Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases

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A B S T R A C T

Background: Hypertriglyceridemia is the third most common cause of acute pancreatitis (AP). It has been shown that hypertriglyceridemia aggravates the severity and related complications of AP; however, detailed analyses of large cohorts are contradictory. Our aim was to investigate the dose-dependent effect of hypertriglyceridemia on AP.
Methods: AP patients over 18 years old who underwent triglyceride measurement within the initial three days were included into our cohort analysis from a prospective international, multicenter AP registry operated by the Hungarian Pancreatic Study Group. Data on 716 AP cases were analyzed. Six groups were created based on the highest triglyceride level (<1.7 mmol/l, 1.7–2.19 mmol/l, 2.2–5.59 mmol/l, 5.6–11.29 mmol/l, 11.3–22.59 mmol/l, ≥22.6 mmol/l).
Results: Hypertriglyceridemia (≥1.7 mmol/l) presented in 30.6% of the patients and was significantly and dose-dependently associated with younger age and male gender. In 7.7% of AP cases, hypertriglyceridemia was considered as a causative etiological factor (≥11.3 mmol/l); however, 43.6% of these cases were associated with other etiologies (alcohol and biliary). Hypertriglyceridemia was significantly and dose-dependently related to obesity and diabetes. The rates of local complications and organ failure and maximum CRP level were significantly and dose-dependently raised by hypertriglyceridemia. Triglyceride above 11.3 mmol/l was linked to a significantly higher incidence of moderately severe AP and longer hospital stay, whereas triglyceride over 22.6 mmol/l was significantly associated with severe AP as well.
Conclusion: Hypertriglyceridemia dose-dependently aggravates the severity and related complications of AP. Diagnostic workup for hypertriglyceridemia requires better awareness regardless of the etiology of AP.

Introduction

Hypertriglyceridemia (HTG) affects 10–30% of the general adult population [1,2]. Classifying HTG is complex; both genetic (primary) and environmental (secondary) factors can lead to an elevated triglyceride (TG) level. In rare cases (2%), primary severe HTG (TG ≥ 10 mmol/l) may arise as a result of autosomal recessive, monogenic familial chylomicronemia syndrome (FCS, former Type I). However, a majority of severe HTG cases are multifactorial and have polygenic (mixed HTG, former Type V) determinants with additional secondary factors. Mild-to-moderate HTG cases (2–9.9 mmol/l TG) are similarly polygenic with complex genetic susceptibility (former Type IV, Type IIB and Type III) [2–4]. As regards environmental factors, alcohol, positive-energy balanced diet, obesity, uncontrolled diabetes mellitus (DM), renal diseases, pregnancy, hypothyroidism and medications (e.g., estrogen, retinoids, thiazides, and b-blockers) were shown to be responsible for a raised TG level usually with the interaction of genetic susceptibility [5,6].

HTG is the third most common cause of acute pancreatitis (AP), and it is responsible for up to 15% of AP cases [7–9]. According to the definition, the majority of experts agree that AP related to TG above 5.6 mmol/l should be considered as suspected hypertriglyceridemia-induced acute pancreatitis (HTG-AP) and AP associated with TG over 11.3 mmol/l is confirmed as HTG-AP [4,10]. Importantly, the occurrence of AP increases with the increase in TG level. There is a 5% possibility of developing AP if TG exceeds 11.3 mmol/l, and it rises to 10–20% if TG elevates over 22.6 mmol/l [4]. HTG-AP is of great importance for several reasons: 1) it has shown a rising incidence worldwide as a result of increasing obesity-related dyslipidemia [11,12]; 2) it raises the risk of severe AP and related complications [8,10,12–16]; and 3) there is no evidence-based therapy for it [17–19].

We aimed to perform a cohort analysis for investigating the dose-dependent effect of HTG on AP and providing data for further prospective randomized clinical trials. In our current cohort study, we show clear evidence that TG level dose-dependently worsens the outcome of AP. The rate of local complications is significantly higher above 5.6 mmol/l, whereas significantly elevated organ failure presents above 11.3 mmol/l TG level, strongly suggesting that TG-lowering therapy can achieve a better outcome of AP at a much lower TG level than we previously thought.

Methods

AP patients (n = 1435) over 18 years old were enrolled in the prospectively collected international, multicenter AP registry operated by the Hungarian Pancreatic Study Group (HPSG) between 2012 and 2017. Post-hoc cohort analysis was performed on 716 AP cases who underwent TG measurement within 72 h from admission. AP was diagnosed based on the International Association of Pancreatology/American Pancreatic Association (IAP/APA) and HPSG evidence-based guidelines [17,18]. Participating countries are shown in Sup. Fig. 1.

The threshold of the normal TG value was determined at 1.7 mmol/l [6]. Six groups were established based on the Endocrine Society Clinical Practice Guideline and previously published clinical data related to HTG-AP [4,6]: Group 1: <1.7 mmol/l; Group 2: 1.7–2.19 mmol/l; Group 3: 2.2–5.59 mmol/l; Group 4: 5.6–11.29 mmol/l; Group 5: 11.3–22.59 mmol/l; and Group 6: ≥22.6 mmol/l. To convert TG from mmol/l to mg/dl multiply by 88.57. In case of each variable, elevated TG groups (Groups 2–6) were compared with the normal TG group (Group 1). TG categories were collapsed to three groups (<1.7 mmol/l; 1.7–11.29 mmol/l; ≥11.3 mmol/l) for the analysis of organ failure because of the low event number.

Seventy-three variables were collected from each AP case as listed in Table S1. The analysis was performed on 42,655/52,268 available data. Local complications, organ failure and severity were defined based on the revised Atlanta classification [20]. The 716 cases investigated have shown the same epidemiological and major outcome distribution as the total cohort (1435 cases), demonstrating that our patients' population represents a normal AP cohort (Sup. Fig. 2).

The registry received ethical permission from the Scientific and Research Ethics Committee of the Medical Research Council

(22254−1/2012/EKU) in 2012, and all the patients provided written informed consent to participate. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki updated in 2013 as reflected in a priori approval by the institution's human research committee.

Statistical analysis

Prior to analysis of the dataset, descriptive statistical tools were used to describe the basic characteristics. Mean and standard error of the mean were calculated for continuous variables, whereas the incidence in each group was determined for categorical variables. Depending on the distribution of the data, the independent Student's t-test or Mann−Whitney U test was used to evaluate differences between continuous parameters. The chi-square test or Fisher's exact test was conducted to analyze the relations between the variables. We compared the confidence intervals (CI) of the proportions to investigate differences in the incidence of moderately severe cases between groups. A p-value less than 0.05 ($\leq$0.05) was determined as statistically significance. All analyses were performed using IBM-SPSS Statistical Software Version 25 (IBM Corporation, Armonk, NY, USA).

Results

In our cohort, 30.6% (n = 219) of the patients presented with elevated TG level ($\geq$1.7 mmol/l). HTG was significantly and dose-dependently linked to younger age and male gender (Fig. 1A−C). In 7.7% of AP cases (n = 55), TG level was above 11.3 mmol/l, which is considered as a causative etiological factor [6,10]. In 56.4% of these cases, HTG-AP patients had no other etiology described; however, raised TG level was also accompanied by alcohol in 38.2% of these cases and by biliary etiology in 5.4%, showing that HTG-AP is associated with other etiologies in a substantial number of cases (Fig. 1D).

Data from patients' medical history revealed that HTG is significantly and dose-dependently linked to obesity and DM (Fig. 2B and C); however, there is no relation to chronic pancreatitis (CP) and the Charlson comorbidity index (CCI) [21] (Fig. 2A and D). The amount of previous AP in the medical history was higher in the HTG group compared to the normal TG group (Fig. 2A). General symptoms of AP and physical examination on admission (incidence, duration and intensity of pain, nausea, vomiting, abdominal tenderness and guarding, and blood pressure) have not shown a significant link to elevated TG level (Fig. 3A and B). However, HTG was significantly related to increased heart rate (Fig. 3C). As regards the laboratory parameters on admission showing significant differences with HTG, amylase, lipase, sodium, and calcium were associated inversely; however, glucose, C-reactive protein (CRP), cholesterol, red blood cell count (RBC), hemoglobin, and hematocrit were related parallel with TG level (Fig. 4). On admission laboratory parameters consistent with cholestasis suggested that HTG is less
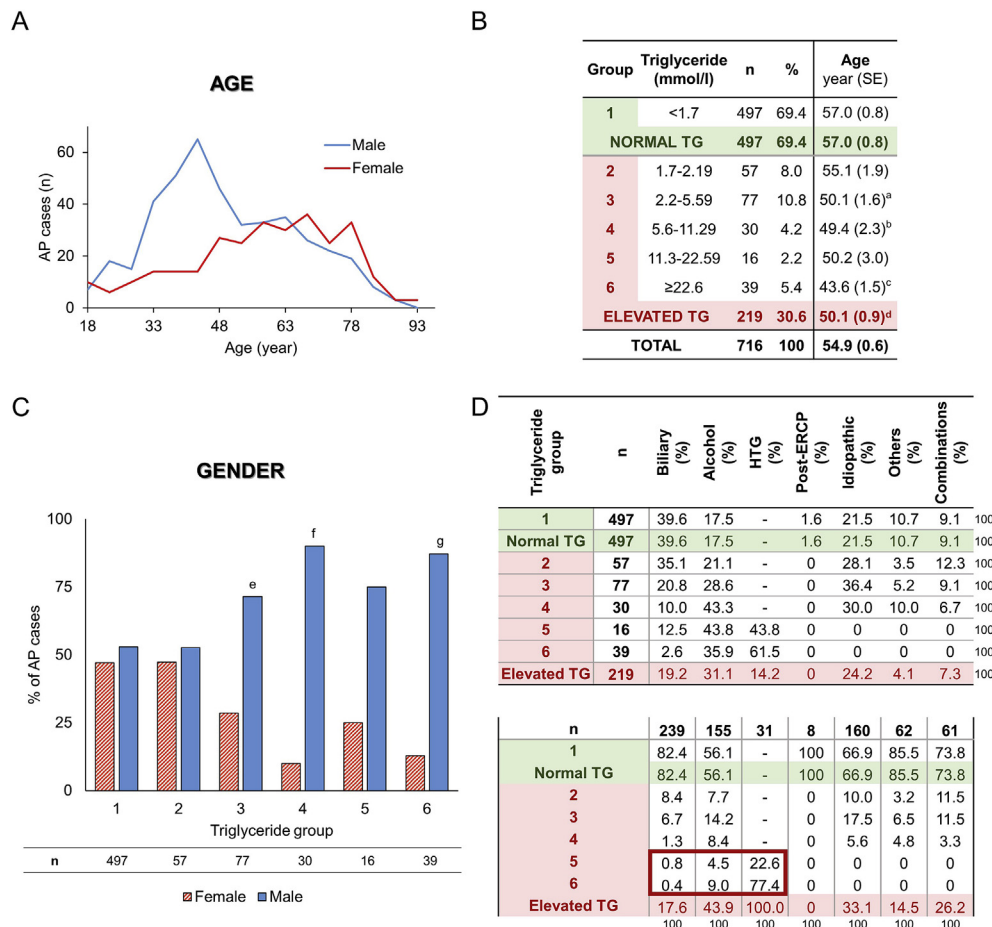
A

AGE

B

Group	Triglyceride (mmol/l)	n	%	Age year (SE)
1	<1.7	497	69.4	57.0 (0.8)
NORMAL TG		497	69.4	57.0 (0.8)
2	1.7-2.19	57	8.0	55.1 (1.9)
3	2.2-5.59	77	10.8	50.1 (1.6)[a]
4	5.6-11.29	30	4.2	49.4 (2.3)[b]
5	11.3-22.59	16	2.2	50.2 (3.0)
6	≥22.6	39	5.4	43.6 (1.5)[c]
ELEVATED TG		219	30.6	50.1 (0.9)[d]
TOTAL		716	100	54.9 (0.6)

C

GENDER

Triglyceride group	n
1	497
2	57
3	77
4	30
5	16
6	39

D

Triglyceride group	n	Biliary (%)	Alcohol (%)	HTG (%)	Post-ERCP (%)	Idiopathic (%)	Others (%)	Combinations (%)	
1	497	39.6	17.5	-	1.6	21.5	10.7	9.1	100
Normal TG	497	39.6	17.5	-	1.6	21.5	10.7	9.1	100
2	57	35.1	21.1	-	0	28.1	3.5	12.3	100
3	77	20.8	28.6	-	0	36.4	5.2	9.1	100
4	30	10.0	43.3	-	0	30.0	10.0	6.7	100
5	16	12.5	43.8	43.8	0	0	0	0	100
6	39	2.6	35.9	61.5	0	0	0	0	100
Elevated TG	219	19.2	31.1	14.2	0	24.2	4.1	7.3	100

	n							
n	239	155	31	8	160	62	61	
1	82.4	56.1	-	100	66.9	85.5	73.8	
Normal TG	82.4	56.1	-	100	66.9	85.5	73.8	
2	8.4	7.7	-	0	10.0	3.2	11.5	
3	6.7	14.2	-	0	17.5	6.5	11.5	
4	1.3	8.4	-	0	5.6	4.8	3.3	
5	0.8	4.5	22.6	0	0	0	0	
6	0.4	9.0	77.4	0	0	0	0	
Elevated TG	17.6	43.9	100.0	0	33.1	14.5	26.2	
	100	100	100	100	100	100	100	

Fig. 1. Epidemiology and etiology. A) Age distribution of acute pancreatitis (AP) cases in males and females. **B)** Age distribution of triglyceride (TG) groups (a, c, d: p=<0.001; b: p = 0.010). **C)** Gender distribution of triglyceride groups (e: p = 0.002; f, g: p < 0.001). **D)** Etiology. HTG = hypertriglyceridemia; ERCP = endoscopic retrograde cholangiopancreatography.
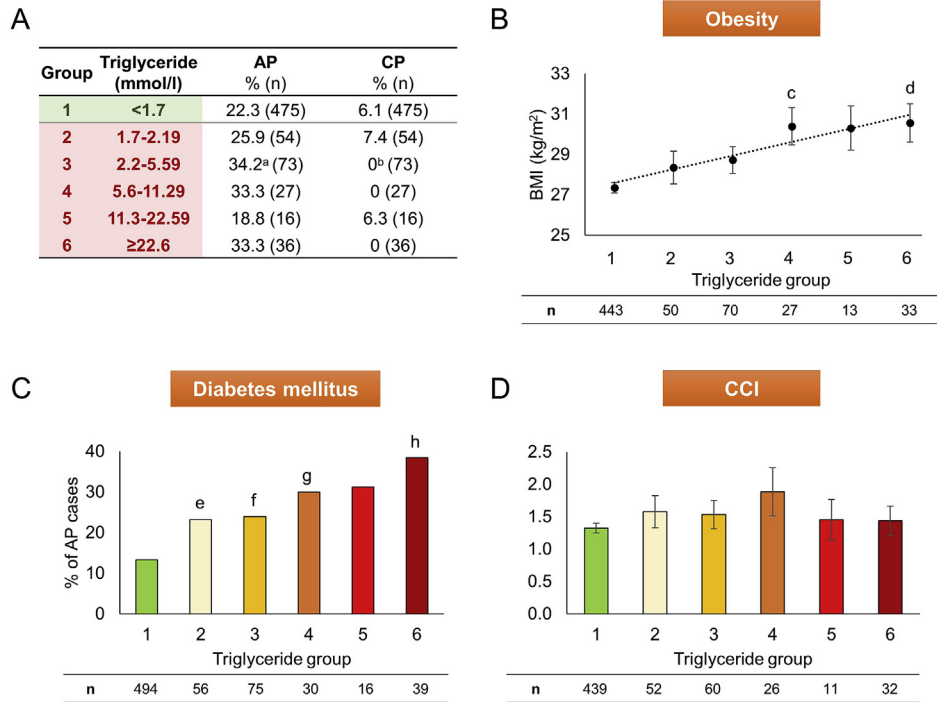
A

Group	Triglyceride (mmol/l)	AP % (n)	CP % (n)
1	<1.7	22.3 (475)	6.1 (475)
2	1.7-2.19	25.9 (54)	7.4 (54)
3	2.2-5.59	34.2[a] (73)	0[b] (73)
4	5.6-11.29	33.3 (27)	0 (27)
5	11.3-22.59	18.8 (16)	6.3 (16)
6	≥22.6	33.3 (36)	0 (36)

B Obesity

C Diabetes mellitus

D CCI

Fig. 2. Medical history of triglyceride groups. A) Acute pancreatitis (AP) and chronic pancreatitis (CP) in patients' medical history (a: p = 0.026; b: p = 0.023). **B)** Obesity (body mass index (BMI), kg/m^2) (c: p = 0.006; d: p = 0.001). **C)** Diabetes mellitus in medical history (e: p = 0.046; f: p = 0.016; g: p = 0.026; h: p < 0.001). **D)** Charlson comorbidity index (CCI). N numbers (n) indicate the total number of cases in each triglyceride group.

A

Group	Triglyceride (mmol/l)	Abdominal pain % (n)	Duration before admission hour±SE (n)	Intensity 1-10±SE (n)	Nausea % (n)	Vomiting % (n)	Abdominal tenderness % (n)	Abdominal guarding % (n)
1	<1.7	98.6 (497)	58.7±5.1 (434)	7.6±0.1 (287)	69.6 (477)	56.3 (485)	86.2 (478)	10.3 (478)
NORMAL TG		98.6	58.7±5.1	7.6±0.1	69.6	56.3	86.2	10.3
2	1.7-2.19	98.2 (57)	37.7±7.1 (46)	7.8±0.4 (27)	79.2 (53)	58.2 (55)	81.5 (54)	11.1 (54)
3	2.2-5.59	100 (77)	50.8±15.1[a] (67)	7.7±0.3 (42)	66.7 (72)	46.7 (75)	87.8 (74)	12.2 (74)
4	5.6-11.29	100 (30)	31.6±7.6 (26)	7.8±0.3 (17)	76.7 (30)	60.0 (30)	100[b] (27)	14.8 (27)
5	11.3-22.59	100 (16)	32.5±7.8 (15)	8.0±0.5 (8)	62.5 (16)	50.0 (16)	100 (16)	13.3 (15)
6	≥22.6	100 (39)	49.0±21.5 (33)	7.7±0.5 (19)	61.1 (36)	45.9 (37)	89.2 (37)	10.8 (37)
ELEVATED TG		99.5	43.1±6.9	7.8±0.2	70.0	51.6	88.9	12.1

B Blood pressure

C Heart rate

Fig. 3. Symptoms and physical findings on admission in the different triglyceride (TG) groups. A) Incidence, duration before admission and intensity of pain. Nausea, vomiting, abdominal tenderness and abdominal guarding (a: p = 0.025; b: p = 0.036). **B)** Systolic and diastolic blood pressures (Hgmm) (c: p = 0.012). **C)** Heart rate (bpm) (d, e: p = 0.010). N numbers (n) indicate the total number of cases in each triglyceride group.

common in cases with biliary etiology. (Sup. Fig. 3). The parallel rise in gamma-glutamyltransferase (γGT) and TG levels confirms that alcohol consumption is linked to HTG (Sup. Fig. 3D). White blood cell count (WBC), thrombocyte, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, and potassium had no significant relation to HTG (Sup. Fig. 4).
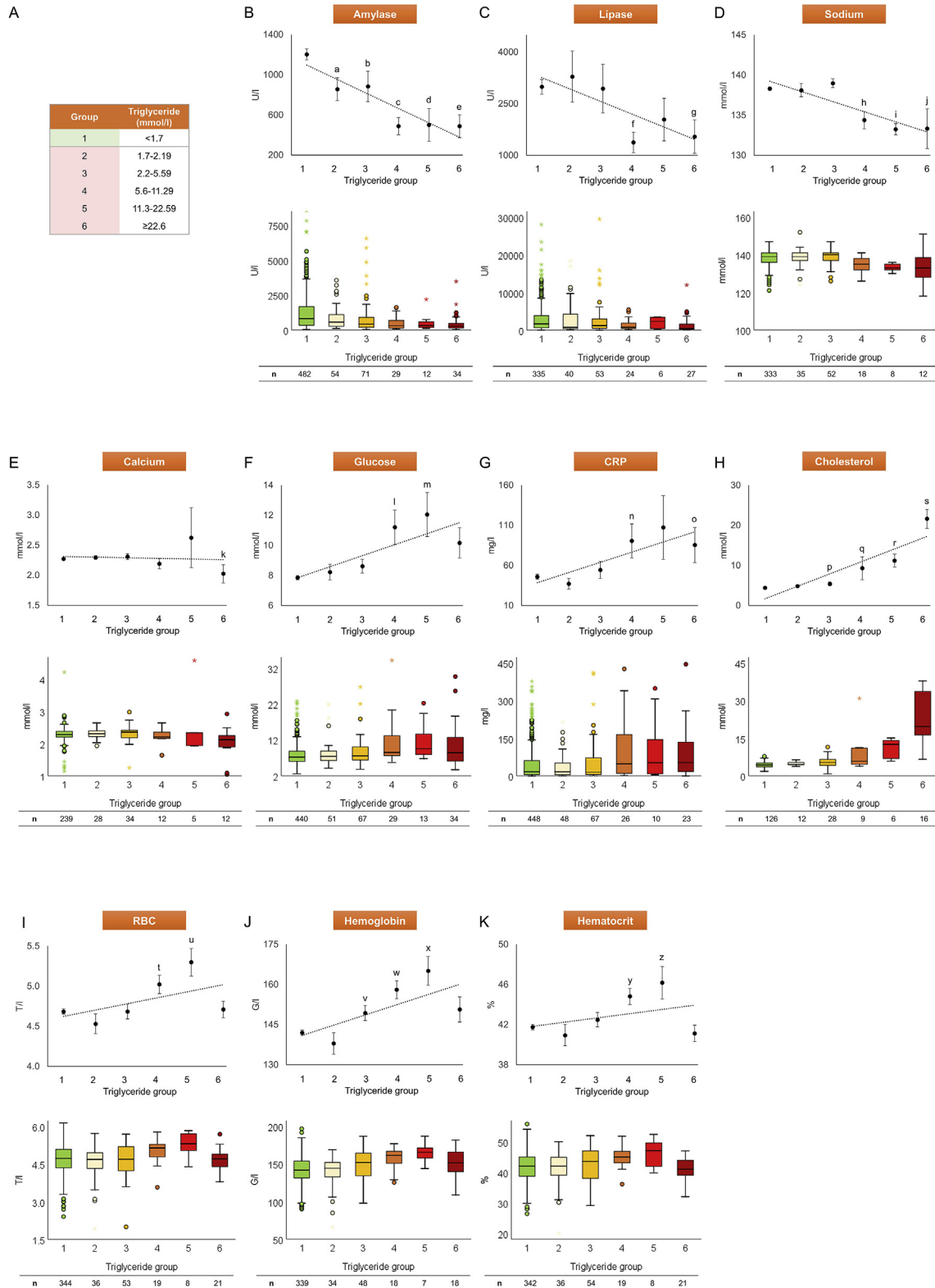
Fig. 4. Laboratory parameters on admission significantly associated with hypertriglyceridemia. A) Triglyceride groups [1–6]. **B)** Amylase (U/l) (a: p = 0.036; b, c, e: p=<0.001; d: p = 0.009). **C)** Lipase (U/l) (f: p = 0.017; g: p = 0.001). **D)** Sodium (mmol/l) (h, i: p=<0.001; j: p = 0.005). **E)** Calcium (mmol/l) (k: p = 0.012). **F)** Glucose (mmol/l) (l, m: p=<0.001). **G)** C-reactive protein (CRP, mg/l) (n: p = 0.021; o: p = 0.014). **H)** Cholesterol (mmol/l) (p: p = 0.008; q: p = 0.006; r, s: p < 0.001). **I)** Red blood cell count (RBC, T/l) (t: p = 0.017; u: p = 0.004) **J)** Hemoglobin (G/l) (v: p = 0.008; w: p < 0.001; x: p = 0.002). **K)** Hematocrit (%) (y: p = 0.009; z: p = 0.014). N numbers (n) indicate the total number of cases in each triglyceride group.

The rate of local complications, including peripancreatic fluid collection, pancreatic necrosis and DM, was significantly and dose-dependently increased with TG level (Fig. 5B–E); however, pancreatic pseudocysts did not show significant differences between the investigated groups above 2.2 mmol/l (Fig. 5F). Organ failure, including heart and renal failure, and maximum CRP level were significantly and dose-dependently raised by TG level (Fig. 6B, D-G); however maximum WBC has not shown any significant differences by HTG (Fig. 6C).

As regards severity, TG level above 11.3 mmol/l was associated with a significantly higher rate of moderately severe AP and longer hospital stay, whereas TG level above 22.6 mmol/l was significantly related to severe AP as well (Fig. 7A and B). Due to the low event rate, the effect of HTG on mortality could not be determined (Fig. 7A). Detailed values of charts and statistical parameters are shown in Tables S2 and S3.

Plasmapheresis was carried out in 36.4% (20/55) of the HTG-AP cases; 85% of these patients had an initial TG level higher than 22.6 mmol/l and the average TG level was 70.1 ± 10.0 mmol/l.

Discussion

HTG-AP has grown in incidence and importance. According to the previously published literature [7,9], HTG is the third most common cause of AP (7.7%). However, it seems more than likely that the incidence of HTG-AP is higher than is usually recorded. The prospective multicenter, international AP cohort run by the HPSG revealed that TG measurement is performed in just 50% (716/1435) of AP cases within the first three days from admission and most probably this rate is even worse in centers which provide no data. Furthermore, our data also confirmed additional etiological factors (alcohol and biliary disease) besides HTG in 43.6% of HTG-AP cases and showed a dose-dependent relation between obesity (body mass index), pre-existing DM and HTG. These data also suggest a higher incidence rate since physicians finding an etiological factor behind AP usually stop further investigation. Our data are in accordance with Scherer et al. who recommend that HTG-AP should be suspected in the case of significant alcohol consumption, poorly controlled DM and metabolic syndrome, including obesity [4]. Although our data clearly show that biliary obstruction may be associated with HTG, serum TG was measured in just 44.3% (266/601) of the biliary AP cases. Furthermore, in the case of biliary AP, there is no recommendation for TG measurement.

Our data analysis confirmed results published by Zheng et al. [12] and Zhu et al. [8] which show that HTG is significantly linked to younger age and male gender. This is not surprising, since underlying genetic abnormalities behind HTG contribute to younger manifestation and alcohol-related HTG affects male gender and younger age more [3,4,22]. In contrast, biliary etiology is accompanied by a higher rate for female gender and older population [3,23].

Diagnosing AP in the presence of HTG can be challenging due to in vitro interference between plasma TG level above 5.6 mmol/l (with grossly turbid plasma) and determination of amylase and lipase activities [24,25]. Our data confirmed a significant reduction of amylase and lipase levels with the elevation of TG. Furthermore, case reports have been published by Singh et al. [26] and Sotello et al. [27], presenting HTG-AP patients with normal amylase and lipase levels.

Our analysis has shown that local complications and organ failure were significantly increased by HTG, just as published in previous reports and a recent meta-analysis by Kiss et al. [10,13,15,28,29]. Nawaz et al. [30] confirmed that TG above 2.3 mmol/l is independently associated with persistent organ failure on a multivariate analysis controlling for age, gender, body mass index, diabetes, and alcohol etiology, whereas Szentesi et al. [31] revealed that hyperlipidemia was an independent predictive factor for local complications and new-onset DM. Although we could not confirm a significantly higher risk of pancreatic pseudocysts in the case of TG above 2.2 mmol/l, it is well known that pseudocysts usually occur more than four weeks after the onset of AP and the average hospital stay was 10.4 ± 0.3 days in our cohort [20].

Based on our data analysis, severity of AP and length of hospitalization were significantly increased by HTG [8,10,12,13,29,30,32]. Navarro et al. [33] and Goyal et al. [34] also confirmed that HTG
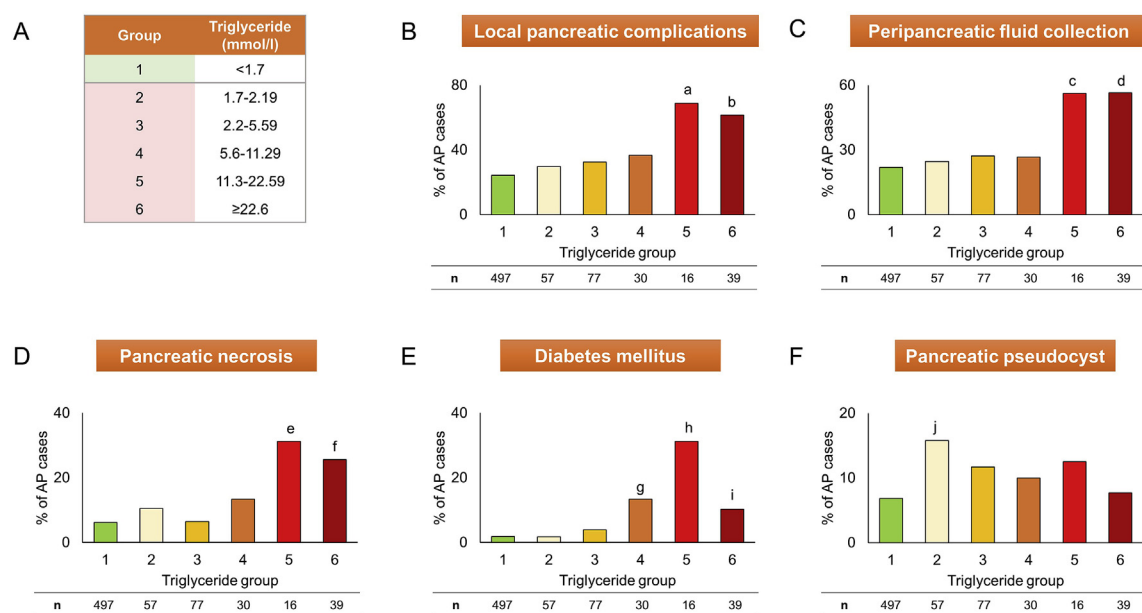

Fig. 5. Local pancreatic complications in the different triglyceride groups. A) Triglyceride groups [1–6]. **B)** Local pancreatic complications (a, b: p < 0.001). **C)** Peripancreatic fluid collection (c: p = 0.004; d: p < 0.001). **D)** Pancreatic necrosis (e: p = 0.003; f: p < 0.001). **E)** Diabetes mellitus as complication (g: p = 0.004; h: p < 0.001; i: p = 0.011). **F)** Pancreatic pseudocyst (j: p = 0.031). N numbers (n) indicate the total number of cases in each triglyceride group.
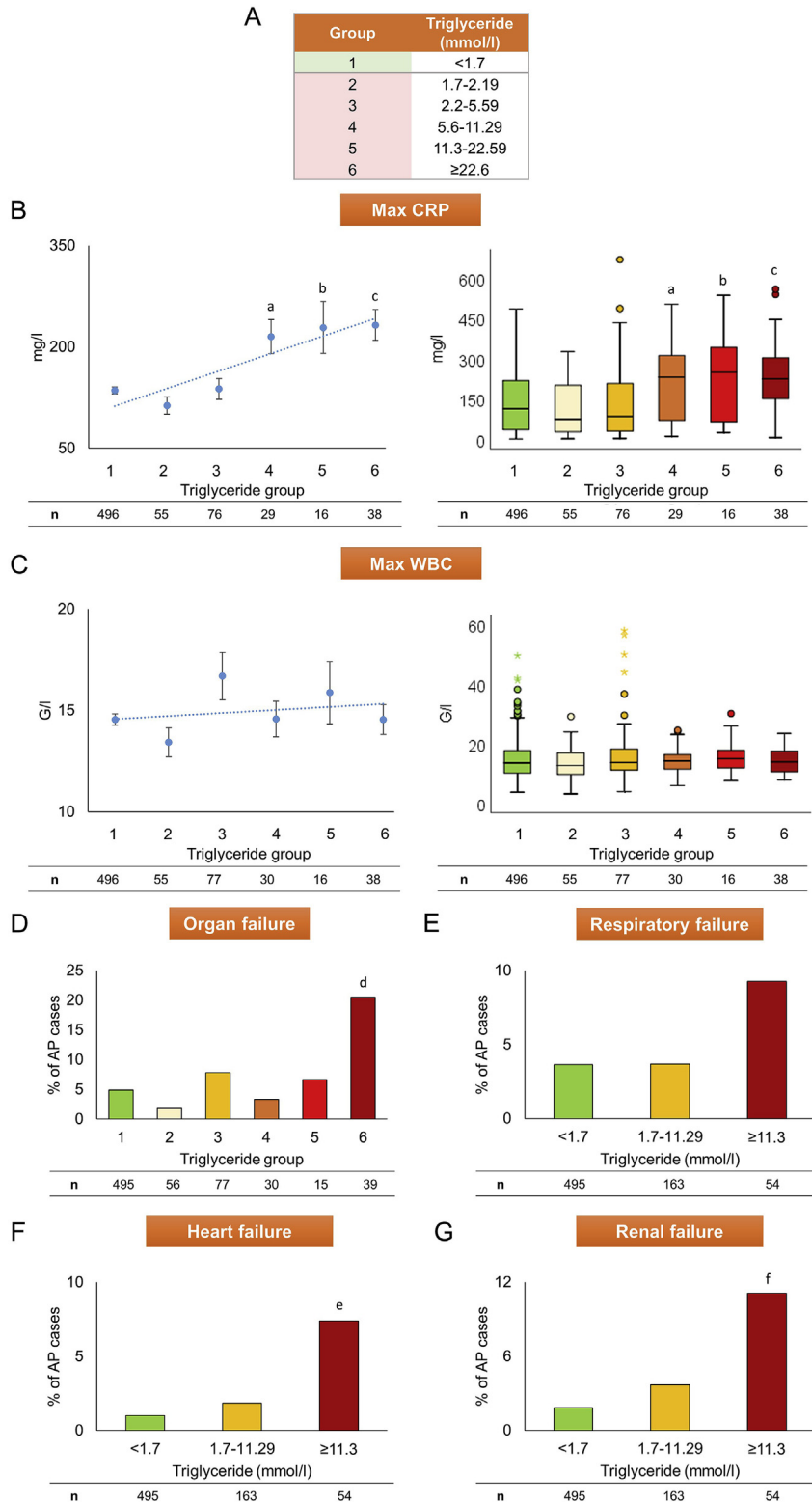
Fig. 6. Systemic inflammatory effect and organ failure in the different triglyceride groups. A) Triglyceride groups [1–6]. **B)** Maximum C-reactive protein (Max CRP, mg/l) (a, c: p < 0.001; b: p = 0.029). **C)** Maximum white blood cell count (Max WBC, G/l). **D)** Organ failure (d: p = 0.001). **E)** Respiratory failure. **F)** Heart failure (e: p = 0.007). **G)** Renal failure (f: p = 0.002). N numbers (n) indicate the total number of cases in each triglyceride group.

aggravates the severity of AP compared to biliary and alcoholic etiology, respectively. The underlying mechanism is clearly complex. Unsaturated free fatty acids (UFAs) generated from TG are responsible for cell injury by membrane lipid peroxidation, long-lasting cytosolic Ca^{2+} elevation and mitochondrial damage [35,36]. In the case of additional alcohol consumption, non-

A

Group	Triglyceride (mmol/l)	LOH day±SE (n)	Mortality event n (n)
1	<1.7	10.1±0.3 (497)	8 (496)
NORMAL TG		**10.1±0.3**	**8**
2	1.7-2.19	10.4±1.2 (57)	0 (56)
3	2.2-5.59	9.7±1.1 (77)	1 (77)
4	5.6-11.29	10.1±1.4 (30)	1 (30)
5	11.3-22.59	13.1±1.9ᵃ (16)	0 (15)
6	≥22.6	14.3±2.1ᵇ (39)	1 (38)
ELEVATED TG		**11.0±0.7**	**3**
TOTAL		**10.4±0.3**	**11**

B

Fig. 7. Outcomes in the different triglyceride (TG) groups. A) Length of hospitalization (LOH, day) and mortality (event n) (a: $p = 0.034$; b: $p = 0.001$). **B)** Severity (c: $p = 0.001$; d: $p < 0.001$). Moderately severe acute pancreatitis (AP) cases (Group 1: 22.6% (95% CI: 19%–26.6%); Group 5: 66.7% (95% CI: 38.4%–88.2%); Group 6: 47.4% (95% CI: 31.0%–64.2%)). Severe AP cases (e: $p = 0.006$). N numbers (n) indicate the total number of cases in each triglyceride group.

oxidative ethanol metabolites (fatty acid ethyl esters, FAEEs) contribute to the persistent Ca^{2+} elevation and drop of ATP level [37,38]. Besides, the raised plasma viscosity caused by hyperchylomicronemia leads to ischemia and acidosis in the pancreatic capillaries [5]. This pathologic environment results in an early trypsinogen activation and pancreatic lipase leakage, leading to further free fatty acid (FFA) release and accumulation [5,35,39]. Moreover, UFAs bring about a systemic pro-inflammation by increased mRNA production of tumor necrosis factor-alpha (TNF-α) and neutrophil chemoattractants, thereby increasing the severity of AP [36]. In our cohort, heart rate and maximum CRP were significantly raised by HTG, confirming the systemic inflammatory effect of relatively high TG level. In contrast, Pothoulakis et al. [40] and Balachandra et al. [41] reported that HTG does not worsen severity. Furthermore, Wang et al. showed that longer hospital stay was associated with higher TG level, but the difference was not significant [29].

The overall mortality of AP is ~1% based on the literature [3,12] and 1.5% in our cohort, but we could not perform a further subgroup analysis because of the low event number. Zhu et al. [8] and Deng et al. [42] confirmed that HTG-AP is accompanied by a significantly higher rate of mortality among severe AP cases compared to biliary AP and non-HTG etiology, respectively. However, Tai et al. [32] showed that mortality was similar in HTG-AP and biliary AP groups in a general AP cohort.

In our cohort, plasmapheresis was carried out in 36.4% of the HTG-AP cases. Although our data clearly suggest that the severity of AP is significantly elevated above 11.3 mmol/l TG level, the average TG level was 70.1 ± 10.0 mmol/l in patients with plasmapheresis and 85% of these cases had a TG level over 22.6 mmol/l. We could not state any further conclusion regarding the therapy because of incomplete data and lack of randomization as a result of the cohort feature of the dataset. Overall, in most cases, TG-lowering therapy, such as plasmapheresis and glucose-heparin-insulin (GLU-HEP-INS) administration, is performed above a TG level of 40 mmol/l. In order to solve this unmet need, the HPSG has initiated a prospective randomized clinical trial to investigate different lipid-lowering therapies in AP [43].

Our study has several limitations. Although all data were collected prospectively, all questions were raised retrospectively. Cases were included into the analysis with TG measurement within the first three days from admission, but unfortunately still just 50% of the entire cohort met the inclusion criteria. We attempted to minimize these limitations by comparing the epidemiological and major outcome distributions of the data analyzed and the whole cohort. We confirmed that the population under investigation represents a normal AP cohort.

Conclusion

Our results confirm that HTG dose-dependently increases the complications and severity of AP and highlights the necessity of better awareness of an accurate determination of causative and influencing risk factors in AP regardless of the etiology. Our data suggest that lipid-lowering therapy may be important clinically at a much lower TG level than we previously thought.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any conflict of interest.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2020.03.018.

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