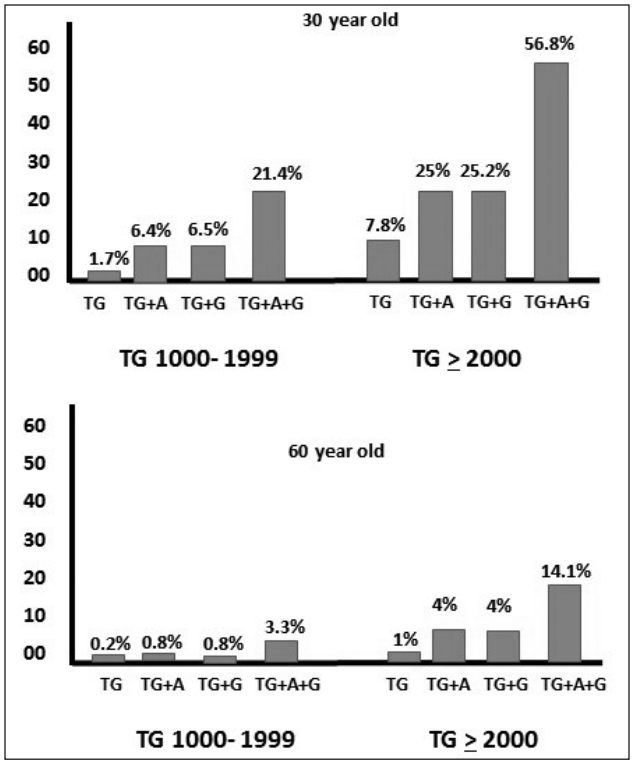

Fig. 3. Calculated risk for developing acute pancreatitis in two hypothetical patients (30 years old and 60 years old) with asymptomatic severe hypertriglyceridemia (triglyceride [TG] level >1,000 mg/dL) and different constellations of risk factors derived from the predictive model. *A* = alcohol; *G* = gallstones.

AP. These results are concordant with previous literature on HTG-AP (20). It is well known that alcohol leads to markedly higher TG levels through inhibition of lipolysis, especially in patients with pre-exiting lipoprotein lipase deficiency (9). Several additional mechanisms have been suggested for the causative role of alcohol intake in AP, including sphincter of Oddi dysfunction, plugging of the pancreatic ductules resulting in acinar injury, stimulation of pancreatic enzyme secretion predisposing to endotoxin-induced damage, direct toxic effect mediated by metabolites such as fatty acid ethyl esters, and, finally, through localized hypoxia produced by increased oxygen requirements during ethanol metabolism (21-25).

Although smoking was not significantly associated with development of HTG-AP, we observed that approximately 50% of patients with a history of alcohol intake were also smokers, and amongst those with a history of smoking, 82.5% had a history of alcohol intake. Therefore, it is evident that these two modifiable risk factors often co-exist. In previous studies, smoking has been shown to increase progression of chronic alcoholic pancreatitis and also potentiate pancreatic ischemia and damage in acute alcoholic pancreatitis (26,27).

Gallstone disease is also a known independent risk factor for AP (15,18,19). Our analysis revealed that gallstone disease was an independent risk factor for HTG-AP development. We also found that in patients with AP, prevalence of gallstone disease was significantly higher in women compared to men, which has been well described in the past (15,18,19).

In addition to the degree of HTG, excessive alcohol intake and presence of gallstones, other factors were associated with AP. Patients who developed AP were younger, and younger age showed to be an independent risk factor associated with HTG-AP. It is not clear why older patients with similar risk factors were less susceptible to developing AP. A recent retrospective comparison of HTG-AP, biliary AP, and alcoholic AP highlighted this fact by reporting that patients with HTG-AP are significantly younger as compared to patients with biliary AP or alcoholic AP (10). We also observed that men clearly outnumbered women in both the overall cohort and the AP subgroup. This finding is similar to a study by Sandhu et al (12), who reported that 70% of the patients in their large cohort of HTG patients were men. Interestingly, despite the lower overall prevalence of women with HTG in our study, there was an equal prevalence of AP in male and female patients (9.1% vs 9.9%).

We found that a large number of patients in our cohort had a previous diagnosis of DM (70.9%), with an average HbA1c of 9.6% (81 mmol/mol), indicating poor glycemic control, especially in men (10.1% [87 mmol/mol] in men vs. 8.1% [65 mmol/mol] in women). Uncontrolled DM has been previously reported in studies on HTG-AP at varying prevalence, ranging from 43 to 72% (4,28). Our data reveal that there is no difference in either prevalence of DM or in mean HbA1c values between patients with and without HTG-AP. These findings are concordant with two studies, one retrospective and one prospective (12,20).

Our study is retrospective and, therefore, has limitations inherent to this type of study. However, we subjected our data to rigorous checks, including periodically choosing random patients and by sorting each continuous variable in ascending order to evaluate accuracy and look for outliers. In addition, the large size of our cohort makes the statistical analysis robust and the results credible. Since our study group is unique in racial composition, it cannot be fully generalized to the general population. Also, when stratifying the patients by TG levels, the number of patients in the highest two quartiles were small. Therefore, caution needs to be observed in interpreting data from these two subgroups. Our data also lacked details of medication usage and body mass index values. These could possibly contribute to unmeasured confounding variables in our regression model.

In this study, the prevalence of AP increased within each TG group with the concomitant presence of excessive alcohol intake and gallstones. In absence of these risk factors, the prevalence of AP was very low (2 to 3%) in the lower TG level groups. These risk predications are further corroborated by the ROC analyses and the predictive model developed. In addition, the predictive model shows the importance of young age as additional important risk factor (Fig. 3). Using this model, younger patients had a much higher risk, as much as 4-fold, to develop pancreatitis than their older counterpart with similar risk factors. However, this model will need further validation. The findings of the study might help risk-stratify patients with severe HTG in the outpatient setting to assess their risk for developing AP. It may also have therapeutic implications and help the clinician to decide on the urgency and intensity of management of severe HTG based on the patient's risk.

CONCLUSION

This large retrospective study is the first report on HTG-AP in a U.S. multi-ethnic minority population. Early detection and counseling on behavioral risk factors in patients with severe HTG may help in reduction of pancreatitis risk. The predictive modelling suggested in this study, if externally validated, may be a useful tool for individualizing therapy in such patients.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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Corrections

In the January 2018 issue of *Endocrine Practice* (Volume 24, Issue 1), on page 96, second column, second paragraph, sixth sentence, the portion of the sentence that reads "although all GLP1 receptor agonists (GLP-1 RAs) are currently contraindicated in stages 4 and 5 CKD" needs to be removed. Exenatide is contraindicated in patients with severe renal impairment or end-stage renal disease, while all other GLP-1 RAs should be used with caution in patient with advance kidney disease.

In the May 2018 issue of *Endocrine Practice* (Volume 24, Issue 5), on page 429, Dr. Michael Morkos' name was misspelled in the author list.

