CHALLENGES IN ACUTE PANCREATITIS: DIAGNOSIS, ETIOLOGY AND TREATMENT

Ph.D. Thesis

Dóra Mosztbacher M.D.

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Doctoral School of Theoretical Medicine, Faculty of Medicine, University of Szeged, Szeged

Dóra Mosztbacher, M.D.

Doctoral School of Theoretical Medicine, Faculty of Medicine, University of Szeged, Szeged

First Department of Paediatrics, Faculty of Medicine, Semmelweis University, Budapest

Institute for Translational Medicine, Medical School, University of Pécs, Pécs

Supervisors:

Péter Hegyi, M.D., Ph.D., D.Sc., MAE

First Department of Medicine, Faculty of Medicine, University of Szeged, Szeged

Institute for Translational Medicine, Medical School, University of Pécs, Pécs

Andrea Párniczky, M.D., Ph.D.

Heim Pál National Institute of Paediatrics, Budapest

Institute for Translational Medicine, Medical School, University of Pécs, Pécs

Doctoral School of Theoretical Medicine, Faculty of Medicine, University of Szeged, Szeged

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PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

I. Mosztbacher D, Hanák L, Farkas N, Szentesi A, Mikó A, Bajor J, et al. Hypertriglyceridemia-induced acute pancreatitis: A prospective, multicenter, international cohort analysis of 716 acute pancreatitis cases. Pancreatology. 2020;20(4):608-616. IF: 3.629

II. Mosztbacher D, Farkas N, Solymár M, Pár G, Bajor J, Szűcs Á, et al. Restoration of energy level in the early phase of acute pediatric pancreatitis. World Journal of Gastroenterology. 2017;23(6):957. IF: 3.3

III. Zsoldos F, Párniczky A, Mosztbacher D, Tóth A, Lásztity N, Hegyi P. Pain in the early phase of pediatric pancreatitis (PINEAPPLE Trial): pre-study protocol of a multinational prospective clinical trial. Digestion. 2016;93(2):121-6. IF: 2.088

SCIENTIFIC METRICS

Number of publications **related to the subject** of the thesis:	3 (2 first author)
Cumulative impact factor of publications related to the thesis:	9.017
Q1: 2, Q2: 1, Q3: -, Q4: -	
Number of **total accepted/published** articles:	14 (4 first author)
Cumulative impact factor of the published articles:	45.799
Q1: 11, Q2: 3, Q3: -, Q4: -	
Number of total citation by **Google Scholar:** https://scholar.google.com/citations?pagesize=100&user=xvok1ZAAAAAJ	245
Hirsch Index:	9
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Hirsch Index:	8

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I. LIST OF ABBREVIATIONS

AIP	autoimmune pancreatitis
ALAT	alanine transaminase
ALP	alkaline phosphatase
AP	acute pancreatitis
APA	American Pancreatic Association
APP	acute pediatric pancreatitis
ARP	acute recurrent pancreatitis
ASAT	aspartate transaminase
ATP	adenosine triphosphate
BUN	blood urea nitrogen
CFTR	cystic fibrosis transmembrane conductance regulator
CI	confidence interval
CP	chronic pancreatitis
CRP	C-reactive protein
CT	computed tomography
DM	diabetes mellitus
EBM	evidence-based medicine
EEN	early enteral nutrition
FAEEs	fatty acid ethyl esters
γGT	gamma-glutamyltransferase
HPSG	Hungarian Pancreatic Study Group
HTG	hypertriglyceridemia
HTG-AP	hypertriglyceridemia-induced acute pancreatitis
IAP	International Association of Pancreatology
ICMJE	International Committee of Medical Journal Editors
ICU	intensive care unit
IVF	intravenous fluid
LDH	lactate dehydrogenase
LOH	length of hospitalization
Max CRP	maximum C-reactive protein

Max WBC	maximum white blood cell count
MOF	multi organ failure
NPO	nil per os
PC	pancreatic cancer
PICO	participants, intervention, comparison and outcomes
PINEAPPLE	Pain IN the EArly phase of Pediatric Pancreatitis
PRISMA-P	preferred reporting items for systematic review and meta-analysis protocol
RBC	red blood cell count
ROC	receiver operating characteristic
SAP	severe acute pancreatitis
SIRS	systemic inflammatory response syndrome
sPEM	serum pancreatic enzyme measurement
TG	triglyceride
TPN	total parenteral nutrition
US	ultrasonography
WBC	white blood cell count
WHO	World Health Organization

II. GENERAL INTRODUCTION

II.1. Challenges in acute pancreatitis

Acute pancreatitis (AP) is one of the most common reasons for gastrointestinal hospitalizations in adults (1, 2). AP has an annual incidence of 13-45 per 100,000 persons and is increasing worldwide as a result of better awareness of the disease and obesity-related gallstone formation and hypertriglyceridemia (HTG) (3, 4). AP represents a remarkable disease burden for healthcare systems and patients' quality of life (5). This burden is further increased by the development of a severe disease course which is accompanied by increased length of hospitalization (LOH), elevated rate of complications, intensive care unit (ICU) stay, the need for invasive interventions, and mortality (5).

According to the revised Atlanta classification, the severity of AP is categorized as mild, moderately severe, and severe (6). Severe acute pancreatitis (SAP) develops in 15-20% of AP cases (1, 6); however, better understanding of the underlying mechanism may provide possibilities for decreasing severity. Although the pathomechanism of AP is still unclear, the most common etiological factors such as bile acids (7-10), fatty acids generated from TG, and non-oxidative ethanol metabolites (fatty acid ethyl esters, FAEEs) (11-16) were shown to cause mitochondrial damage with resultant adenosine triphosphate (ATP) and energy depletion in the exocrine pancreas. In addition, HTG contributes to systemic pro-inflammation and local hypoxia-induced acidosis caused by hyperviscosity (17, 18). According to these data, HTG was shown to increase the risk of the development of SAP (19-26) and aggravate the severity of AP compared to alcoholic and biliary etiologies (27, 28). In contrast, early enteral nutrition (EEN) as early ATP restoration has been shown to be beneficial in AP compared with nil per os (NPO) therapy and total parenteral nutrition (TPN) regardless of the severity of AP (29-34). Accordingly, initial and appropriate lipid-lowering therapy may be beneficial in the case of hypertriglyceridemia-induced acute pancreatitis (HTG-AP), whereas energy restoration via enteral nutrition may play a key part of the therapy in all cases of AP. However, detailed analysis and evidence-based therapy for HTG-AP is missing, and despite the fact that the clinical characteristics of AP differ by age, nutritional guidelines for childhood-onset AP are limited and adopted from the adult protocols (35-41).

Not only therapeutic, but also diagnostic pediatric guidelines for AP are adopted from adult protocols (37, 38). Some of these guidelines are based on the consensus of expert pediatric pancreatologists, but not on evidence-based pediatric data (42, 43). The recently published APP

guideline has low evidence as well (37). It is not surprising that the overall incidence of acute pediatric pancreatitis (APP) is lower compared to the adult population (1 per 100,000 persons or even less versus 13-45 per 100,000); however, two major studies have proven that the real incidence of APP (3.6–13.2 per 100,000) is much higher than we previously thought (3, 44-46). The reason is probably multifactorial, but it has been published by Morinville et al., that diagnostic workup influences the incidence of the disease (44). Their data showed that increased pancreatic enzyme testing could account for 94% of the change in all AP admissions in childhood, suggesting that APP is an underdiagnosed disease.

In contrast with the current diagnostic practice, there is significant importance in recognizing and diagnosing AP in childhood. Acute recurrent pancreatitis (ARP) develops in 10-35% of children following an initial AP (38, 47, 48), and idiopathic ARP is likely to be a transition phase between AP and chronic pancreatitis (CP) (49, 50) with 1-3.79 years of median time (51, 52). However, based on a multicenter study, 16% of the pediatric CP patients had no documented prior episode of ARP (51). ARP and CP are of great importance because both are associated with a notable disease burden by pain, exocrine and endocrine dysfunction, frequent ER visits, hospitalizations, and school absenteeism (51). The most common risk factors of CP are alcohol and smoking in adults; however these are uncommon in children (53). Pediatric ARP and CP are frequently associated with pancreatobiliary obstructions in ~30% and genetic abnormalities in up to 73% (51, 54, 55). Genetic involvement was shown to carry the fastest rate of progression from AP to CP (55). These data highlight the necessity of an appropriate and evidence-based diagnostic guideline for childhood-onset AP.

II.2. Motivation for my scientific work

As a pediatric resident I recognized the importance of evidence-based clinical practice compared to decisions based on the experiences of individual physicians. First, we aimed to estimate the real incidence of APP and improve the diagnostic workup of childhood onset AP by establishing an international, multicenter observational clinical trial called PINEAPPLE (Pain IN the EArly phase of Pediatric Pancreatitis) (56). Furthermore, we reviewed the literature to analyze the effect of EEN versus NPO therapy on the outcome of APP and aggregate the information to increase the statistical power of nutritional AP guidelines in childhood compared to individual studies (57). Finally, we performed a cohort analysis of 716 adult AP cases to investigate the dose-dependent effect of HTG on AP and provide detailed data for further prospective randomized clinical trials (58, 59).

III. DOSE-DEPENDENT EFFECT OF HYPERTRIGLYCERIDEMIA ON ACUTE PANCREATITIS

III.1. Introduction

HTG affects 10–30% of the general adult population (60, 61). 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) (3, 61, 62). Regarding environmental factors, alcohol, positive-energy balanced diet, obesity, uncontrolled diabetes mellitus (DM), renal diseases, pregnancy, hypothyroidism, and medications (e.g., estrogen, retinoids, thiazides, and β-blockers) were shown to be responsible for a raised TG level, usually with the interaction of genetic susceptibility (18, 63).

HTG is the third most common cause of AP, and is responsible for up to 15% of AP cases (26, 64, 65). According to the definition, the majority of experts agree that AP related to TG above 5.6 mmol/l should be considered as suspected HTG-AP, and AP associated with TG over 11.3 mmol/l is confirmed as HTG-AP (24, 62). 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 this rises to 10–20% if TG elevates to over 22.6 mmol/l (62). HTG-AP is of great importance for several reasons: i) it has shown a rising incidence worldwide as a result of increasing obesity-related dyslipidemia (4, 25); ii) it raises the risk of severe AP and related complications (20, 24-26, 66-68); and iii) there is no evidence-based therapy for it (35, 36, 39, 40).

III.2. Aims

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.

III.3. 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 hours of admission. AP was diagnosed based on International Association of Pancreatology/American Pancreatic Association (IAP/APA) and HPSG evidence-based guidelines (35, 36). Participating countries are shown in Fig. 1.

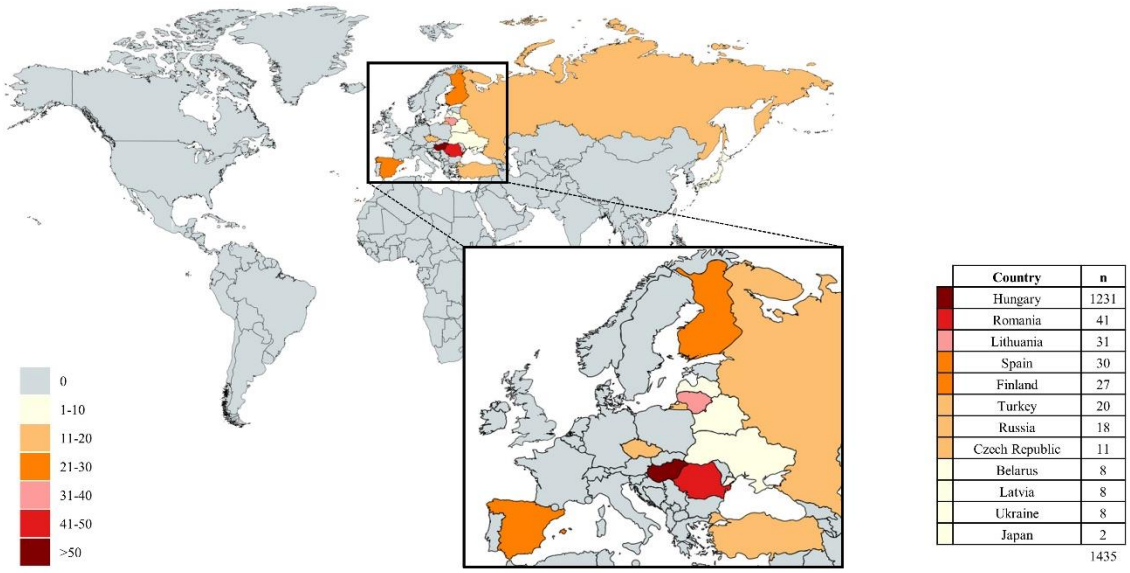
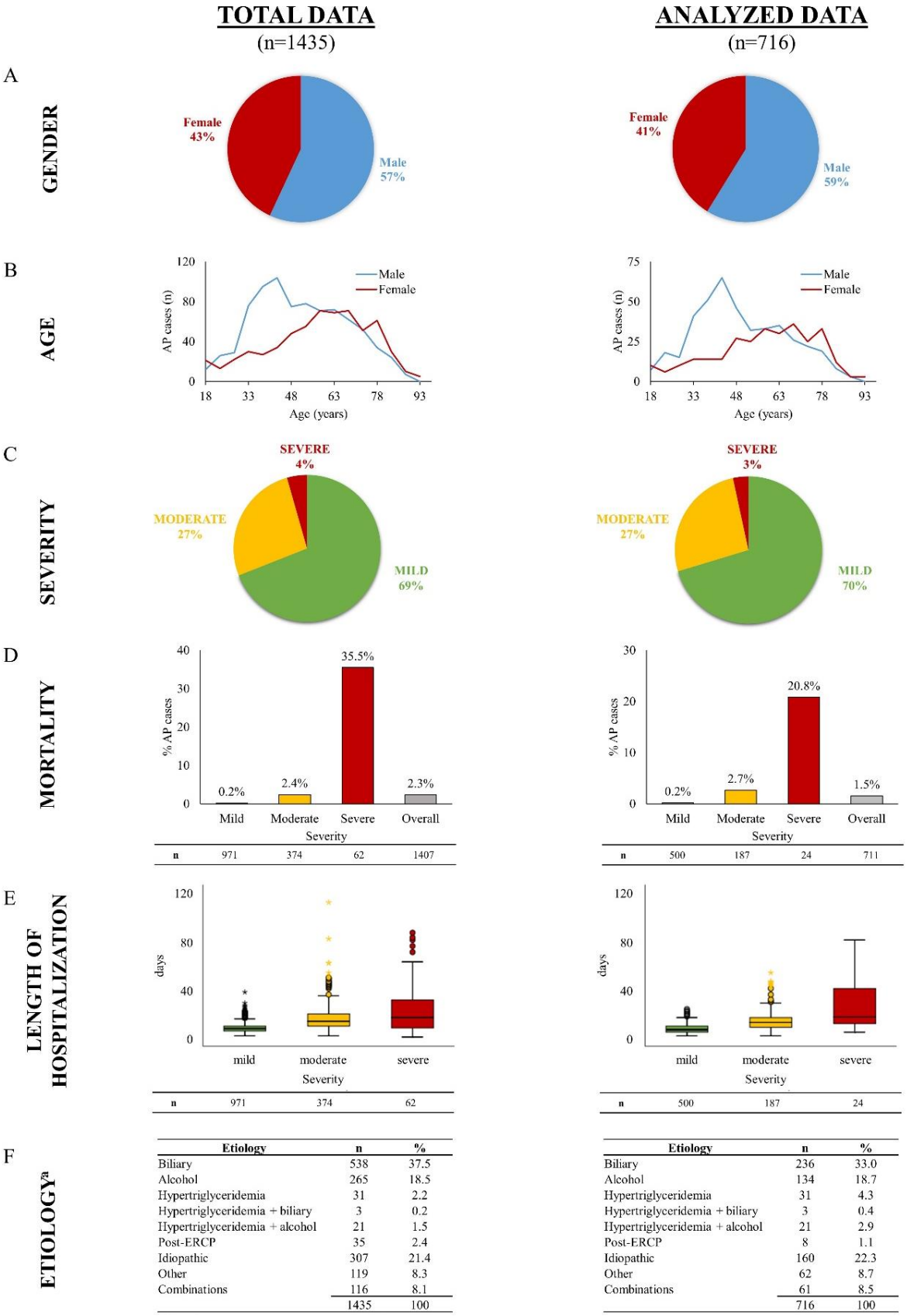


Fig. 1. Participating countries. Distribution of participating countries and number of enrolled acute pancreatitis cases (n=1435).

The threshold of the normal TG value was determined at 1.7 mmol/l (63). Six groups were established based on the Endocrine Society Clinical Practice Guideline and previously published clinical data related to HTG-AP (62, 63): 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 the 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. 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 (6). The 716 cases investigated showed the same epidemiological and major outcome distribution as the total cohort (1435 cases), demonstrating that our patient population represents a normal AP cohort (Fig. 2).



Etiology	n	%
Biliary	538	37.5
Alcohol	265	18.5
Hypertriglyceridemia	31	2.2
Hypertriglyceridemia + biliary	3	0.2
Hypertriglyceridemia + alcohol	21	1.5
Post-ERCP	35	2.4
Idiopathic	307	21.4
Other	119	8.3
Combinations	116	8.1
	1435	100

Etiology	n	%
Biliary	236	33.0
Alcohol	134	18.7
Hypertriglyceridemia	31	4.3
Hypertriglyceridemia + biliary	3	0.4
Hypertriglyceridemia + alcohol	21	2.9
Post-ERCP	8	1.1
Idiopathic	160	22.3
Other	62	8.7
Combinations	61	8.5
	716	100

Fig. 2. Representation of enrolled patients (n=716) compared to the entire cohort (n=1435). A) Gender distribution of acute pancreatitis (AP) cases. **B)** Age distribution of AP cases in males and females. **C)** Severity

distribution of AP cases. **D)** Mortality of AP cases in the different severity groups. **E)** Length of hospitalization of AP cases in the different severity groups. **F)** Etiology distribution of AP cases (a: p=0.007). ERCP=endoscopic retrograde cholangiopancreatography. N numbers (n) indicate the total number of cases in each triglyceride group.

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.

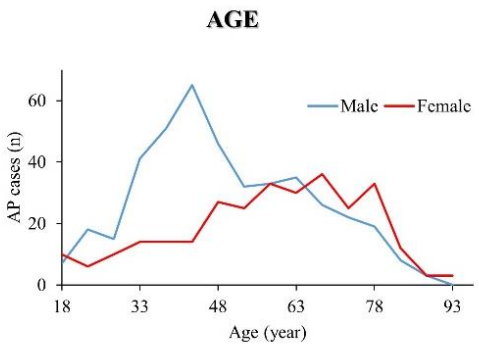
Statistical analysis

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 categorical 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 (≤ 0.05) was determined as statistically significant. All analyses were performed using IBM-SPSS Statistical Software Version 25 (IBM Corporation, Armonk, NY, USA).

III.4. 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. 3A-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 (24, 63). 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. 3D).

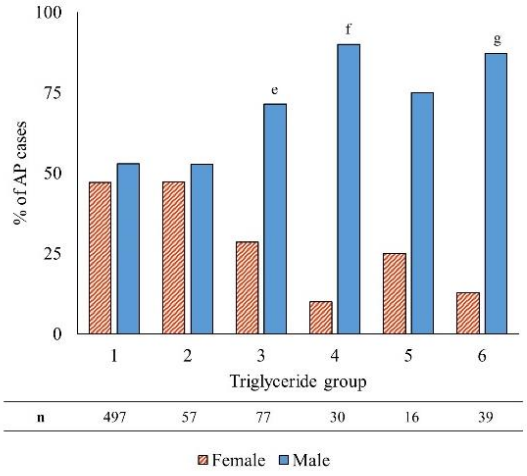
A



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



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	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. 3. 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. N numbers (n) indicate the total number of cases in each triglyceride group.

Data from patients' medical history revealed that HTG is significantly and dose-dependently linked to obesity and DM (Fig. 4B, C); however, there is no relation to CP and the Charlson comorbidity index (CCI) (69) (Fig. 4A, D). The amount of previous AP in the medical history was higher in the HTG group compared to the normal TG group (Fig. 4A).

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)

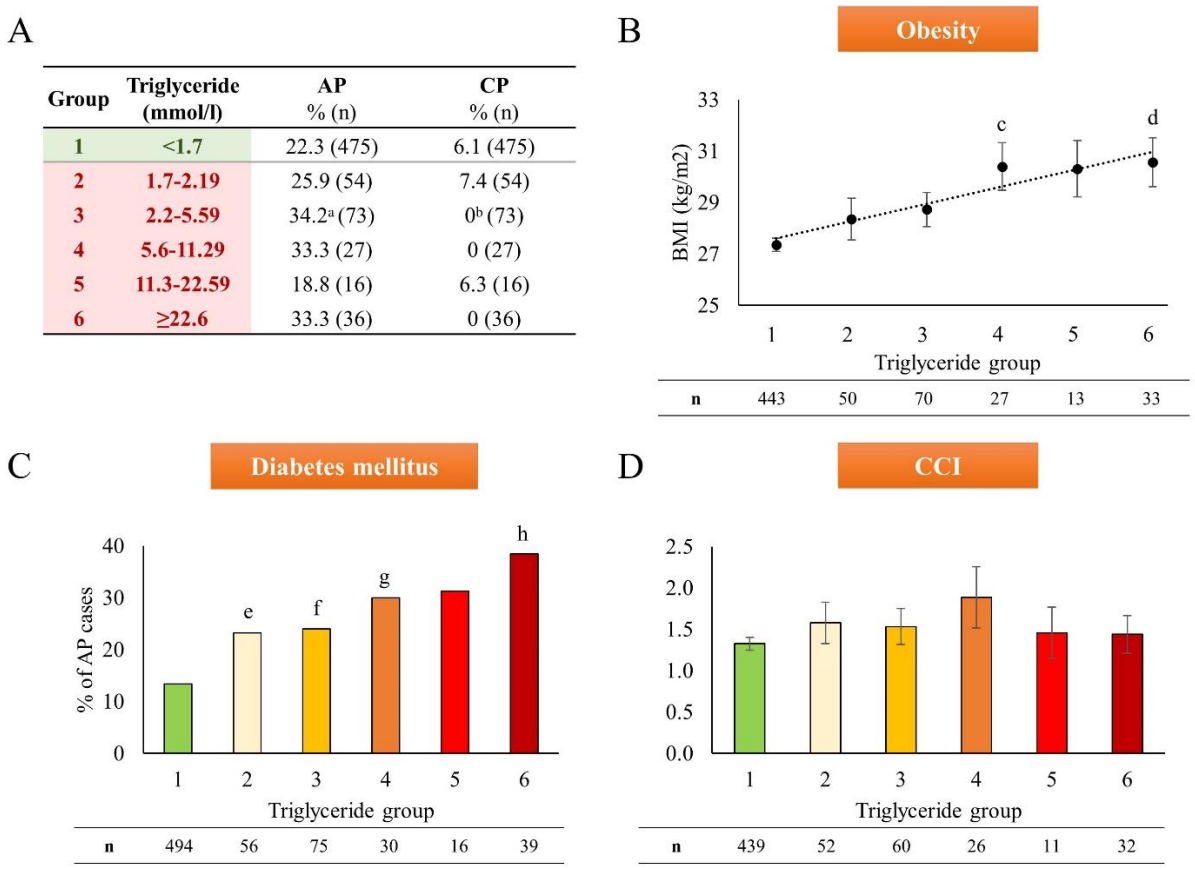


Fig. 4. Patients' medical history of triglyceride groups. A) Acute pancreatitis (AP) and chronic pancreatitis (CP) in patients' medical history (a: p=0.026; b: p=0.023). **B)** Obesity (body mass index (BMI), kg/m^2) (c: p=0.006; d: p=0.001). **C)** Diabetes mellitus in medical history (e: p=0.046; f: 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.

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. 5A, B). However, HTG was significantly related to increased heart rate (Fig. 5C). Regarding 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 in parallel with TG level (Fig. 6).

A

Group	Triglyceride (mmol/l)	Abdominal pain % (n)	Abdominal pain Duration before admission hour±SE (n)	Abdominal pain 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**

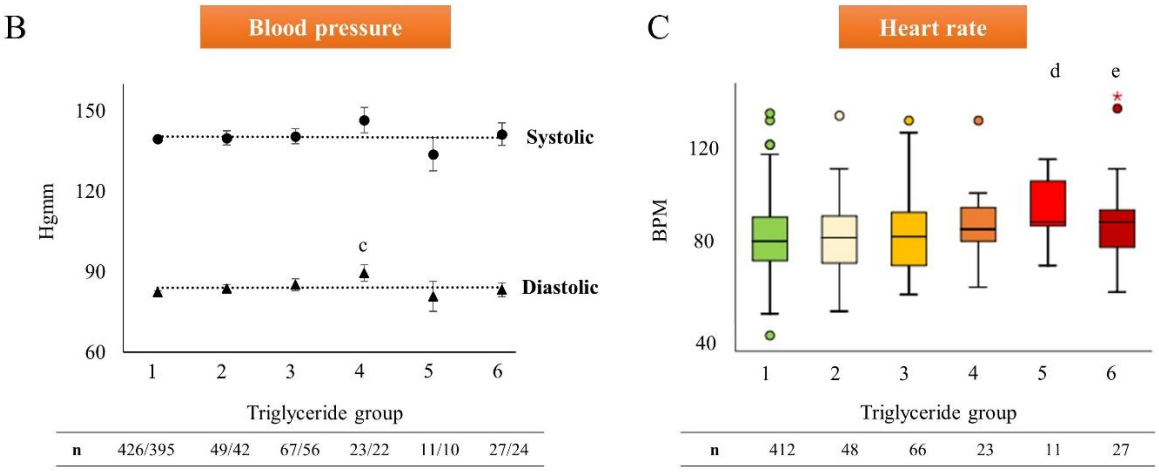


Fig. 5. Symptoms and physical findings on admission in the different triglyceride (TG) groups. A) Incidence, duration before admission and intensity of pain. Nausea, vomiting, abdominal tenderness and abdominal guarding (a: p=0.025; b: p=0.036). **B)** Systolic and diastolic blood pressure (Hgmm) (c: 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.

On admission, laboratory parameters consistent with cholestasis suggested that HTG is less common in cases with biliary etiology (Fig. 7). The parallel rise in gamma-glutamyltransferase (γGT) and TG levels confirms that alcohol consumption is linked to HTG (Fig. 7D). White blood cell count (WBC), thrombocyte, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, and potassium had no significant relation to HTG (Fig. 8).

The rate of local complications, including peripancreatic fluid collection, pancreatic necrosis, and DM was significantly and dose-dependently increased with TG level (Fig. 9B-E); however, pancreatic pseudocysts did not show significant differences between the investigated groups above 2.2 mmol/l (Fig. 9F).

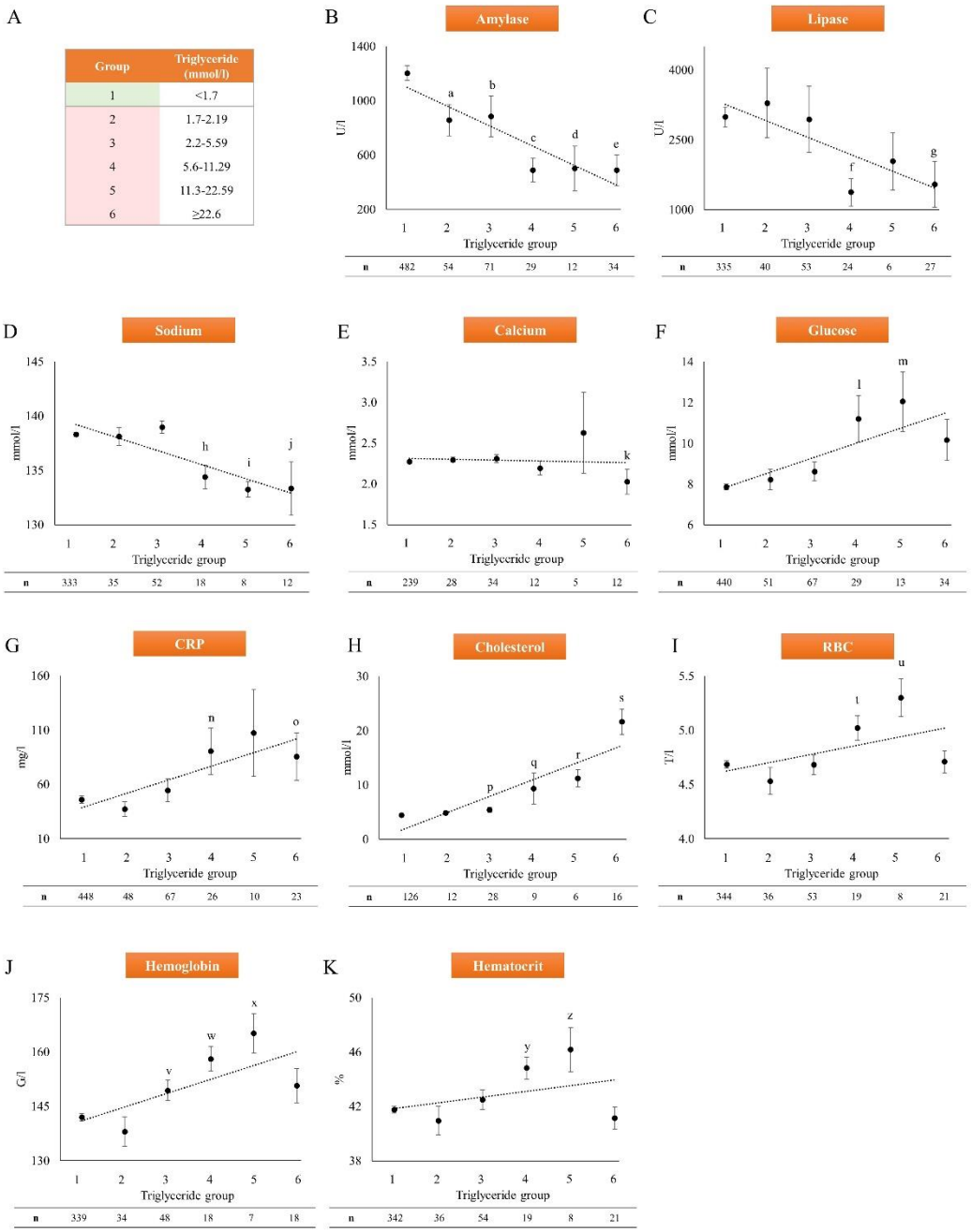


Fig. 6. Laboratory parameters on admission significantly associated with hypertriglyceridemia. A) Triglyceride groups (1–6). **B)** Amylase (U/l) (a: p=0.036; b, c, e: p=<0.001; d: p=0.009). **C)** Lipase (U/l) (f: p=0.017; g: p=0.001). **D)** Sodium (mmol/l) (h, i: p=<0.001; j: p=0.005). **E)** Calcium (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.

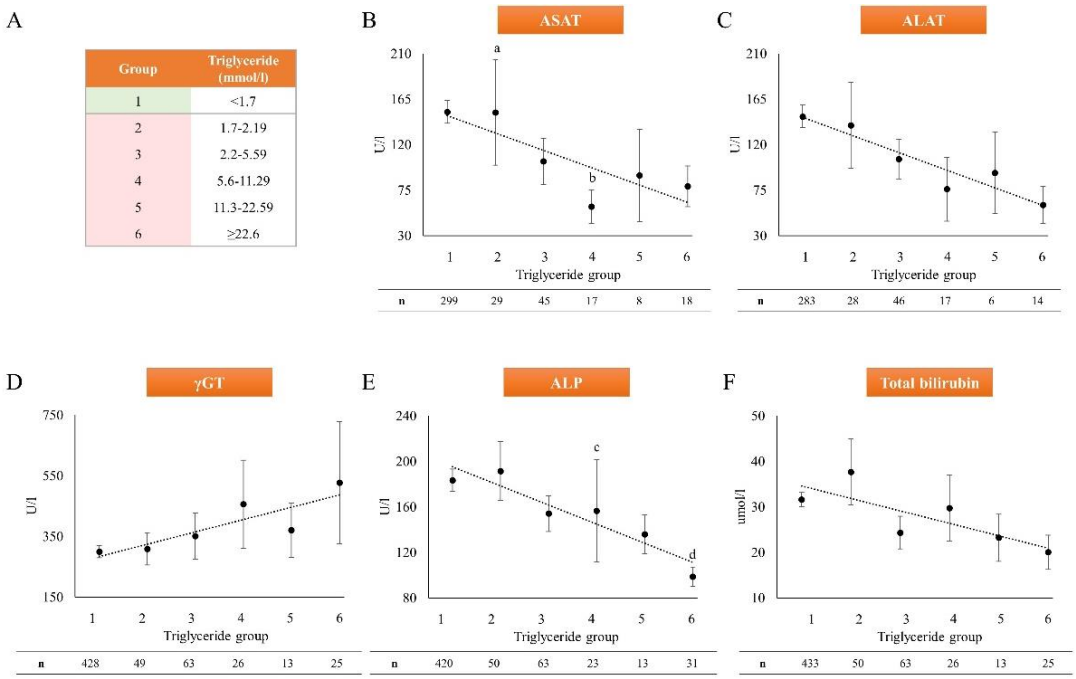


Fig. 7. Laboratory parameters representing hepatobiliary system on admission in the different triglyceride groups. A) Triglyceride groups (1–6). **B)** Aspartate transaminase (ASAT, U/l) (a: p=0.050; b: p=0.037). **C)** Alanine transaminase (ALAT, U/l). **D)** Gamma-glutamyltransferase (γGT, U/l). **E)** Alkaline phosphatase (ALP, U/l) (c: p=0.028; d: p=0.003). **F)** Total bilirubin (umol/l). N numbers (n) indicate the total number of cases in each triglyceride group.

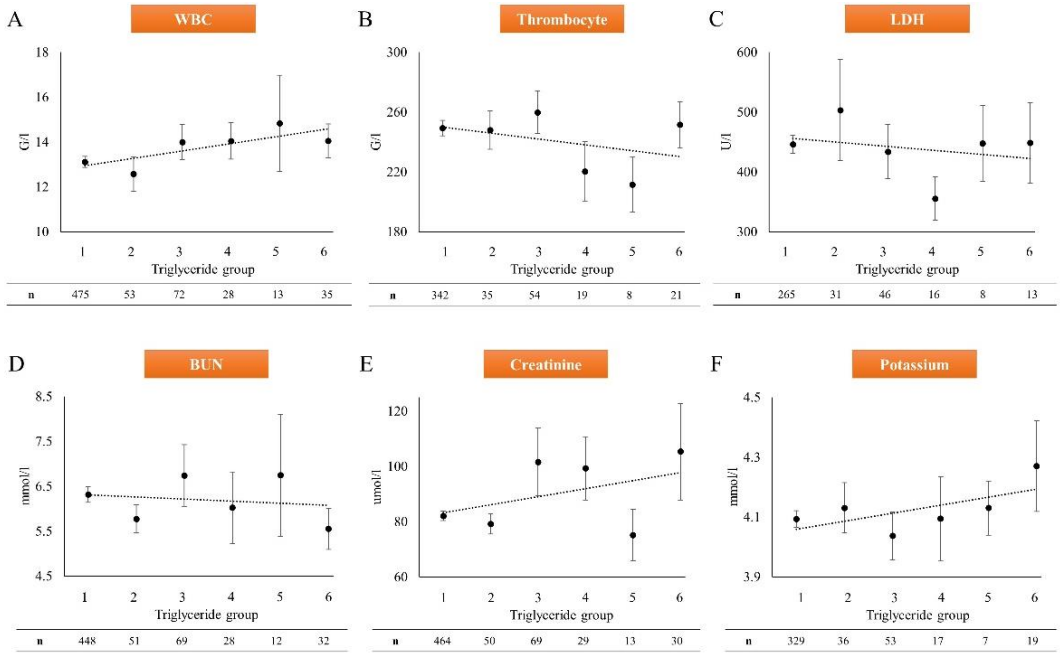


Fig. 8. Laboratory parameters on admission without significant alterations with hypertriglyceridemia. A) White blood cell count (WBC, G/l). **B)** Thrombocyte (G/l). **C)** Lactate dehydrogenase (LDH, U/l). **D)** Blood urea nitrogen (BUN, mmol/l). **E)** Creatinine (umol/l). **F)** Potassium (mmol/l). N numbers (n) indicate the total number of cases in each triglyceride group.

Organ failure, including heart and renal failure, and maximum CRP level were significantly and dose-dependently raised by TG level (Fig. 10A, C, E, F); however, respiratory failure and maximum WBC count did not show any significant differences by HTG (Fig. 10B, D).

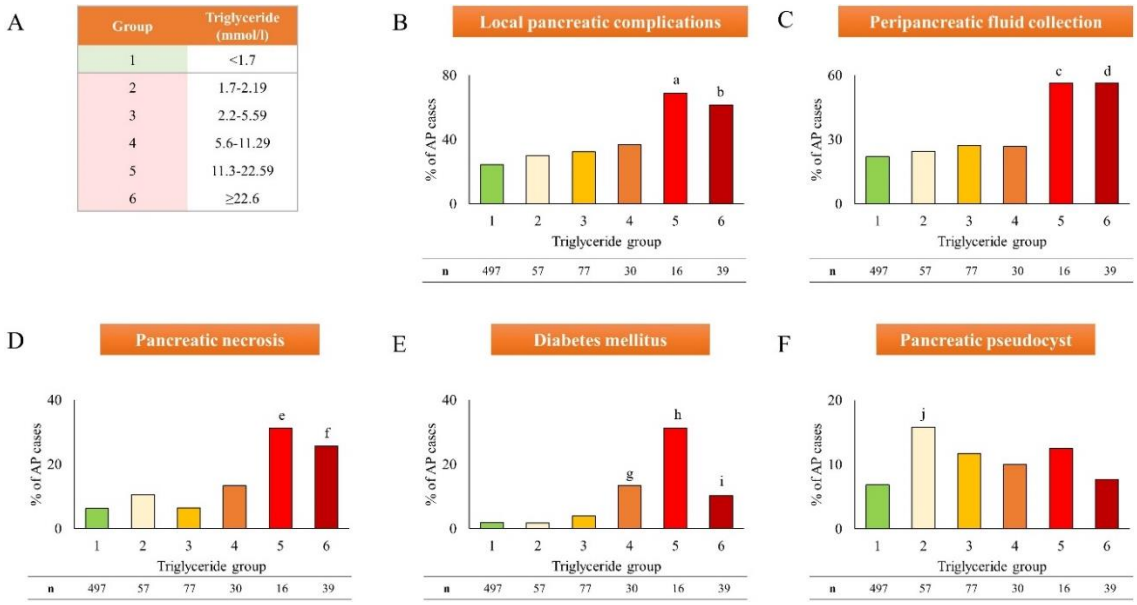


Fig. 9. Local pancreatic complications in the different triglyceride groups. A) Triglyceride groups (1–6). **B)** Local pancreatic complications (a, b: p<0.001). **C)** Peripancreatic fluid collection (c: p=0.004; d: p<0.001). **D)** Pancreatic necrosis (e: p=0.003; f: p<0.001). **E)** Diabetes mellitus as complication (g: p=0.004; h: p<0.001; i: p=0.011). **F)** Pancreatic pseudocyst (j: p=0.031). AP=acute pancreatitis. N numbers (n) indicate the total number of cases in each triglyceride group.

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. 11A, B). Due to the low event rate, the effect of HTG on mortality could not be determined (Fig. 11A). Detailed values of charts and statistical parameters are shown in Tables 1 and 2. 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.

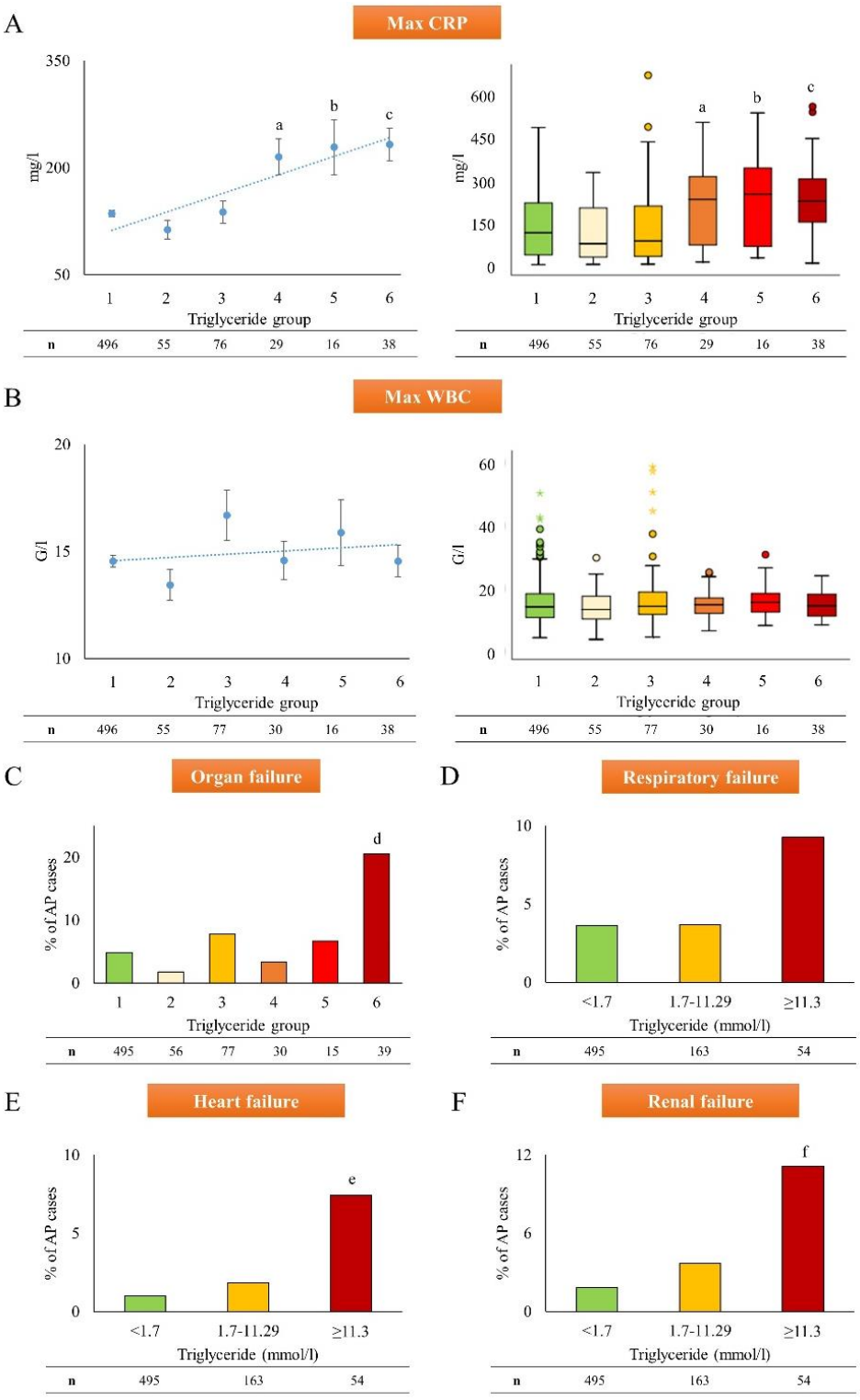


Fig. 10. Systemic inflammatory effect and organ failure in the different triglyceride groups. A) Maximum C-reactive protein (Max CRP, mg/l) (a, c: p<0.001; b: p=0.029). **B)** Maximum white blood cell count (Max WBC, G/l). **C)** Organ failure (d: p=0.001). **D)** Respiratory failure. **E)** Heart failure (e: p=0.007). **F)** Renal failure (f: p=0.002). AP=acute pancreatitis. N numbers (n) indicate the total number of cases in each triglyceride group. 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; Group 6: ≥22.6 mmol/l.

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±1.9[a] (16)	0 (15)
6	≥22.6	14.3±2.1[b] (39)	1 (38)
ELEVATED TG		11.0±0.7	3
TOTAL		10.4±0.3	11

B

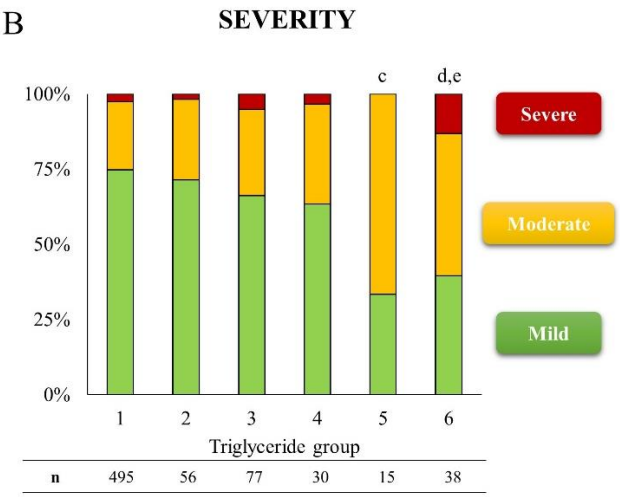


Fig. 11. Outcomes in the different triglyceride (TG) groups. A) Length of hospitalization (LOH, day) and mortality (n) (a: p=0.034; b: p=0.001). **B)** Severity (c: p=0.001; d: p<0.001). Moderately severe acute pancreatitis (AP) cases (Group 1: 22.6% (95% CI: 19%–26.6%); Group 5: 66.7% (95% CI: 38.4%–88.2%); 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.

III.5. Discussion

HTG-AP has grown in incidence and importance. According to the previously published literature (64, 65), 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 of admission, and most probably this rate is even lower in centers that 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 do not undertake 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 (62). 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. (25) and Zhu et al. (26) 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 the male gender and younger ages more (3, 62, 70). In contrast, biliary etiology is accompanied by a higher rate for the female gender and older population (3, 71).

Diagnosing AP in the presence of HTG can be challenging due to in vitro interference between plasma TG levels above 5.6 mmol/l (with grossly turbid plasma) and determination of amylase and lipase activities (72, 73). 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. (74) and Sotello et al. (75), 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, as published in previous reports and a recent meta-analysis by Kiss et al. (19, 20, 23, 24, 67). Nawaz et al. (21) 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. (76) 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 (6).

Based on our data analysis, severity of AP and LOH were significantly increased by HTG (20-26). Navarro et al. (28) and Goyal et al. (27) also confirmed that HTG 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 (17, 77). In the case of additional alcohol consumption, non-oxidative ethanol metabolites FAEEs contribute to the persistent Ca^{2+} elevation and drop in ATP level (11, 78). Additionally, the raised plasma viscosity caused by hyperchylomicronemia leads to ischemia and acidosis in the pancreatic capillaries (18). This pathologic environment results in an early trypsinogen activation and pancreatic lipase leakage, leading to further free fatty acid (FFA) release and accumulation (18, 77, 79). Moreover, UFAs

bring about a systemic pro-inflammation through increased mRNA production of tumor necrosis factor-alpha (TNF-α) and neutrophil chemoattractants, thereby increasing the severity of AP (17). In our cohort, heart rate and maximum CRP were significantly raised by HTG, suggesting the systemic inflammatory effect of relatively high TG levels. In contrast, Pothoulakis et al. (80) and Balachandra et al. (81) 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 (23).

The overall mortality of AP is ~1% based on the literature (3, 25) and 1.5% in our cohort, but we could not perform a further subgroup analysis because of the low event number. Zhu et al. (26) and Deng et al. (82) 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. (22) 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 the 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 conclusions regarding the therapy because of incomplete data and lack of randomization as a result of the cohort feature of the dataset. Overall and 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 (58).

Our study has several limitations. Although all data were collected prospectively, all questions were raised retrospectively. Cases were included in the analysis with TG measurement within the first three days of admission, but unfortunately only 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.

III.6. Conclusion

Our results confirm that HTG dose-dependently increases the complications and severity of AP, and highlight 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.

Table 1. Values. Values on charts in the different triglyceride groups (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; Group 6: ≥22.6 mmol/l). DM=diabetes mellitus.

Parameter	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
FIG. 3						
Gender, male %	52.9	52.6	71.4	90.0	75.0	87.2
FIG. 4						
Obesity, body mass index, kg/m^2 (SE)	27.4 (0.3)	28.4 (0.8)	28.7 (0.7)	30.4 (0.9)	30.3 (1.1)	30.6 (1.0)
DM in the personal history, %	13.4	23.2	24.0	30.0	31.3	38.5
Charlson comorbidity index (CCI) (SE)	1.3 (0.1)	1.6 (0.2)	1.5 (0.2)	1.9 (0.4)	1.5 (0.3)	1.4 (0.2)
FIG. 5						
Blood pressure – systolic, Hgmm (SE)	139.5 (1.1)	139.9 (2.6)	140.5 (2.8)	146.5 (4.7)	133.8 (6.3)	141.3 (4.2)
Blood pressure – diastolic, Hgmm (SE)	82.2 (0.7)	83.7 (1.5)	85.2 (2.2)	89.5 (3.1)	80.8 (5.6)	83.3 (2.6)
Heart rate, BPM (SE)	81.6 (0.7)	82.3 (2.3)	83.5 (2.1)	87.0 (2.8)	93.3 (4.1)	89.3 (3.4)
FIG. 6						
Amylase, U/l (SE)	1203.2 (55.6)	857.2 (114.8)	884.7 (151.3)	488.6 (86.7)	501.6 (163.9)	488.4 (113.5)
Lipase, U/l (SE)	2993.2 (209.5)	3290.7 (741.6)	2942.5 (708.9)	1376.5 (298.9)	2040.2 (619.3)	1543.6 (485.4)
Sodium, mmol/l (SE)	138.3 (0.2)	138.1 (0.8)	139.0 (0.6)	134.4 (1.1)	133.3 (0.7)	133.3 (2.5)
Calcium, mmol/l (SE)	2.3 (0)	2.3 (0)	2.3 (0)	2.2 (0.1)	2.6 (0.5)	2.0 (0.2)
Glucose, mmol/l (SE)	7.9 (0.1)	8.2 (0.5)	8.6 (0.5)	11.2 (1.1)	12.1 (1.5)	10.2 (1.0)
C-reactive protein (CRP), mg/l (SE)	46.0 (3.2)	37.2 (6.9)	54.5 (10.5)	90.5 (21.2)	107.3 (39.7)	85.5 (21.9)
Cholesterol, mmol/l (SE)	4.4 (0.1)	4.9 (0.2)	5.4 (0.4)	9.3 (2.9)	11.2 (1.6)	21.6 (2.4)
Red blood cell count (RBC), T/l (SE)	4.7 (0)	4.5 (0.1)	4.7 (0.1)	5.0 (0.1)	5.3 (0.2)	4.7 (0.1)
Hemoglobin, G/l (SE)	142.0 (1.0)	138.0 (4.0)	149.4 (2.8)	158.1 (3.4)	165.1 (5.4)	150.7 (4.7)
Hematocrit, % (SE)	41.8 (0.3)	41.0 (1.1)	42.5 (0.7)	44.8 (0.8)	46.2 (1.6)	41.1 (0.8)
FIG. 7						
Aspartate transaminase (ASAT), U/l (SE)	152.4 (11.4)	151.9 (52.0)	103.5 (22.7)	58.6 (16.9)	89.5 (45.7)	78.7 (20.2)
Alanine transaminase (ALAT), U/l (SE)	147.8 (11.2)	139.2 (42.7)	105.7 (19.5)	76.0 (31.6)	92.0 (40.3)	60.2 (18.2)
Gamma-glutamyltransferase(γGT), U/l (SE)	299.7 (20.3)	308.8 (53.3)	351.1 (76.9)	455.8 (145.6)	370.4 (89.6)	526.7 (201.0)
Alkaline phosphatase (ALP), U/l (SE)	183.4 (9.8)	191.5 (25.9)	154.2 (15.8)	156.6 (45.0)	135.9 (17.2)	98.7 (8.5)
Total bilirubin, umol/l (SE)	31.6 (1.6)	37.7 (7.2)	24.4 (3.6)	29.7 (7.3)	23.2 (5.2)	20.0 (3.8)
FIG. 8						
White blood cell count (WBC), G/l (SE)	13.1 (0.2)	12.6 (0.8)	14.0 (0.8)	14.0 (0.8)	14.8 (2.1)	14.0 (0.8)
Thrombocyte, G/l (SE)	249.3 (5.2)	248.0 (12.9)	259.8 (14.1)	220.2 (20.0)	211.5 (18.3)	251.6 (15.4)
Lactate dehydrogenase (LDH), U/l (SE)	446.2 (15.1)	503.1 (84.5)	433.9 (45.1)	355.3 (36.2)	447.6 (63.2)	448.3 (67.2)
Blood urea nitrogen (BUN), mmol/l (SE)	6.3 (0.2)	5.8 (0.3)	6.7 (0.7)	6.0 (0.8)	6.7 (1.4)	5.6 (0.5)
Creatinine, umol/l (SE)	82.1 (1.7)	79.1 (3.6)	101.6 (12.2)	99.3 (11.4)	75.1 (9.3)	105.3 (17.4)
Potassium, mmol/l (SE)	4.1 (0)	4.1 (0.1)	4.0 (0.1)	4.1 (0.1)	4.1 (0.1)	4.3 (0.2)
FIG. 9						
Local pancreatic complications, %	24.3	29.8	32.5	36.7	68.8	61.5
Peripancreatic fluid collection, %	21.9	24.6	27.3	26.7	56.3	56.4
Pancreatic necrosis, %	6.2	10.5	6.5	13.3	31.3	25.6
DM as complication, %	1.8	1.8	3.9	13.3	31.3	10.3
Pancreatic pseudocyst, %	6.8	15.8	11.7	10.0	12.5	7.7

Table 1 (continued)

FIG. 10						
Maximum C-reactive protein (CRP), mg/l (SE)	135.8 (5.0)	113.2 (13.1)	137.8 (15.5)	215.2 (25.3)	228.8 (38.3)	232.4 (22.7)
Maximum white blood cell count (WBC), G/l (SE)	14.6 (0.3)	13.4 (0.7)	16.7 (1.2)	14.6 (0.9)	15.9 (1.5)	14.5 (0.7)
Organ failure, %	4.8	1.8	7.8	3.3	6.7	20.5
Respiratory failure, %	3.6	3.7			9.3	
Heart failure, %	1.0	1.8			7.4	
Renal failure, %	1.8	3.7			11.1	
FIG. 11						
Mild acute pancreatitis, %	74.7	71.4	66.2	63.3	33.3	39.5
Moderately severe acute pancreatitis, %	22.6	26.8	28.6	33.3	66.7	47.4
Severe acute pancreatitis, %	2.6	1.8	5.2	3.3	0	13.2

Table 2. Statistics. P-values of parameters analyzed in the different triglyceride (TG) groups (Normal: <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; Group 6: ≥22.6 mmol/l). Significant differences ($p \leq 0.05$) are in grey and emboldened. AP=acute pancreatitis; CP=chronic pancreatitis; DM=diabetes mellitus.

Parameter	Normal vs Group 2	Normal vs Group 3	Normal vs Group 4	Normal vs Group 5	Normal vs Group 6
FIG. 3					
Age	0.290	**<0.001**	**0.010**	0.075	**<0.001**
Gender	0.967	**0.002**	**<0.001**	0.081	**<0.001**
FIG. 4					
AP in the medical history	0.548	**0.026**	0.185	1.000	0.130
CP in the medical history	0.764	**0.023**	0.391	1.000	0.251
Obesity (body mass index)	0.229	0.056	**0.006**	0.057	**0.001**
DM in the medical history	**0.046**	**0.016**	**0.026**	0.058	**<0.001**
Charlson comorbidity index (CCI)	0.247	0.345	0.085	0.276	0.215
FIG. 5					
Abdominal pain	0.583	0.602	1.000	1.000	1.000
Duration of abdominal pain before admission	0.051	**0.025**	0.135	0.420	0.226
Intensity of abdominal pain	0.656	0.850	0.903	0.824	0.671
Nausea	0.144	0.615	0.413	0.544	0.288
Vomiting	0.788	0.119	0.691	0.618	0.222
Abdominal tenderness	0.348	0.701	**0.036**	0.146	0.608
Abdominal guarding	0.844	0.618	0.512	0.661	0.784
Blood pressure – systolic	0.902	0.742	0.159	0.431	0.697
Blood pressure – diastolic	0.476	0.215	**0.012**	0.734	0.712
Heart rate	0.758	0.334	0.087	**0.010**	**0.010**
FIG. 6					
Amylase	**0.036**	**<0.001**	**<0.001**	**0.009**	**<0.001**
Lipase	0.220	0.117	**0.017**	0.825	**0.001**
Sodium	0.929	0.072	**<0.001**	**<0.001**	**0.005**
Calcium	0.509	0.371	0.257	0.860	0.012
Glucose	0.506	0.091	**<0.001**	**<0.001**	0.087
C-reactive protein (CRP)	0.926	0.698	**0.021**	0.067	**0.014**
Cholesterol	0.126	**0.008**	**0.006**	**<0.001**	**<0.001**
Red blood cell count (RBC)	0.155	0.990	**0.017**	**0.004**	0.850
Hemoglobin	0.995	**0.008**	**<0.001**	**0.002**	0.070
Hematocrit	0.368	0.324	**0.009**	**0.014**	0.575

Table 2 (continued)

FIG. 7					
Aspartate transaminase (ASAT)	**0.050**	0.070	**0.037**	0.321	0.165
Alanine transaminase (ALAT)	0.094	0.537	0.095	0.939	0.148
Gamma-glutamyltransferase (γGT)	0.627	0.704	0.320	0.140	0.575
Alkaline phosphatase (ALP)	0.514	0.631	**0.028**	0.968	**0.003**
Total bilirubin	0.652	0.056	0.512	0.555	0.060
FIG. 8					
White blood cell count (WBC)	0.492	0.213	0.370	0.443	0.324
Thrombocyte	0.940	0.458	0.711	0.265	0.914
Lactate dehydrogenase (LDH)	0.557	0.524	0.221	0.593	0.975
Blood urea nitrogen (BUN)	0.799	0.520	0.395	0.964	0.233
Creatinine	0.534	0.246	0.081	0.147	0.146
Potassium	0.673	0.463	0.990	0.847	0.145
FIG. 9					
Local pancreatic complications	0.365	0.128	0.130	**<0.001**	**<0.001**
Peripancreatic fluid collection	0.651	0.297	0.545	**0.004**	**<0.001**
Pancreatic necrosis	0.255	1.000	0.129	**0.003**	**<0.001**
DM as complication	1.000	0.210	**0.004**	**<0.001**	**0.011**
Pancreatic pseudocyst	**0.031**	0.133	0.459	0.311	0.744
FIG. 10					
Maximum C-reactive protein (CRP)	0.147	0.886	**<0.001**	**0.029**	**<0.001**
Maximum white blood cell count (WBC)	0.197	0.079	0.982	0.398	0.999
Organ failure	0.498	0.273	1.000	0.535	**0.001**
Respiratory failure	0.979			0.065	
Heart failure	0.416			**0.007**	
Renal failure	0.221			**0.002**	
FIG. 11					
Length of hospitalization	0.598	0.221	0.969	**0.034**	**0.001**
Severity	0.762	0.221	0.372	**0.001**	**<0.001**
Severe AP	1.000	0.267	0.566	1.000	**0.006**

FIG. 2	
Parameter	**Total cohort vs analyzed data**
Gender	0.363
Age	0.369
Severity	0.505
Severe AP	0.256
Mortality	0.148
Length of hospitalization	0.084
Etiology	**0.007**

FIG. 11			
TG group	**Moderately severe AP**	**95% CI**	
1	**22.6%**	19.0%	26.6%
2	**26.8%**	15.8%	40.3%
3	**28.6%**	18.8%	40.0%
4	**33.3%**	17.3%	52.8%
5	**66.7%**	38.4%	88.2%
6	**47.4%**	31.0%	64.2%

IV. CHILDREN ARE NOT SMALL ADULTS

Since childhood onset pancreatitis is a different entity compared with pancreatitis in adults, there are remarkable differences in incidence, etiology, clinical course and severity between the two age groups (38, 46, 83). However, trials are limited and based on small cohorts or completely lacking in children. Therefore, most of the pediatric guidelines are adopted from the adult protocols.

IV.1. THE PINEAPPLE STUDY

IV.1.1. Introduction

Several publications describe an increasing incidence of AP in both children and adults (45, 46, 84-87). Although the overall incidence of APP is below 1 per 100,000 worldwide, two major studies have proven that the incidence of AP is not much less in children than in adults (3.6–13.2 per 100,000 versus 13-45 per 100,000) (44-46). Diagnosis of AP requires at least two of the following parameters: (1) abdominal pain, (2) serum amylase and/or lipase values ≥ 3 times upper limits of normal, and (3) characteristic imaging findings for AP (36, 37). A retrospective trial in Pittsburgh revealed a close relationship between the number of serum amylase and lipase measurements and the rising incidence of the disease (44). Their data showed that the increased pancreatic enzyme testing could account for 94% of the change in all childhood AP admissions, suggesting that APP is an underdiagnosed disease.

There are factors which make the diagnosis of APP challenging: (i) abdominal pain is a common complaint in kids; 50% of the cases are in the category of pain-predominant functional gastrointestinal disorder with no significant morbidity (88); (ii) hospitals cannot afford to measure serum amylase/lipase in every child experiencing abdominal pain (88); (iii) the clinical course of AP, pancreatic exocrine function, and radiological preferences differ by age (38, 46, 89); (iv) pediatric trials are lacking, so diagnostic criteria for APP are based on adult protocols and no evidence-based medicine (EBM) guidelines are available to provide proper instruction concerning the necessity of diagnostic tests for AP during abdominal pain in children (37). Therefore, most of the ordered pancreatic enzyme tests and abdominal ultrasonography (US) are based on individual pediatrician experience, and APP may be delayed or underdiagnosed as a result of the decreased awareness of diagnostic workup (90). Overall,

international observational clinical trials are crucially needed to understand the most common clinical characteristics of AP in children.

IV.1.2. Aims

We aimed to perform a review of our current clinical practice in order to estimate the real incidence of APP and to provide a fast, simple, and authentic scoring system that helps to evaluate (in a reliable and cost-efficient way) the necessity of pancreatic enzyme tests and abdominal US when a child has abdominal pain.

IV.1.3. Methods

We initiated an international, multicenter, clinical trial called PINEAPPLE. The study has been established and drafted by the HPSG. The trial consists of a retrospective and a prospective subtrial.

PINEAPPLE-R is a retrospective review of electronic computerized records of children (under 18 years old) appearing at emergency units, centered around their clinical symptoms, serum pancreatic enzyme measurement (sPEM), and abdominal imaging examinations. Inclusion and exclusion criteria are shown in Table 3. Diagnosis and data concerning abdominal pain [yes/no] are required for all patients appearing at ER units. Diagnosis of abdominal pain is decided based on the doctor's record. If the patient had abdominal pain, information about basic clinical symptoms (vomiting, nausea), sPEM (either amylase or lipase; if yes: amylase/lipase [normal/increase less than 3x/increase more than 3x the upper threshold]) and imaging examination of the pancreas (if yes: type and result) are obligatory. Data are collected into a uniform harmonized Excel sheet.

PINEAPPLE-P is the prospective part of the study and has a questionnaire-style data collection method. Each patient under 18 years old presenting at ER units with acute abdominal pain is enrolled to the study regardless of the etiology (Table 3). Acute abdominal pain was defined as pain of less than one month duration.

Table 3. Inclusion and exclusion criteria of the PINEAPPLE study.

	PINEAPPLE-R	PINEAPPLE-P
Inclusion criteria	• Age under 18 years old • Accurate electronic data mentioned in the protocol	• Age under 18 years old • Acute abdominal pain
Exclusion criteria	• Age above 18 years old • Inaccurate electronic data mentioned in the protocol	• Age above 18 years old • No or chronic abdominal pain (91)

Detailed pediatric patients' data are collected via a questionnaire, sPEM and abdominal US are performed in all cases (Table 4). Patients and parents must be informed accordingly, and the 'informed consent form' is required to be signed.

The definition of APP is based on the fulfillment of '2 out of 3' of the following criteria: (i) abdominal pain compatible with AP; (ii) serum amylase and/or lipase ≥3x upper limit of normal; (iii) characteristic findings of AP by abdominal imaging (35, 36).

Table 4. Summary of clinical data required for PINEAPPLE-P. AP=acute pancreatitis; CP=chronic pancreatitis; AIP=autoimmune pancreatitis; PC=pancreatic cancer; US=ultrasonography; CT=computed tomography.

1. Patient personal details	
Gender	Male/female
2. Medical history	
(a) Family medical history	
Pancreas disorders in family history: AP/CP/AIP/PC	Yes/no/unknown, if yes: relationship to the patient
Other diseases in family history	Yes/no/unknown, if yes: description of them
(b) Personal medical history	
Known diseases	Yes/no/unknown, if yes: description of them
Abdominal surgery	Yes/no/unknown, if yes: description of the surgery
New medications taken in the last 2 weeks	Yes/no/unknown, if yes: description of them
Medications taken regularly	Yes/no/unknown, if yes: description of them
New symptoms, diagnosed diseases in the last 2 weeks	Yes/no/unknown, if yes: description of them
New diet, change in diet in the last 2 weeks	Yes/no/unknown, if yes: description of it
Any events strongly affecting the child emotionally in the last 2 weeks	Yes/no/unknown, if yes: description of it
Change in the environment of the child in the last 2 weeks	Yes/no/unknown, if yes: description of it
Any other event in the last 2 weeks	Yes/no/unknown, if yes: description of it
Has the patient had any examination concerning abdominal pain?	Yes/no/unknown, if yes: description of it
Length of breast milk feeding	Number of months/unknown
3. Complaints, symptoms	
(a) Abdominal pain	
How many hours have passed since the pain started?	Number of hours/unknown
Intensity	Number: 1–10 scale/unknown
Tendency	Decreasing/intensifying/stagnating/ unknown
Continuity	Continuous/intermitting/changing/ unknown
Forced posture	Yes/no/unknown
Nature	Dull/sharp/cramping/unknown
Location	Diffuse/localized/unknown; if localized: region (1-9)
(b) In the case of abdominal pain lasting longer than 48 hours	
Was everyday activity influenced?	Yes/no/unknown
Did the child wake up at night because of the pain?	Yes/no/unknown

Table 4. (continued)

In which part of the day did the pain appear mostly?	Unrelated/after waking up/in the morning/in the afternoon/in the evening/at night/unknown
Was it related to eating?	Yes/no/unknown; if yes: before/while/after
(c) Other complaints	
Nausea	Yes/no/unknown
Vomiting	Yes/no/unknown; if yes: How many times? Content of cast?
Fever	Yes/no/unknown; if yes: Since when? Temperature? (C°)
Appetite	Good/retained/bad/unknown
Weight loss	Yes/no/unknown, if yes: How much? (kg), How long has it taken? (weeks/months)
Jaundice	Yes/no/unknown
Stool	Normal/diarrhea/constipation/fatty/putrid/undigested food/bloody/mucus/unknown
4. Physical examination	
Blood pressure	Number (mmHg)
Heart rate	Number (BPM)
Body weight	Number (kg)
Body height	Number (m)
Respiratory rate	Number (/min)
Body temperature	Number (°C)
Abdominal tenderness	Yes/no, if yes: location of abdominal tenderness
Abdominal guarding	Yes/no
Jaundice	Yes/no
Bowel sounds	No/hypoactive/normal/hyperactive
5. Laboratory parameters	
Amylase and/or lipase	Number (U/l)
6. Imaging examinations	
Pancreas abnormalities suggesting AP	Yes/no
Pancreas abnormalities suggesting CP	Yes/no
Abdominal US	Yes/no, if yes: description
Abdominal CT scan	Yes/no, if yes: description
7. Diagnosis	
8. Diagnosis – main group	
9. Further step	Admission/discharged/other

We aim to analyze patient data in different age groups. Association between each collected parameter and AP will be determined. Statistical analysis will be carried out by data mining methods. The applied methods will be determined based on the main characteristics of the collected data, and the most suitable method – or method combination – will be chosen. The following data mining methods are being contemplated: logistic regression, discriminant analysis, random forest analysis, decision tree, and cluster analysis. ROC (receiver operating characteristic) analysis will be performed to evaluate the predictive power of the classification algorithm.

Four quality control points are established. First, the local clinical research assistant must upload the data electronically and confirm that the data are the same as those in the hard copy. Second, the local institutional principal investigator (who must have a medical doctoral degree) must recheck the uploaded data and confirm their validity and accuracy. Third, the central data administrator, who is based at HPSG headquarters, must control the accuracy, and finally, the trial leader must go through the details. Patients with inadequate or insufficient data will be excluded.

The protocols were introduced at our international meeting held in Szeged in November 2014, which was attended by some of the best-established pediatric pancreatologists. Around 100 clinicians – 60 Hungarians and 40 international investigators from 9 different countries – attended. The trial was discussed and the suggested modifications have been included. The study has been accepted by the scientific committee of the IAP, and is therefore running under the auspices of HPSG and IAP. The PINEAPPLE trial has been registered at the ISRCTN registry (ISRCTN35618458), a primary clinical trial registry recognized by the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) which accepts all clinical research studies, providing content validation and curation as well as the unique identification number necessary for publication.

The study received the relevant ethical approval (No.: ad.52857-2/2014) issued by the National Hungarian Ethical Authority (ETT TUKEB) in 2014. Completion of the ‘Letter of intent’ form is mandatory for registering the participation of each institution. Study management strictly follows the Ethical Guidelines for Observational Studies.

IV.1.4. Expected results

The PINEAPPLE trial is ongoing and expected to be finished by December 2020. The PINEAPPLE-R study will aid understanding of our current clinical practice of APP in children with abdominal pain in different countries and centers. The PINEAPPLE-P study will provide the real incidence of APP and help to establish a fast, simple, and authentic scoring system to evaluate the necessity of pancreatic enzyme tests and abdominal US when a child has abdominal pain. As of the preparation of the thesis, 48,170 patient records have been enrolled into PINEAPPLE-R, and 926 patients have been involved in PINEAPPLE-P.

IV.1.5. Discussion

The ‘2 out of 3’ criterion is used to diagnose AP both in adults and children (abdominal pain, sPEM, and abdominal imaging) (36, 37, 39, 40, 42). Therefore, without measuring serum pancreatic enzymes and/or performing transabdominal imaging, AP may remain undiagnosed.

According to previous pediatric studies in AP, abdominal pain is present in 66 to 95% of the children with AP (48, 92-97); however, inconsistency and high variability exist between the studies. Most of the trials investigating the characteristics of abdominal pain have either low numbers or missing parameters causing inconsistencies between their data. Based on the review of Bai et al. (38), abdominal pain was most commonly localized to the epigastric region (62–89% of cases) (89, 92, 98) and was rarely associated with back pain (<10%) in children with AP (48, 94). Radiation to the back was seen only in 1.6–5.6% (95, 97, 98) of the cases. Diffuse abdominal pain was found in 12–20% of AP patients (92, 95, 97), guarding in 29–37% (92, 94), whereas abdominal distension was reported in 21–46% (92-94, 96, 97). Nausea or vomiting was noted in 40–80% of the AP cases (48, 89, 95-101). Other symptoms might be fever, ascites, pleural effusion, and jaundice. Symptoms of infants and toddlers are much more unspecific: abdominal pain was found in 43%, epigastric tenderness in 57%, and nausea in 29% (89). In a study from Pittsburgh, 16% of the infants and toddlers had abdominal distension and 40% had fever (102).

In summary, a large, international prospective cohort is necessary to understand the complaints and symptoms of AP in children. We have proposed an international observational clinical trial to collect a critical mass of data from children with abdominal pain in order to develop an EBM guideline concerning the necessity for obtaining serum pancreatic enzyme testing and abdominal US in pediatric patients who present at the emergency room with abdominal pain.

IV.2. EARLY ENTERAL NUTRITION IN ACUTE PEDIATRIC PANCREATITIS

IV.2.1. Introduction

Common characteristics in both age groups are that no specific therapy is available to treat AP, and the general supportive treatment at the early phase of the disease frequently consists of volume resuscitation and NPO diet (35, 36, 39, 40). Although there is clear evidence in the literature that appropriate volume therapy is beneficial, the latter treatment is questionable.

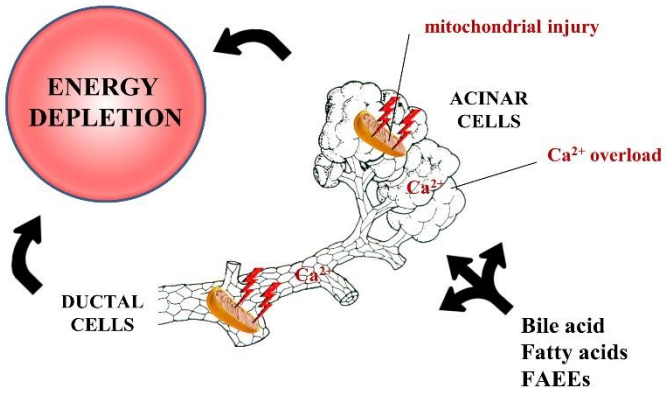


Fig. 12. Early events in acute pancreatitis. Bile acids, fatty acids or non-oxidative ethanol metabolites (fatty acid ethyl esthers, FAEEs) induce calcium overload, causing mitochondrial damage and a resultant decrease in intracellular adenosine triphosphate (ATP) concentration both in acinar and ductal cells. This will lead to general energy depletion in the pancreas.

One of the main reasons for the debate is that the pathogenesis of the disease clearly suggests the opposite. Irrespective of the etiological factors, mitochondrial damage and energy depletion are the leading intracellular responses in the early phase of the disease in the exocrine pancreas (11, 13, 78, 103). Bile acids (7-10), fatty acids, and non-oxidative ethanol metabolites (FAEEs) (11-16) were shown to elevate the intracellular Ca^{2+} concentration, causing mitochondrial damage and a resultant decrease of intracellular ATP concentration (Fig. 12). This leads to inhibited fluid and bicarbonate secretion and dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl^- channel in the ductal cells with resultant secretory block and intrapancreatic trypsinogen activation (11, 12, 104, 105). In addition, hypercatabolism secondary to pancreatic and extrapancreatic inflammation further aggravates the energy deficit (106). Consequently, restoration of ATP level both in acinar and ductal cells prevents (at least in part) the toxic effect of the harmful causative factors noted above (78, 107, 108). These data strongly suggest that early energy supply should be favorable for AP patients compared to nil energy. Moreover, energy supply given by enteral nutrition in AP patients was shown to be beneficial as a first-line treatment compared to TPN for several reasons: (i) EEN significantly decreases pathogenic bacteria in the stool and alteration of intestinal flora; (ii) gut plays an important role as a barrier in the immune system and EEN is able to optimize intestinal permeability; (iii) this mucosal barrier integrity decreases the bacterial translocation from the gut, therefore resultant bacteraemia and levels of serum endotoxins are reduced; (iv) EEN has a favorable effect on immune dysregulation caused by SAP which can reduce the rate of pancreatic infection, systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome as well as duration of ICU stay (34, 106, 109). Accordingly, enteral nutrition either via oral, nasogastric- or nasojejunal tube feeding has been shown to be beneficial regarding visual analogue pain score, LOH, systemic infection, multi organ failure

(MOF), need for surgical interventions, and mortality (29-33, 110-114). Additionally, enteral nutrition further improves the outcome of AP if it is started within 48-72 hours (34, 36, 115, 116). The type of enteral nutrition is administered based on disease severity (117).

Furthermore, enteral nutrition has already been proven to be beneficial in other inflammatory gastrointestinal diseases. The first-line recommendation to induce remission in pediatric Crohn's disease is exclusive enteral nutrition (118). Enteral nutrition could also be effective in the maintenance of pediatric inflammatory bowel disease remission (119).

Regarding AP, three of the recent and most up-to-date guidelines for AP in adults have shown the positive effect of early enteral tube feeding in moderately severe and SAP (36, 39, 40). Moreover, nasogastric tube feeding was shown to be as safe and as effective as nasojejunal tube feeding in SAP (114). In the case of patients with predicted mild AP, oral feeding is preferred as soon as possible (36, 39, 40). However, no systematic review is available concerning the role of EEN in children.

IV.2.2. Aims

We aimed to review the literature to analyze the effect of EEN versus NPO therapy on the outcome of APP, and to aggregate the information in childhood onset AP, leading to a higher statistical power and more robust point estimate than is possible from the individual studies.

IV.2.3. Methods

The preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) was followed (120). Our structured literature search was based on the participants, intervention, comparison and outcomes (PICO) format [P: patients under the age of twenty-one suffering from AP; I: EEN (per os/nasogastric- or nasojejunal tube started within 24-48 hours); C: NPO therapy (per os/nasogastric- or enteral tube started after 24-48 hours); O: length of hospitalization, need for ICU, complications, necessity of antibiotics, surgical/non-surgical interventions, and mortality].

In February 2016, a literature search was performed on the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (https://www.embase.com) databases using the following Medical Subject Headings and search terms: "pediatric" OR "paediatric" AND "pancreatitis". The search was limited to human studies, full-text publications with abstracts in English with no time period, resulting in 632 articles altogether (PubMed: 131;

EMBASE: 501). The articles were checked separately. Meta-analyses, reviews, case reports and articles on CP were excluded and duplicates were removed (Fig. 13). Potentially eligible papers were selected, and finally five of them with relevant data on EEN or with NPO therapy

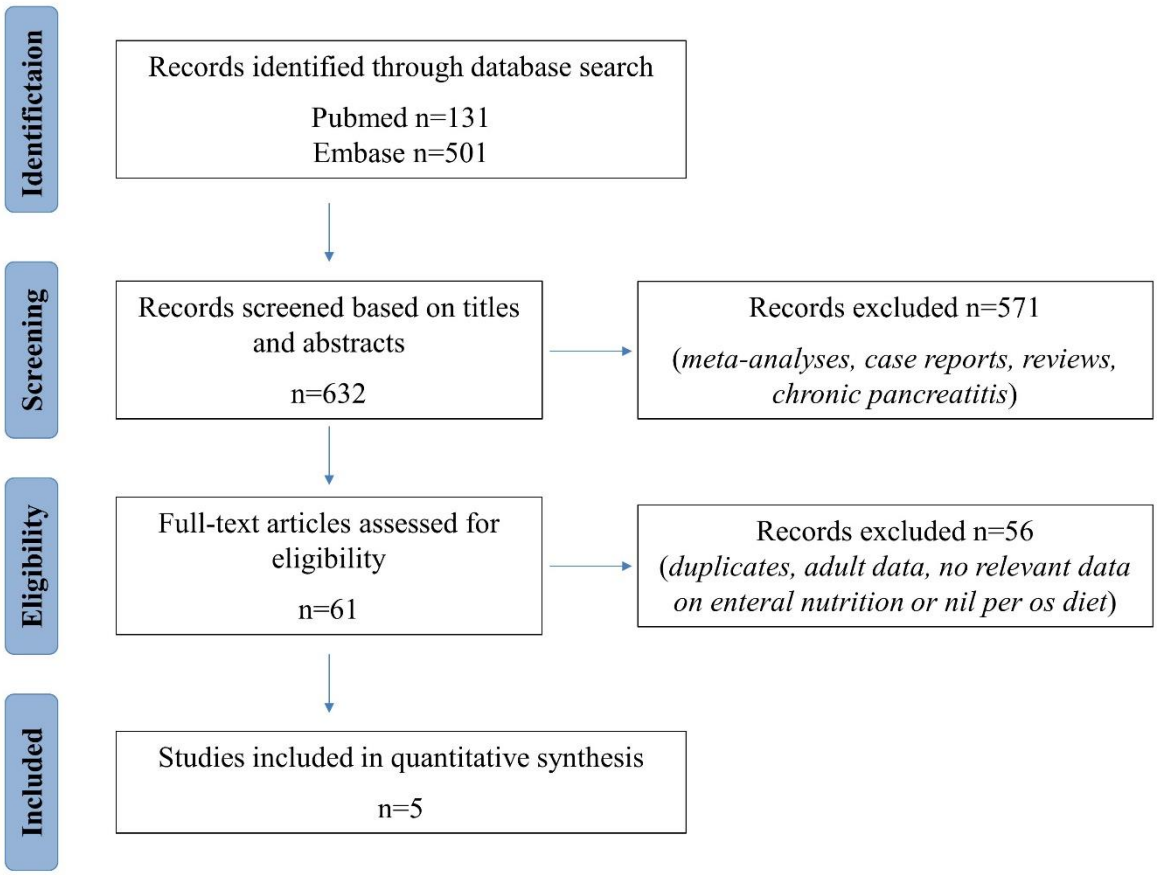


Fig. 13. Flow chart on the methods used in the literature search.

in APP in patients under 21 years old were included (Table 5). Details in the collected articles were checked, and only articles where both EEN and NPO were presented separately were used. Two articles met this criterion which contained three separate data pairs, where EEN was compared to NPO (Fig. 14A). The following parameters were collected: LOH, need for treatment at ICU, and development of SAP. Only

Table 5. Studies included in the quantitative synthesis. EEN=early enterals nutrition; NPO=nil per os; IVF=intravenous fluid; lo=low; hi=high.

Ref.	Data	Groups	n
Abu-El-Haija et al., 2016 (121)	yes	EEN	24
		NPO	14
Flores-Calderón et al., 2009 (122)			18
Goh et al., 2003 (100)			12
Raizner et al., 2013 (123)			7
Szabo et al., 2015 (124)	yes	EEN + IVF lo	55
		NPO + IVF lo	20
	yes	EEN + IVF hi	96
		NPO + IVF hi	30

one of the three investigated parameters (LOH) contained a minimum of three items, which were analyzed statistically.

The meta-analytic calculation was made with Comprehensive MetaAnalysis (V3) software using the random effects model (the DerSimonian-Laird method). We calculated a weighted standard difference in means and 95% CI. In the case of one study (Abu-El-Haija *et al.*, 2016 (121)), we converted the median and range values to means and standard deviation using the modified Hozo's formula by Wan *et al.*, 2014 *(125)*. For a visual inspection, we used a forest plot.

A

Articles		Therapy	n	LOH	Need for ICU	Severe AP
Abu-El-Haija et al., 2016	1	EEN (<24 h)	24	81.7 h		
		NPO (<24 h)	14	94.7 h		
Szabo et al., 2015	2	NPO (<48h) + IVF lo (<24h)	20	7.1 d (1.01 SE)	20% (8.94 SE)	35% (10.7 SE)
		EEN (<48h)+ IVF lo (<24h)	55	2.8 d (0.24 SE)	1.8% (1.80 SE)	9.1% (3.88 SE)
	3	NPO (<48h)+ IVF hi (<24h)	30	5 d (0.58 SE)	13% (6.21 SE)	17% (6.80 SE)
		EEN (<48h)+ IVF hi (<24h)	96	3.2 d (0.22 SE)	1% (1.04 SE)	4.2% (2.04 SE)

B

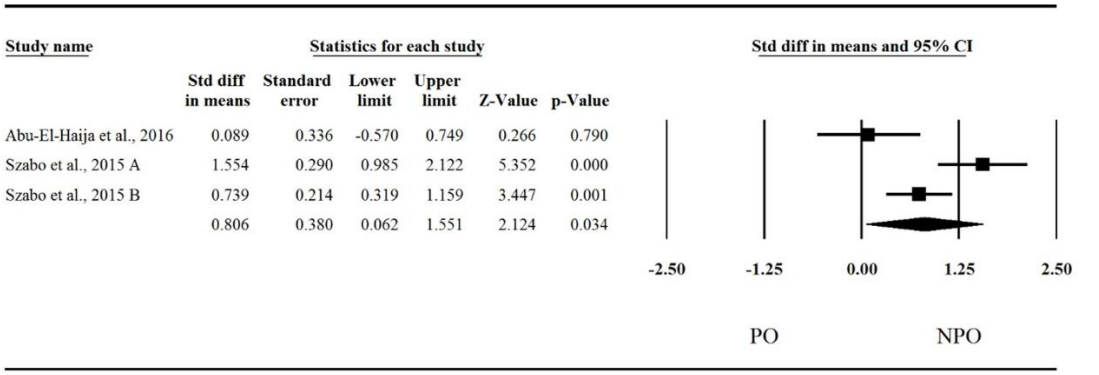


Fig. 14. Two articles containing three separate data pairs. A) Collected parameters. **B)** Forest plot analyses on length of hospitalization (LOH). EEN=early enteral nutrition; NPO=nil per os; IVF=intravenous fluid; lo=low; hi=high; ICU=intensive care unit; AP=acute pancreatitis; PO=per os.

IV.2.4. Results

Fig. 14A shows the parameters collected from the articles. It was only possible to perform forest plot analyses on LOH (Fig. 14B). EEN significantly decreased LOH (SD= 0.806, $p = 0.034$) compared to the standard NPO diet in case of APP.

IV.2.5. Discussion

Several therapeutic recommendations are available in the literature on nutrition in AP. The IAP/APA guideline suggests enteral tube feeding as the first-line therapy in patients with predicted SAP, and oral feeding in the case of predicted mild AP (36). According to the Japanese guideline, enteral nutrition can decrease the incidence of complications and elevate the survival rate in the early phase of SAP (40). Recent meta-analysis of adult studies revealed that EEN decreases mortality, rate of interventions, and the incidence of MOF in SAP. Moreover, group analysis of 17 parameters including laboratory parameters (such as CRP and WBC) and symptoms (such as pain or presence of SIRS) suggested that EEN also has merits in mild AP (31).

Since the incidence of APP has risen in the past twenty years (3.6 and 13.2 per 100,000 children affected annually), we systematically reviewed the literature to understand whether there is any beneficial effect of EEN versus NPO therapy in children (44, 45). We faced several difficulties during our review: (i) APP is still underdiagnosed, thus decreasing the possibility of performing clinical trials; (ii) the number of studies on the management of these patients is very low, and there is still only a small number of studies focused on understanding the characteristics of the childhood onset disease (126); (iii) studies have not focused on the early management of the patients, therefore the groups were not separated; and finally, (iv) the quality of the methods sections and data presentation in these articles is very low. Consequently, in many cases it was impossible to obtain quality analyzable data from the articles for proper broad-spectrum meta-analysis. By the end of the search, we identified five articles containing relevant data on nutritional management during the early phase of APP. Raizner *et al.* (123) published a retrospective analysis involving seven children with necrotizing pancreatitis. All the children received a strict NPO diet for 1-11 days, five patients received TPN for 8-18 days, and just one patient was treated with nasojejunal feeding for 7 days. All the children required intensive supportive treatment and a prolonged hospital stay (with a mean of 20 days) because of the complications. Goh *et al* (100) included twelve patients in their retrospective study. One patient needed a distal pancreatectomy, and eleven patients recovered with conservative management. Three patients received TPN, and eight patients were kept on bowel rest and nasogastric aspiration. Two patients had acute complications, and two patients had recurrent AP. Flores-Calderon *et al* (122) studied eighteen patients with AP caused by L-asparaginase due to acute lymphoblastic leukemia. All the patients were treated with bowel resting for a mean of 22 days (range: from 3-66 days), fourteen of the patients

received TPN, and four had an elementary diet. Two of the patients required ICU admission, and local complications developed in twelve patients. None of the patients died from complications related to AP. Although these studies point out several disadvantages of the NPO diet, none of them could be enrolled in our meta-analysis. Finally, it was possible to collect three sets of analyzable data pairs where both NPO and EEN were present. Abu-El-Haija *et al* (121) conducted a prospective study of 33 patients (38 admissions) suffering from mild AP, and retrospectively investigated the relationship of nutrition with abdominal pain and LOH. EEN feeding meant per os feeding, and NPO was identified as oral feeding not being allowed for 24 hours. Importantly, EEN, even with high fat intake, did not cause elevation in pain in children, suggesting that EEN is a well tolerable nutritional possibility in children. The fact that LOH was shorter in the EEN group versus the NPO group points to EEN as a better way of treating APP. The most advanced study was performed by Szabo *et al* (124), where several parameters were collected to understand the effect of EEN on the course of APP. A total of 201 patients suffering from mild AP on admission were enrolled retrospectively. They compared EEN versus NPO both with and without aggressive fluid resuscitation. Fluid therapy was administered during the first 24 hours, and the type of nutrition was determined during the first 48 hours. Besides the beneficial effects of EEN on LOH, they also showed that EEN reduced the severity of the disease and the rate of ICU transfer.

Although our aim was to perform a meta-analysis on several parameters to understand the differences between EEN and NPO in childhood onset AP, we were only able to perform the statistical analysis on LOH, which suggested that EEN is not only a safe method of nutrition but also substantially decreases LOH, resulting in a better and less expensive treatment of APP (124).

IV.3. CONCLUSION

Based on our current knowledge, there are remarkable differences between childhood and adult onset AP (46). However, the majority of the current pediatric guidelines are adopted from adult data (37). Therefore, prospective observational and interventional pediatric clinical trials would be necessary to understand the differences between childhood and adult onset AP and to be able to provide appropriate patient care to children suffering from AP. However, most of the pediatric cohorts are limited as a result of the low incidence of AP and small sample size, which is particularly due to missing evidence-based diagnostic guidelines and lower awareness

of AP among pediatricians. Consequently, the HPSG aimed to solve this unmet need and established the PINEAPPLE study to estimate the real incidence of AP in children, and to create an evidence-based diagnostic guideline for APP. Additionally, not only diagnostic, but also therapeutic guidelines for childhood onset AP are based on adult data. EEN was proven to be beneficial for treating AP in adults compared to NPO and TPN therapy. Therefore, we aimed to collect all the relevant data on EEN in APP from the literature to achieve a higher level of evidence in childhood as well. Our meta-analysis suggests that EEN should have priority in treating APP compared to NPO therapy, and confirmed the necessity of further clinical trials in children.

V. SUMMARY AND NEW DISCOVERIES

Chapter III: Dose-dependent effect of hypertriglyceridemia on acute pancreatitis

1. Although we confirmed that biliary etiology is less common with HTG-AP, HTG-AP was associated with biliary etiology in 5.4%, but with alcoholic etiology in 38.2%.
2. HTG was significantly and dose-dependently linked to younger age, male gender, obesity and pre-existing DM in AP patients.
3. Amylase and lipase levels have shown a significant and dose-dependent reduction with the elevation of TG in AP.
4. Our analysis has shown that local complications and organ failure were significantly and dose-dependently increased by HTG in AP.
5. 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 SAP as well.
6. Our data suggest that lipid-lowering therapy may be important clinically at a much lower TG level in HTG-AP patients than we previously thought.

Chapter IV: Children are not small adults

The PINEAPPLE study will help to estimate the real incidence of AP in children and create evidence-based diagnostic guidelines for APP.

Our meta-analysis: (i) proves that EEN shortens the LOH in the case of AP not only in adults, but also in children; (ii) suggests that EEN is safe and should have priority in treating APP compared to NPO therapy, and; (iii) confirms the necessity of further interventional clinical trials in children.

VI. CONTRIBUTION

During my PhD work, we aimed to improve the clinical practice of AP in children and adults. This has allowed me to learn the clinical methodologies of study design, observational clinical trial, meta-analysis, and cohort analysis.

VI.1. Mosztbacher et al. Pancreatology, 2020.

I took part in the study design, data analysis and data interpretation, and I wrote the article with the contributions of Péter Hegyi and Andrea Párniczky. Furthermore, figures were created by myself and Lilla Hanák. I contributed to the patient involvement in the AP registry operated by the HPSG.

VI.2. Mosztbacher et al. World J Gastroenterol, 2017.

I contributed to the study design and data interpretation, and I wrote the article with the help of Péter Hegyi and Andrea Párniczky. Furthermore, figures were created by myself and Nelli Farkas.

VI.3. Zsoldos et al. Digestion, 2016

As the principle investigator of the study, I am responsible for making presentations at national and international conferences in order to involve as many centers as possible. In addition, I organize and maintain relations with the enrolled centers and provide the professional supervision of the study. I have enrolled 133 patients to the PINEAPPLE-P and 2 centers to the PINEAPPLE-R studies. I am responsible for data control and data analysis of both subtrials.

VII. ACKNOWLEDGEMENT

First, I would like to thank my supervisor **Péter Hegyi,** for his support. He managed my scientific studies and assisted my work with his advice and experience. I would also like to express my thanks to **Andrea Párniczky**, who convinced me to join the HPSG and begin my scientific work, and then supported me as a supervisor. Furthermore, I would like to thank **Miklós Sahin-Tóth** and **Jonas Rosendahl** for the opportunity to widen my knowledge and do basic research in the field of pancreas genetics.

I am also grateful to the interdisciplinary research unit led by **Andrea Szentesi**. My PhD work would not have been possible without the work of administrators, patient coordinators, local clinical investigators, and biobank leaders of the **HPSG** and the **Institute for Translational Medicine, University of Pécs**. Furthermore, I would like to thank **Nelli Farkas** and **Lilla Hanák** for their help in the statistical calculations.

My deepest gratefulness goes to **my parents and my family** who supported me during my studies and research work. I would also like to thank my close **friends** who always assured me that I would be able to manage and finish my PhD work.

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

Dóra Mosztbacher [a, b, c], Lilla Hanák [b], Nelli Farkas [d], Andrea Szentesi [b, e], Alexandra Mikó [f], Judit Bajor [f], Patrícia Sarlós [f], József Czimmer [f], Áron Vincze [f], Péter Jenő Hegyi [b], Bálint Erőss [b], Tamás Takács [g], László Czakó [g], Balázs Csaba Németh [g], Ferenc Izbéki [h], Adrienn Halász [h], László Gajdán [h], József Hamvas [i], Mária Papp [j], Ildikó Földi [j], Krisztina Eszter Fehér [j], Márta Varga [k], Klára Csefkó [k], Imola Török [l], Hunor Pál Farkas [m], Artautas Mickevicius [n], Elena Ramirez Maldonado [o], Ville Sallinen [p, q], János Novák [r], Ali Tüzün Ince [s], Shamil Galeev [t], Barnabás Bod [u], János Sümegi [v], Petr Pencik [w], Zsolt Dubravcsik [x], Dóra Illés [g], Szilárd Gódi [y], Balázs Kui [g], Katalin Márta [b], Dániel Pécsi [b], Péter Varjú [b, f], Zsolt Szakács [b], Erika Darvasi [e], Andrea Párniczky [b, c, z, 1, **], Péter Hegyi [b, e, y, aa, 1, *], on behalf of the Hungarian Pancreatic Study Group

[a] First Department of Paediatrics, Faculty of Medicine, Semmelweis University, Budapest, Hungary
[b] Institute for Translational Medicine, Szentágothai Research Center, Medical School, University of Pécs, Pécs, Hungary
[c] Doctoral School of Theoretical Medicine, Faculty of Medicine, University of Szeged, Szeged, Hungary
[d] Institute of Bioanalysis, Medical School, University of Pécs, Pécs, Hungary
[e] Centre for Translational Medicine, First Department of Medicine, Faculty of Medicine, University of Szeged, Szeged, Hungary
[f] First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[g] First Department of Medicine, Faculty of Medicine, University of Szeged, Szeged, Hungary
[h] Szent György Teaching Hospital of County Fejér, Székesfehérvár, Hungary
[i] Bajcsy-Zsilinszky Hospital, Budapest, Hungary
[j] Department of Internal Medicine, Division of Gastroenterology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[k] Department of Gastroenterology, Dr. Réthy Pál Hospital of County Békés, Békéscsaba, Hungary
[l] County Emergency Clinical Hospital, George Emil Palade University of Medicine, Pharmacy, Sciences and Technology of Târgu Mureș, Târgu Mureș, Romania
[m] George Emil Palade University of Medicine, Pharmacy, Sciences and Technology of Târgu Mureș, Târgu Mureș, Romania
[n] Vilnius University Hospital Santaros Clinics, Clinics of Abdominal Surgery, Nephrourology and Gastroenterology, Faculty of Medicine, Vilnius University, Vilnius, Lithuania
[o] Consorci Sanitari Del Garraf, Sant Pere de Ribes, Barcelona, Spain
[p] Department of Transplantation and Liver Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[q] Department of Abdominal Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[r] Pándy Kálmán Hospital of County Békés, Gyula, Hungary
[s] Hospital of Bezmialem Vakif University, School of Medicine, Istanbul, Turkey
[t] Saint Luke Clinical Hospital, St. Petersburg, Russia
[u] Dr. Bugyi István Hospital, Szentes, Hungary
[v] Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital, Miskolc, Hungary
[w] Centrum Péče o Zažívací Trakt, Vítkovická Nemocnice a.s., Ostrava, Czech Republic
[x] Department of Gastroenterology, Bács-Kiskun County Hospital, Kecskemét, Hungary
[y] Division of Translational Medicine, First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary
[z] Department of Gastroenterology, Heim Pál Children's Hospital, Budapest, Hungary
[aa] Hungarian Academy of Sciences–University of Szeged, Momentum Gastroenterology Multidisciplinary Research Group, Szeged, Hungary

* Corresponding author. 2nd floor, 12 Szigeti Road, Pécs, 7624, Hungary. PO BOX 99, Pécs, 7601, Hungary.
** Corresponding author. 2nd floor, 12 Szigeti Road, Pécs, 7624, Hungary. PO BOX 99, Pécs, 7601, Hungary.
E-mail addresses: a.parniczky@tm-centre.org (A. Párniczky), hegyi.peter@pte.hu (P. Hegyi).
[1] Péter Hegyi and Andrea Párniczky (contributed equally).

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ABSTRACT

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.

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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

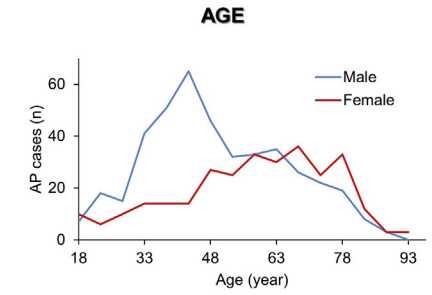
Prior to analysis of the dataset, descriptive statistical tools were used to describe the basic characteristics. Mean and standard error of the mean were calculated for continuous variables, whereas the incidence in each group was determined for categorical variables. Depending on the distribution of 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

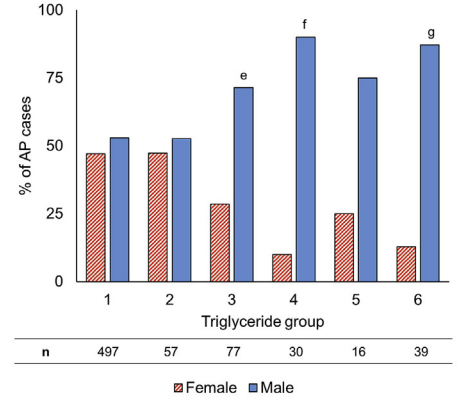
A



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



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	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)

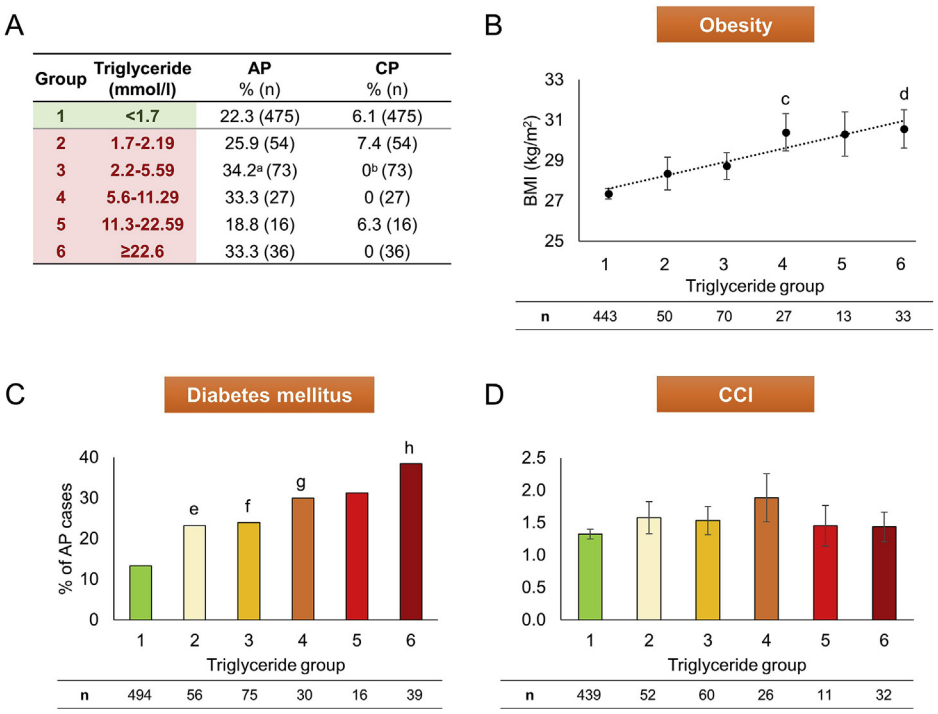


Fig. 2. Medical history of triglyceride groups. A) Acute pancreatitis (AP) and chronic pancreatitis (CP) in patients' medical history (a: p = 0.026; b: p = 0.023). **B)** Obesity (body mass index (BMI), kg/m^2) (c: p = 0.006; d: p = 0.001). **C)** Diabetes mellitus in medical history (e: p = 0.046; f: 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)	Abdominal pain Duration before admission hour±SE (n)	Abdominal pain 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

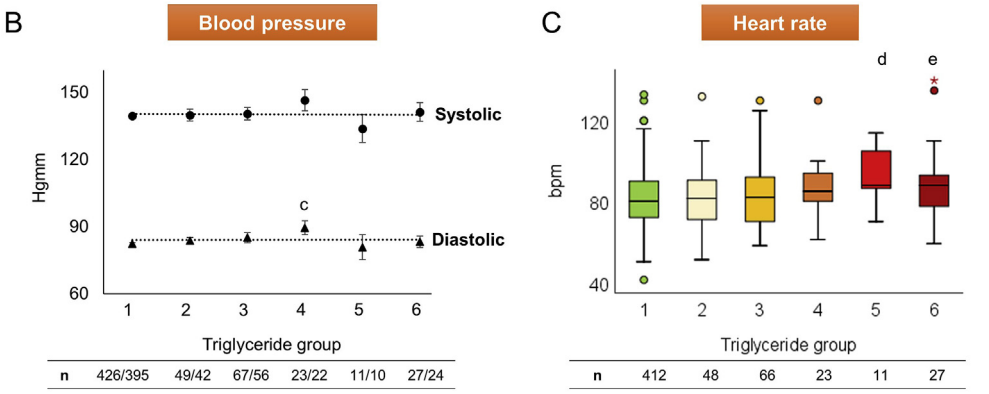


Fig. 3. Symptoms and physical findings on admission in the different triglyceride (TG) groups. A) Incidence, duration before admission and intensity of pain. Nausea, vomiting, abdominal tenderness and abdominal guarding (a: p = 0.025; b: p = 0.036). **B)** Systolic and diastolic blood pressures (Hgmm) (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).

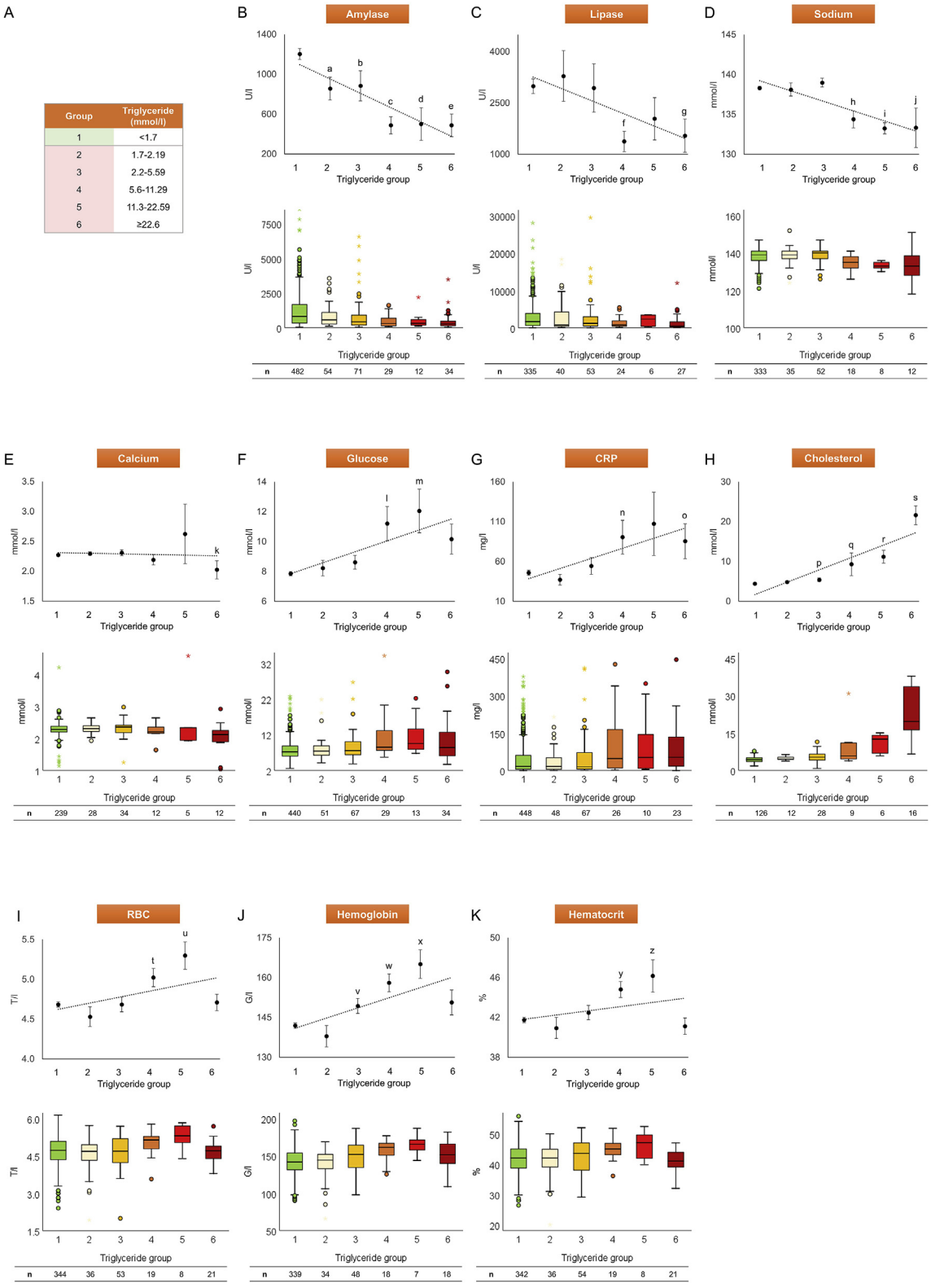


Fig. 4. Laboratory parameters on admission significantly associated with hypertriglyceridemia. A) Triglyceride groups [1–6]. **B)** Amylase (U/l) (a: p = 0.036; b, c, e: p=<0.001; d: p = 0.009). **C)** Lipase (U/l) (f: p = 0.017; g: p = 0.001). **D)** Sodium (mmol/l) (h, i: p=<0.001; j: p = 0.005). **E)** 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

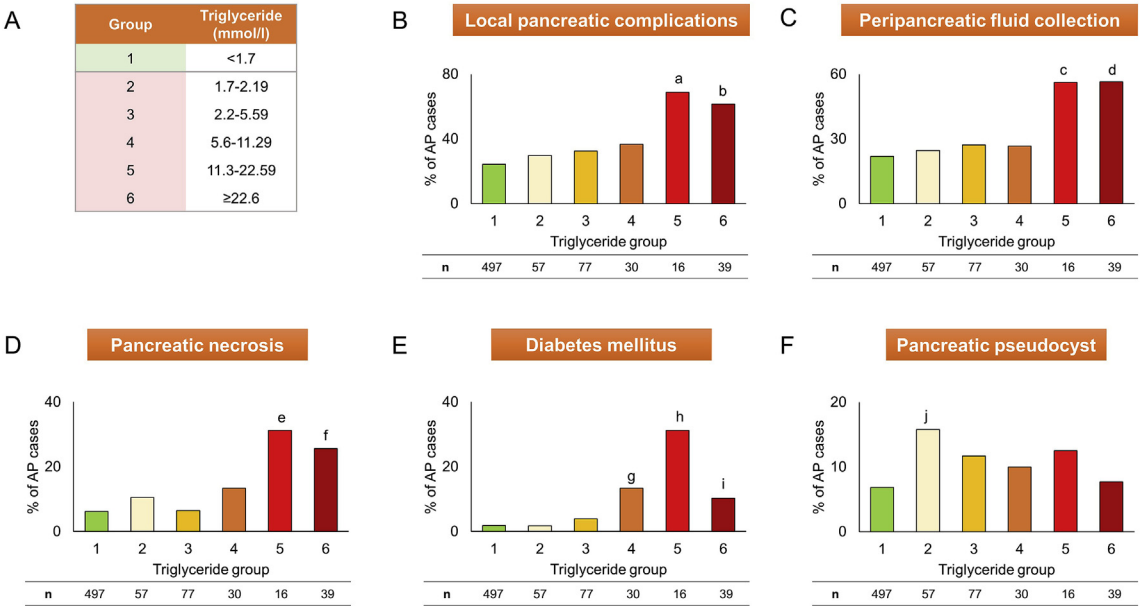


Fig. 5. Local pancreatic complications in the different triglyceride groups. A) Triglyceride groups [1–6]. **B)** Local pancreatic complications (a, b: $p < 0.001$). **C)** Peripancreatic fluid collection (c: $p = 0.004$; d: $p < 0.001$). **D)** Pancreatic necrosis (e: $p = 0.003$; f: $p < 0.001$). **E)** 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.

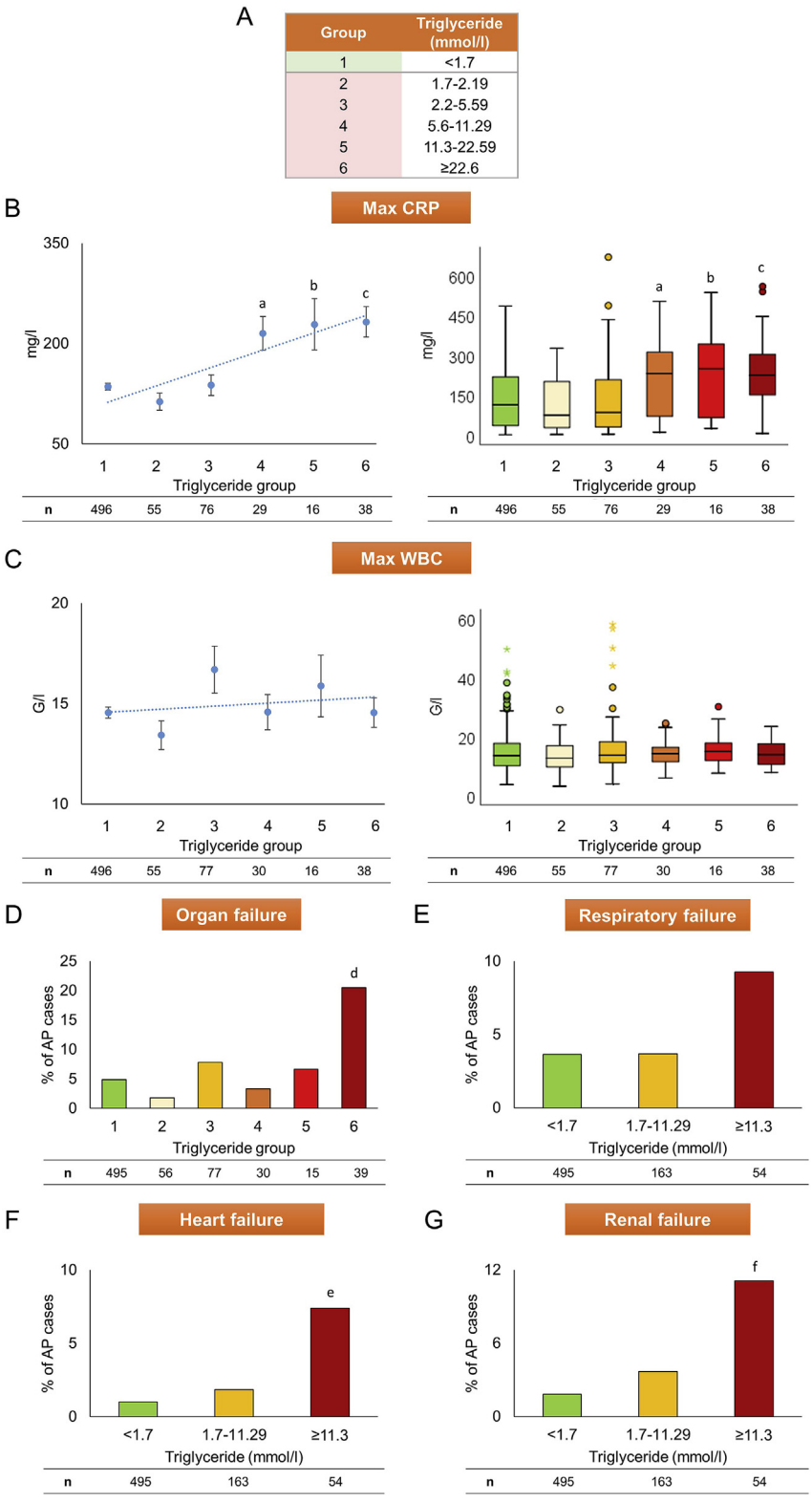


Fig. 6. Systemic inflammatory effect and organ failure in the different triglyceride groups. A) Triglyceride groups [1–6]. **B)** Maximum C-reactive protein (Max CRP, mg/l) (a, c: $p < 0.001$; b: $p = 0.029$). **C)** Maximum white blood cell count (Max WBC, G/l). **D)** Organ failure (d: $p = 0.001$). **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±1.9[a] (16)	0 (15)
6	≥22.6	14.3±2.1[b] (39)	1 (38)
ELEVATED TG		11.0±0.7	3
TOTAL		10.4±0.3	11

B

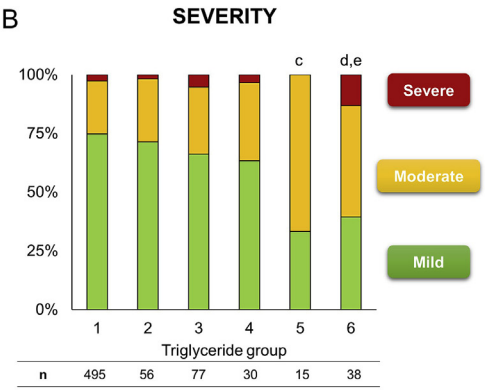


Fig. 7. Outcomes in the different triglyceride (TG) groups. A) Length of hospitalization (LOH, day) and mortality (event n) (a: $p = 0.034$; b: $p = 0.001$). **B)** Severity (c: $p = 0.001$; d: $p < 0.001$). Moderately severe acute pancreatitis (AP) cases (Group 1: 22.6% (95% CI: 19%–26.6%); Group 5: 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.

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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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Restoration of energy level in the early phase of acute pediatric pancreatitis

Dóra Mosztbacher, Nelli Farkas, Margit Solymár, Gabriella Pár, Judit Bajor, Ákos Szűcs, József Czimmer, Katalin Márta, Alexandra Mikó, Zoltán Rumbus, Péter Varjú, Péter Hegyi, Andrea Párniczky

Dóra Mosztbacher, First Department of Pediatrics, Semmelweis University, 1083 Budapest, Hungary

Dóra Mosztbacher, Nelli Farkas, Margit Solymár, Katalin Márta, Alexandra Mikó, Zoltán Rumbus, Péter Varjú, Péter Hegyi, Andrea Párniczky, Institute for Translational Medicine, University of Pécs, 7624 Pécs, Hungary

Nelli Farkas, Institute for Bioanalyses, University of Pécs, 7624 Pécs, Hungary

Gabriella Pár, Judit Bajor, József Czimmer, Department of Gastroenterology, First Department of Medicine, University of Pécs, 7624 Pécs, Hungary

Judit Bajor, Péter Hegyi, Department of Translational Medicine, First Department of Medicine, University of Pécs, 7624 Pécs, Hungary

Ákos Szűcs, First Department of Surgery, Semmelweis University, 1082 Budapest, Hungary

Péter Hegyi, Hungarian Academy of Sciences - University of Szeged, Momentum Gastroenterology Multidisciplinary Research Group, 6720 Szeged, Hungary

Andrea Párniczky, Heim Pál Children's Hospital, 1089 Budapest, Hungary

Author contributions: Solymár M, Pár G, Bajor J, Szűcs Á and Czimmer J searched for the articles in Pubmed and screened them using the titles and abstracts; Márta K, Mikó A, Rumbus Z and Varjú P searched for the articles in Embase and screened them using the titles and abstracts; data was collected from the eligible papers by Mosztbacher D and Párniczky A; Farkas N performed the statistical analysis; Mosztbacher D, Hegyi P and Párniczky A drafted the manuscript.

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Correspondence to: Andrea Párniczky, MD, Institute for Translational Medicine, University of Pécs, Szigeti út 12., II. em., 7624 Pécs, Hungary. andrea.parniczky@gmail.com
Telephone: +36-72-536246
Fax: +36-72-536247

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Abstract

Acute pancreatitis (AP) is a serious inflammatory disease with rising incidence both in the adult and pediatric populations. It has been shown that mitochondrial injury and energy depletion are the earliest intracellular events in the early phase of AP. Moreover, it has been revealed that restoration of intracellular ATP level restores cellular functions and defends the cells from death. We have recently shown in a systematic review and meta-analysis that early enteral feeding is beneficial in adults; however, no reviews are available concerning the effect of early enteral feeding in pediatric AP. In this minireview, our aim was to systematically analyse the literature on the treatment

of acute pediatric pancreatitis. The preferred reporting items for systematic review (PRISMA-P) were followed, and the question was drafted based on participants, intervention, comparison and outcomes: P: patients under the age of twenty-one suffering from acute pancreatitis; I: early enteral nutrition (per os and nasogastric- or nasojejunal tube started within 48 h); C: nil per os therapy; O: length of hospitalization, need for treatment at an intensive care unit, development of severe AP, lung injury (including lung oedema and pleural effusion), white blood cell count and pain score on admission. Altogether, 632 articles (PubMed: 131; EMBASE: 501) were found. After detailed screening of eligible papers, five of them met inclusion criteria. Only retrospective clinical trials were available. Due to insufficient information from the authors, it was only possible to address length of hospitalization as an outcome of the study. Our mini-meta-analysis showed that early enteral nutrition significantly (SD = 0.806, P = 0.034) decreases length of hospitalization compared with nil per os diet in acute pediatric pancreatitis. In this minireview, we clearly show that early enteral nutrition, started within 24-48 h, is beneficial in acute pediatric pancreatitis. Prospective studies and better presentation of research are crucially needed to achieve a higher level of evidence.

Key words: Pediatric pancreatitis; Enteral nutrition; Nil per os diet; ATP restoration; Length of hospitalization

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Core tip: Acute pancreatitis is a serious inflammatory disease with rising incidence both in adult and pediatric medicine. Despite the existing research activities in this field, no specific therapy is available to treat this disease. Results in basic science strongly suggest that early energy restoration could be the first-line treatment for acute pancreatitis. Our minireview suggests that early enteral nutrition should have priority in the treatment of acute pediatric pancreatitis.

Mosztbacher D, Farkas N, Solymár M, Pár G, Bajor J, Szűcs Á, Czimmer J, Márta K, Mikó A, Rumbus Z, Varjú P, Hegyi P, Párniczky A. Restoration of energy level in the early phase of acute pediatric pancreatitis. *World J Gastroenterol* 2017; 23(6): 957-963 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i6/957.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i6.957

INTRODUCTION

Acute pancreatitis (AP) is a serious inflammatory disease with rising incidence both in adult and pediatric populations[1,2]. Common characteristics in both age groups are that no specific therapy is available to treat the disease and that the general supportive treatments at the early phase of the disease are usually volume resuscitation and a nil per os (NPO) diet[3-6]. However, while there is clear evidence in the literature that volume therapy is beneficial, the latter treatment is questionable.

One of the main reasons for the debate is that the pathogenesis of the disease clearly suggests the opposite. Irrespective of the etiological factors, mitochondrial damage and energy depletion are the leading intracellular responses in the early phase of the disease in the exocrine pancreas[7-10]. Bile acids[11-14], ethanol, fatty acids and their non-oxidative metabolites, fatty acid ethyl esthers[8,9,15-18] were shown to elevate the intracellular Ca^{2+} concentration, causing mitochondrial damage and a resultant decrease of intracellular ATP concentration. This will lead to inhibited fluid and bicarbonate secretion and CFTR Cl^- channel dysfunction in the ductal cells and secretory block and intracellular trypsinogen activation in the acinar cells (Figure 1)[9,16,19,20]. Very importantly, restoration of ATP levels both in acinar and ductal cells prevents (at least in part) the toxic effects of the etiological factors[7,21,22] noted above. These data strongly suggest that an energy supply, for example, *via* enteral nutrition, should be beneficial for patients as compared to nil energy.

Notably, early enteral nutrition (EEN) either *via* oral, nasogastric- or nasojejunal tube feeding is beneficial as regards systemic infections, complications, multi-organ failure, need for surgical interventions and mortality[6,23-30]. Enteral nutrition has already been proven to be beneficial in other inflammatory gastrointestinal diseases. The first-line recommendation to induce remission in pediatric Crohn's disease is exclusive enteral nutrition[31]. Enteral nutrition could also be effective in the maintenance of pediatric inflammatory bowel disease remission[32]. With regard to acute pancreatitis, three of the recent and most up-to-date guidelines for acute pancreatitis in adults clearly show the positive effect of enteral nutrition in moderate and severe AP[6,23,24]. Besides the energy supply, enteral nutrition in patients can also have other advantages as a first-line treatment for patients. It is well documented that the gut plays an important role as an immune barrier in the immune system and that EEN facilitates this barrier function. EEN significantly decreases pathogenic bacteria in the stool, alteration of intestinal flora and levels of serum endotoxins. EEN has a favourable effect on immune dysregulation caused by severe acute pancreatitis, which can reduce APACHE II scores, pancreatic sepsis, initial incidences of systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome[33,34].

Recent meta-analyses of adult data showed that EEN is beneficial in all severity groups in AP; however, no systematic review is available concerning the role of EEN in pediatrics[35]. Therefore, the aim was to review

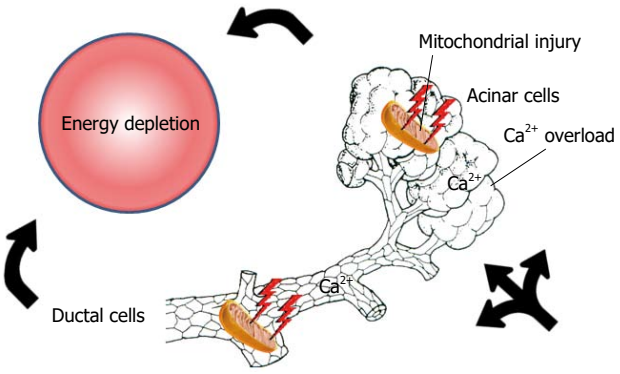

Figure 1 Early events in acute pancreatitis. Bile acids, ethanol, fatty acids or their non-oxidative metabolites, fatty acid ethyl esthers, induce calcium overload, causing mitochondrial damage and a resultant decrease in intracellular ATP concentration both in acinar and ductal cells. This will lead to general energy depletion in the pancreas.

the literature to analyse the effect of EEN *vs* NPO therapy on the outcome of acute pediatric pancreatitis (APP) and aggregate the information in APP leading to a higher statistical power and more robust point estimate than is possible from the individual studies.

The preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) were followed[36]. Our structured literature search was based on the participants, intervention, comparison and outcomes format: P: patients under the age of twenty-one suffering from acute pancreatitis; I: early enteral nutrition (per os and nasogastric- or nasojejunal tube started within 48 h); C: NPO therapy [per os/nasogastric- or enteral tube after 48 h and total parenteral nutrition (TPN) within or after 48 h]; O: length of hospitalization, need for intensive care unit (ICU), complications, necessity of antibiotics, surgical/non-surgical interventions and mortality.

In February 2016, a literature search was performed on the PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and EMBASE (https://www.embase.com) databases using the following Medical Subject Headings and search terms: "pediatric" OR "paediatric" AND "pancreatitis". The search was limited to human studies, full-text publications with abstracts in English with no time period, resulting in 632 articles altogether (PubMed: 131; EMBASE: 501).

The articles were checked separately. Meta-analyses, reviews, case reports and articles on chronic pancreatitis were excluded and duplicates were removed (Figure 2). Potentially eligible papers were selected, and, finally, five of them with relevant data on EEN or/with NPO therapy in acute pediatric pancreatitis in patients under twenty-one years old were included (Table 1)[37-41]. To reduce the risk of bias, the literature search was independently performed by three researchers following the inclusion criteria noted above.

The details in the collected articles were checked, and only articles where both EEN and NPO were presented separately were used. Two articles met this criterion. The two articles contained three separate data pairs, where EEN was compared to NPO (Figure 3). The following parameters were collected: length of hospitalization (LOH), need for treatment at an ICU, development of severe AP, lung injury (including lung oedema and pleural effusion), white blood cell count and pain score on admission. Only one of the five investigated parameters (LOH) contained a minimum of three items, which were analysed statistically.

Table 1 Studies included in the quantitative synthesis

Ref.	Data	Groups	NO. of patients
Abu-El-Haija *et al*[37], 2016	Yes	EEN	24
		NPO	14
Flores-Calderón *et al*[41], 2009		Only NPO	18
Goh *et al*[40], 2003		Only NPO	12
Raizner *et al*[39], 2013		Only NPO	7
Szabo *et al*[38], 2015	Yes	EEN + IVF lo	55
		NPO + IVF lo	20
	Yes	EEN + IVF hi	96
		NPO + IVF hi	30

EEN: Early enteral nutrition; NPO: Nil per os.

The meta-analytic calculation was made with Comprehensive MetaAnalysis (V3) software using the random effects model (the DerSimonian-Laird method). We calculated a weighted standard difference in means and 95%CI. In the case of one study (Abu-El-Haija *et al*[37], 2016), we converted the median and range values to means and standard deviation using the modified Hozo's formula by Wan *et al*[42]. For a visual inspection, we used a forest plot.

Figure 3 shows the parameters collected from the articles. It was only possible to perform forest plot analyses on LOH. EEN significantly decreased LOH (SD = 0.806, P = 0.034) compared to the standard NPO diet (Figure 3).

DISCUSSION

Several therapeutic recommendations are available in the literature on nutrition in acute pancreatitis. The IAP/APA guideline suggests enteral tube feeding as the first-line therapy in patients requiring nutritional support with predicted severe and severe acute pancreatitis[6]. According to the Japanese guideline, enteral nutrition in the early phase of severe acute pancreatitis can decrease the incidence of complications and elevate the survival rate[24]. Recent meta-analyses of adult studies revealed that EEN decreases mortality, rate of interventions and the incidence of multi-organ failure in severe acute pancreatitis. Moreover, group analyses of 17 parameters including laboratory parameters (such as CRP and white blood cells) and symptoms (such as pain or presence of SIRS) suggested that EEN also has merits in mild acute pancreatitis. Since the incidence of APP has risen in the past twenty years (with 3.6 and 13.2/100000 children affected annually), we

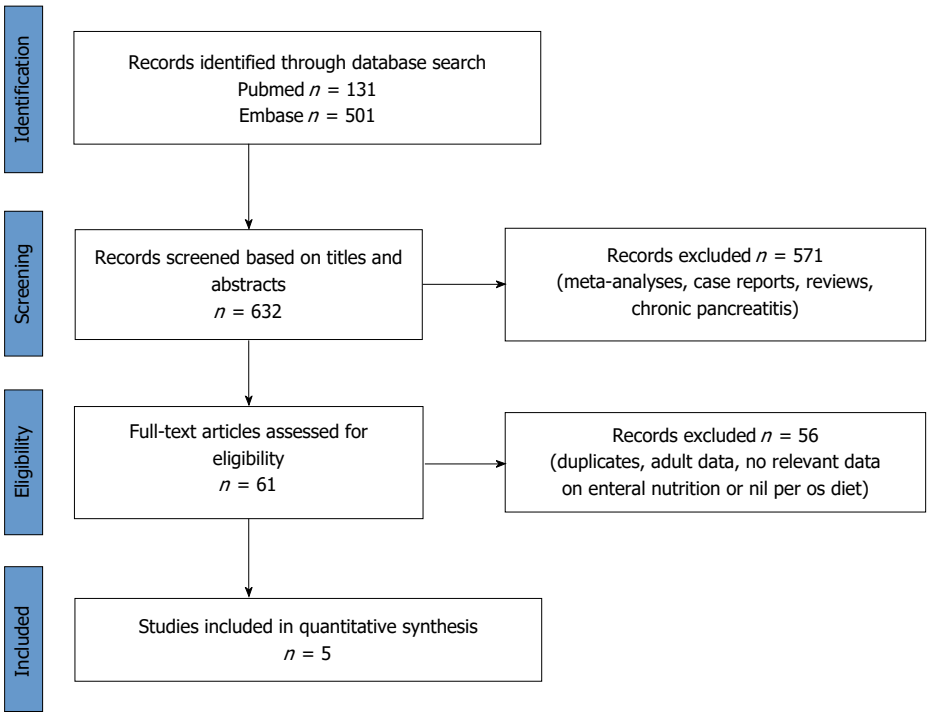

Figure 2 Flow chart on the methods used in the literature search.

Ref.		Therapy	*n*	LOH	Need for ICU	Severe AP	Lung injury	WBC	Pain score
Abu-El-Haija *et al*[37], 2016	1	EEN (< 24 h)	24	81.7 h					
		NPO (< 24 h)	14	94.7 h					
Szabo *et al*[38], 2015	2	NPO (< 48 h) + IVF lo (< 24 h)	20	7.1 d (1.01 SE)	20.0% (8.94 SE)	35.0% (10.7 SE)	11	13.60 (6.44 SD)	4.95 (3.75 SD)
		EEN (< 48 h) + IVF lo (< 24 h)	55	2.8 d (0.24 SE)	1.8% (1.80 SE)	9.1% (3.88 SE)	21	9.89 (3.89 SD)	4.62 (3.50 SD)
	3	NPO (< 48 h) + IVF hi (< 24 h)	30	5.0 d (0.58 SE)	13.0% (6.21 SE)	17.0% (6.80 SE)	14	13.30 (4.76 SD)	6.08 (3.19 SD)
		EEN (< 48 h) + IVF hi (< 24 h)	96	3.2 d (0.22 SE)	1.0% (1.04 SE)	4.2% (2.04 SE)	4	11.30 (5.25 SD)	5.47 (3.57 SD)

Study name	Statistics for each study					
	Std diff in means	Standard error	Lower limit	Upper limit	Z value	*P* value
Abu-El-Haija *et al*[37], 2016	0.089	0.336	-0.570	0.749	0.266	0.790
Szabo *et al*[38], 2015 A	1.554	0.290	0.985	2.122	5.352	0.000
Szabo *et al*[38], 2015 B	0.739	0.214	0.319	1.159	3.447	0.001
	0.806	0.380	0.062	1.551	2.124	0.034

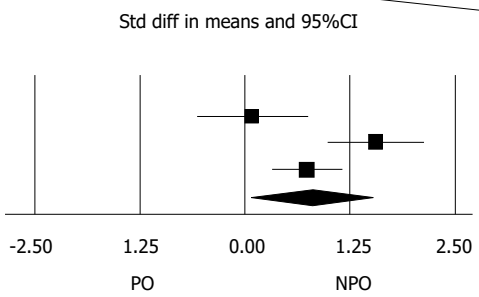

Figure 3 Two articles contained three separate data pairs where early enteral nutrition was compared to nil per os. LOH: Length of hospitalization; EEN: Early enteral nutrition; NPO: Nil per os. ICU: Intensive care unit; AP: Acute pancreatitis; WBC: White blood cell count.

systematically reviewed the literature to understand whether there is any beneficial effect of EEN *vs* NPO in children[43,44].

We faced several difficulties during our review: (1) APP is still underdiagnosed, thus decreasing the possibility of performing clinical trials[45]; (2) the number of studies on the management of these patients is very low, and there is still only a small number of studies focused on understanding the characteristics of the disease[46]; (3) the studies have not focused on the early management of the patients; the groups were therefore not separated; and (4) finally, but very importantly, the methods sections and the quality of data presentation in these articles are very low. Consequently, in many cases, it was impossible to obtain quality analysable data from the manuscripts for a proper broad-spectrum meta-analysis[37-39].

By the end of the search, we identified five articles containing relevant data on nutritional management during the early phase of APP. Raizner *et al*[39] published a retrospective analysis involving seven children with necrotizing pancreatitis. All the children received a

strict NPO diet, five patients received TPN and just one patient was treated with nasojejunal feeding for seven days. All the children required a prolonged hospital stay (with a mean of 20 d) for acute complications, with three of them suffering from late complications[39]. Goh *et al*[40] included twelve patients in their retrospective study. One patient needed a distal pancreatectomy, and eleven patients recovered with conservative management, with none of them receiving EEN. Two patients had acute complications, and two patients had recurrent AP[40]. Flores-Calderon *et al*[41] studied eighteen patients with acute pancreatitis caused by L-asparaginase due to acute lymphoblastic leukemia. All the patients were treated with bowel resting for a mean of 22 d, fourteen of the patients received TPN and four had an elementary diet. Two of the patients required intensive care unit admission, with local complications developing in twelve patients. None of the patients died from complications related to AP. Although these studies point out several disadvantages of that NPO diet, none of them could be enrolled in our meta-analysis.

Finally, it was possible to collect three sets of analysable data pairs where both NPO and EEN were present. Abu-El-Haija *et al*[37] conducted a prospective study of 38 children suffering from mild AP and retrospectively investigated the relationship of nutrition with pain and LOS. EEN feeding meant per os feeding and NPO was identified as oral feeding not being allowed for 24 h. Importantly, EEN, even with high fat intake, did not cause an elevation in pain in children, suggesting that EEN is a well tolerable nutritional possibility in children. The fact that LOS was much shorter in group EEN *vs* NPO points to EEN as a better way of treating APP[37]. The most advanced study was performed by Szabo *et al*[38], where several parameters were collected to understand the effect of EEN on the course of APP. Two hundred and one children suffering from mild AP were enrolled retrospectively. They compared EEN *vs* NPO both with and without aggressive fluid resuscitation. Fluid therapy was administered during the first 24 h, and the type of nutrition was determined during the first 48 h. Besides the beneficial effects of EEN on LOS, they also showed that EEN reduces the severity of the disease. Although our aim was to perform a meta-analysis on several parameters to understand the differences between EEN and NPO, we were only able to perform the statistical analyses on LOS, which clearly showed that EEN is not only a safe method of nutrition but also substantially decreases LOS, resulting in a better and less expensive treatment of mild APP[38].

CONCLUSION

The information collected by basic scientists, retrospective clinical studies and meta-analyses suggests that EEN should have priority in treating APP. However, it is perhaps self-evident that randomized multicenter clinical intervention trials would be crucial to achieving a higher level of evidence.

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Pain in the Early Phase of Pediatric Pancreatitis (PINEAPPLE Trial): Pre-Study Protocol of a Multinational Prospective Clinical Trial

Fanni Zsoldos[c, e] Andrea Párniczky[a, c] Dóra Mosztbacher[d] Anna Tóth[b] Natália Lásztity[c] Peter Hegyi[a] on behalf of the Hungarian Pancreatic Study Group and the International Association of Pancreatology

[a] 1st Department of Medicine, University of Szeged, MTA-SZTE Momentum Translational Gastroenterology Research Group, and [b] Department of Pediatrics, University of Szeged, Szeged, [c] Heim Pál Children's Hospital, Budapest, Hungary, [d] Balassa János Hospital Country of Tolna, Szekszárd, Hungary, and [e] Department of Pediatrics, Paracelsus Medical University, Salzburg, Austria

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What Is Known

- AP is an underdiagnosed disease in children.
- No evidence-based guidelines are available to give proper instruction concerning the necessity of pancreatic enzyme measurement during abdominal pain.
- No large worldwide prospective clinical trials exist for understanding the most common clinical characteristics of AP.

What Is New

- A multinational prospective clinical trial is registered and open for all centers.
- This is the first large worldwide study to explore the route from the first sign of abdominal pain to the diagnosis of AP (PINEAPPLE-P).
- This trial will help to diagnose AP in a reliable and cost-efficient way.

Key Words
Pediatric pancreatitis · Acute pancreatitis · Abdominal pain · Pancreatic enzyme · Evidence-based medicine

Abstract
Background: There are unexpectedly large differences between the incidences of acute pancreatitis (AP) as indicated by different hospitals. Retrospective studies suggest that the reason behind this is the large differences that exist between the local managements of abdominal pain at emergency units. Unfortunately, no evidence-based medicine (EBM) guidelines are available to give proper instruction concerning the necessity of serum pancreatic enzyme measurement during abdominal pain. ***Summary:*** Pain in Early Phase of Pediatric Pancreatitis (PINEAPPLE) is an observational, multinational observational clinical trial to explore the route from the first sign of abdominal pain to the diagnosis of pancre-

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Péter Hegyi, MD, PhD, DSc
Professor of Medicine, 1st Department of Medicine
University of Szeged Korányi fasor 8
6720 Szeged (Hungary)
E-Mail hegyi.peter@med.u-szeged.hu

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atitis (PINEAPPLE trial). The PINEAPPLE-R subtrial is a retrospective review on the records of children (patients under 18) appearing at emergency units – a review of their clinical symptoms, results of imaging examinations and laboratory parameters. The PINEAPPLE-P subtrial is a prospective trial designed to develop a fast and simple EBM guideline that helps to evaluate (in a reliable and cost-efficient way) the necessity of pancreatic enzyme test and abdominal ultrasonography (or even computed tomography) when a child has abdominal pain. The trial has been registered at the ISRCTN registry and has received the relevant ethical approval. ***Key Message:*** The PINEAPPLE trial will help to recognize AP in children in a highly efficient manner. © 2015 S. Karger AG, Basel

Introduction

Several publications describe an increasing incidence of acute pancreatitis (AP) in both children and adults [1–3]. Importantly, AP became the most common reason of hospitalization in the United States in 2012 with over 270,000 discharges [4]. The reason behind the impressive incidence of AP could be either improved awareness of the disease and/or the elevated number of the new incidence [5–7].

Although two major studies have proved that the incidence of AP is not much less in children than in adults (3.6–13.2 per 100,000), the overall incidence is below 1 per 100,000 or even less worldwide [8, 9]. A retrospective trial in Pittsburgh suggested a close relationship between the number of serum amylase and lipase measurement and the rising incidence of the disease [7]. Their data showed that the increased pancreatic enzyme testing could account for 94% of the change in all AP admission, suggesting that pediatric pancreatitis is an underdiagnosed disease.

There are factors that make the diagnosis of AP challenging when it comes to ordering pancreatic enzymes: (i) abdominal pain is a common complaint in kids; 50% of the cases are in the category of pain-predominant functional gastrointestinal disorder with no significant morbidity [10], (ii) most of the hospitals cannot afford measuring serum amylase/lipase in every children having abdominal pain [10], however (iii) no evidence-based medicine (EBM) guidelines are available to give proper instruction concerning the necessity of pancreatic enzyme measurement during abdominal pain. Therefore, most of the pancreatic enzyme test ordering are based on individual experience of the clinicians. It is almost needless to say that international clinical observational trials are crucially needed to understand the most common clinical characteristics of AP.

The Hungarian Pancreatic Study Group (HPSG) was established in 2011 in order to improve patients' life suffering in pancreatic diseases. To achieve our aims, we (i) developed an electronic data registry and biobank for patients (www.pancreas.hu), (ii) published the currently available EBM guidelines [11–15], (iii) established specific study sessions including a pediatric session, and (iv) organized multicentre clinical trials [16, 17].

Here we propose a multicenter, clinical trial called PINEAPPLE (Pain in Early Phase of Pediatric Pancreatitis), which is open to all institutions to join in. The trial protocol aims at exploring the route from the first sign of abdominal pain to the diagnosis of pancreatitis in a retrospective (PINEAPPLE-R) and prospective (PINEAPPLE-P) way.

Methods

Preliminary Settings

The study has been initiated and drafted by the HPSG. The protocols have been introduced in our latest international meeting held in Szeged in November 2014 (http://pancreas.hu/sites/info/files/conferences/ALPD2014-Program.pdf), which was attended by some of the well-established pediatric pancreatologists. Around 100 clinicians – 60 Hungarians and 40 international (from 9 different countries) investigators attended. The trial has been discussed and the suggested modifications have been included. The study has been discussed and accepted by the scientific committee of the International Association of Pancreatology (IAP), and therefore, it is running under the auspices of HPSG and IAP.

Ethical Issues

The studies have received the relevant ethical approval (No.: ad.52857-2/2014) issued by the National Hungarian Ethical Authority (ETT TUKEB). Study management will strictly follow the Ethical Guidelines for Observational Studies.

Trial Registration

The PINEAPPLE trial has been registered at the ISRCTN registry (ISRCTN35618458), which is a primary clinical trial registry recognized by WHO and ICMJE, which accepts all clinical research studies, providing content validation and curation and the unique identification number necessary for publication.

Centers throughout the world are welcome to participate in the PINEAPPLE trial. 'Online Call for Centers' will be available at http://www.pancreas.hu/en/studies/pineapple. Completion of the 'LETTER OF INTENT' form will be mandatory for registering participation of each institution. HPSG will acknowledge receipt of the 'LETTER OF INTENT' form and will contact centers providing them with additional study information.

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Patients and Centers Involved in the Trial

The PINEAPPLE trial is divided into 2 subtrials.

The aim of PINEAPPLE-R is a retrospective review on records of children (patients under 18) appearing at emergency units in one or two months depending on the size of the center; the review is centered around their clinical symptoms, results of imaging examinations and laboratory parameters.

The aim of PINEAPPLE-P is to provide a fast, simple and authentic system that helps to evaluate (in a reliable and cost-efficient way) the necessity of pancreatic enzyme test and abdominal ultrasonography (or even computed tomography) when a child has abdominal pain.

For the PINEAPPLE-R subtrial, we aim to collect around 1,000–2,000 cases (appearing in the ER unit with any kind of reasons/symptoms) from each center. Preliminary data suggested that around 5–10% of children admitted to the ER unit have abdominal pain. Therefore, per center, we expect around 100–200 cases with abdominal pain. Altogether, we wish to collect around 20,000 cases with abdominal pain within 3 years.

The PINEAPPLE-P is for patients under 18 years old appearing at ER unit with a leading symptom of abdominal pain. Our aim was to collect around 100 cases from each center. Altogether we wish to collect around 20,000 cases with abdominal pain within 3 years (http://www.pancreas.hu/en/studies/pineapple).

Protocol for Retrospective Data Collection for PINEAPPLE-R

This is a pure retrospective review of electronic computerized records of the relevant centers. Diagnosis and data concerning basic clinical symptoms (abdominal pain [yes/no], vomiting [yes/no], nausea [yes/no]) are required for all patients appearing on the ER unit. A diagnosis of abdominal pain is decided based on the doctor's opinion/record. If the patient has abdominal pain, information about the imaging examination of the pancreas (yes/no, if yes: positive/negative for pancreatitis) and laboratory parameters pancreatic enzyme measurements (either amylase or lipase, yes/no, if yes whether it is increased with 3×) are obligatory. Where data are available, information concerning the experience of the doctor in charge needs to be given (experienced doctor: at least 10 years experience with board certification, beginner: others). The information is collected into a uniform harmonized excel sheet that can be downloaded from the study website (http://pancreas.hu/en/studies/pineapple).

Inclusion Criteria for PINEAPPLE-R

- Under 18 years old
- Accurate electronic data mentioned in the protocol

Exclusion Criteria for PINEAPPLE-R

- Above 18 years old
- Inaccurate electronic data mentioned in the protocol

Protocol for Prospective Data Collection for PINEAPPLE-P

The PINEAPPLE-P subtrial has a questionnaire style data-collection method. The form is available on the web system http://www.pancreas.hu/en/studies/pineapple (table 1). The patients and parents have to be informed accordingly. The 'informed consent form' needs to be signed and the 'Questionnaire' needs to be filled out. Four quality control points are established. First, the local clinical research assistant must upload the data electronically and confirm that the data are the same as those in the hard copy. Second, the local institutional principal investigator (who has to have a medical doctoral degree) must recheck the uploaded data and confirm their validity and accuracy. Third, the central data administrator, who is based at the headquarters of HPSG, must control the accuracy and finally, the trial leader must go through the details. Patients with inadequate or insufficient data will be excluded.

Inclusion Criteria for PINEAPPLE-P

- Under 18 years old
- The leading symptom is acute abdominal pain

Exclusion Criteria for PINEAPPLE-P

- Above 18 years old
- No or chronic abdominal pain

Statistical Analyses

Patients data will be analyzed in 4 different age categories (0–6, 6–10, 10–16, 16–18 years). Association between each collected parameters (medical history, symptoms, etc.) and AP will be determined. Statistical analysis will be carried out by data mining methods. The applied methods will be determined based on the main characteristics of the collected data, and the most suitable method – or method combination – will be chosen. The following data mining methods are being contemplated: logistic regression, discriminant analysis, random forest analysis, decision tree, cluster analysis. ROC analysis and/or confusion matrix will be performed to evaluate the predictive power of the classification algorithm.

Expected Results

PINEAPPLE-R study will help to understand our current clinical practice on patients with abdominal pain in different countries and centers. The PINEAPPLE-P study will help to establish an EBM guideline, which will help to provide a fast, simple and authentic system to evaluate (in a reliable and cost-efficient way) the necessity of the pancreatic enzyme test and abdominal ultrasonography when a child has abdominal pain.

Authorship Policy

In order to give appropriate credit to each investigator/center, we will use standardized authorship policy. Concerning the PINEAPPLE-R subtrial: under 1,500 patients will generate 1, whereas above 1,500 patients will generate maximum of 2 co-authors from the center PINEAPPLE-P: every 100 patients will generate 1 co-author. All other investigators/contributors who do not meet the criteria for authorship will be listed in an 'Acknowledgements' section. For example, those who provide purely technical help or a department chair who provided only general support will appear in this section.

Discussion

The 2 out of 3 criteria rule is used to dianose AP both in adults and children [9, 11, 13]. Two of the following parameters are required: (1) abdominal pain, (2) serum amylase and/or lipase values ≥3 times upper limits of

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Table 1. Summary of clinical data required for PINEAPPLE-P

1. Patient personal details	
Gender	Male/female
Ethnicity/race	White/Black/Asian-Indian/not known
2. Details from the medical history	
(a) Family medical history	
Pancreas disorders in family history: AP/CP/AIP/PC	Yes/no, if yes: relationship to patient
(b) Medical history of the child	
Known diseases	Yes/no, if yes: description of the disease
Abdominal surgery	Yes/no, if yes: description of the disease
New medications taken in the last 2 weeks	Yes/no, if yes: description of them
New symptoms in the last 2 weeks	Yes/no, if yes: description of them
New diet, change in diet in the last 2 weeks	Yes/no, if yes: description of it
Any event strongly affecting the child emotionally in the last 2 weeks	Yes/no, if yes: description of it
Any event strongly affecting the child emotionally in the last 2 weeks	Yes/no, if yes: description of it
Change in the environment of the child in the last 2 weeks	Yes/no, if yes: description of it
Was there any examination concerning abdominal pain?	Yes/no, if yes: description of it
Length of breast milk feeding	Number of months
3. Complaints, symptoms	
(a) Abdominal pain	
How many hours have passed since the pain started?	Number of hours
How long did it last?	Number of hours
Intensity on a 1–10 scale	Number
Intensity	Decreasing/intensifying/stagnating
Forced posture	Yes/no
Nature	Dull/sharp/cramping
Location	Diffuse/localized
(b) In case of abdominal pain longer than 48 h	
Was the everyday activity influenced?	Yes/no
Did the child wake up at night because of the pain?	Yes/no
Which part of the day the pain appeared mostly?	After waking up/in the morning/in the Afternoon/in the evening/at night
Was it connected to eating?	Yes/no
Subfebrility, fever	Before eating/while eating/after eating
(c) Other complains	
Nausea	Yes/no
Vomiting	Yes/no, if yes: how many times?, and content of cast
Subfebrility, fever	Yes/no, if yes: since when? Temperature
Appetite	Good/retained/bad
Weight loss	Yes/no, if yes: how much? (kg), how long did it take? (weeks)
Jaundice	Yes/no, if yes: since when?
Stool	Normal/diarrhea/constipation/fatty/putrid/undigested food/bloody/mucus
4. Admission details, status	
Blood pressure, mm Hg, heart rate, /min	Number
Body weight, kg, body height, m	Number
Respiratory rate, /min	Number
Body temperature, °C	Number
Abdominal tenderness	Yes/no, location of abdominal tenderness
Abdominal guarding	Yes/no
Jaundice	Yes/no
Bowel sounds	No/hypoactive/normal/hyperactive
5. Laboratory parameters	
Amylase and/or lipase, U/l	

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Table 1. (continued)

6. Imaging examinations at admission	
Pancreas deviation suggesting AP	Yes/no
Pancreas deviation suggesting CP	Yes/no
7. Diagnosis	
8. Diagnosis – main group	Unknown, autoimmun, cardiology, dermatology, endocrinology, gastroenterology, etc.
9. What happened with the patient?	Admission to an inpatient department/went home/other

normal, (3) characteristic imaging finding for AP. Therefore, without measuring serum pancreatic enzymes and/or performing either transabdominal ultrasonograpy or CT, AP cannot be diagnosed. According to previous pediatric studies in AP, abdominal pain is present in 66 to 95% of the children with AP [18–24]; however, inconsistency and high variability exist between the studies. Most of the trials investigating the characteristics of abdominal pain have either low numbers or missing parameters causing inconsistencies between their data. Abdominal pain was most commonly localized to the epigastric region (62–89% of cases) [18, 25, 26] and was rarely associated with back pain (<10%) [20, 24]. Radiation to the back was only in 1.6–5.6% [22, 23, 26] of the cases. Diffuse abdominal pain was reported in 12–20% of patients [18, 22, 23], guarding at 29–37% [18, 20], whereas nausea or vomiting was found in 40–80% of patients [21–29]. A clinical study from Mexico described ileus at just under 50% of the children [27]. Abdominal distension was reported in 21–46% of the patients [18–22]. Other symptoms might be fever, ascites, pleural effusion and jaundice. Palpable abdominal mass was reported in a quarter of the patients in a study from Taiwan [26]. Symptoms of infants and toddlers are much more unspecific: fever with abdominal pain is found in 43%, epigastric tenderness in 57%, nausea in 29% [25]. In a study from Pittsburgh, 16% of the infants and toddlers had abdominal distension and 40% had fever [30]. Therefore, it is almost needless to say that a large international prospective cohort is necessary to understand the complaints and symptoms of AP in children.

In summary, here we propose an international observational clinical trial (PINEAPPLE) to collect a critical mass of clinical data from children with abdominal pain in order to develop EBM guidelines concerning the necessity for obtaining serum pancreatic enzyme testing and pancreatic imaging in pediatric patients who present to the emergency room with abdominal pain.

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Disclosure Statement

All authors disclose any sponsorship or funding arrangements relating to their research and disclose any possible conflicts of interest.

Authors' Contributions

P.H. initiated, whereas F.Z. and P.H. drafted the study. All of the authors were involved in designing and conducting discussions on the study.

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