Risk factors of chronic pancreatitis and pancreatic cancer

PhD Dissertation

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1. List of abbreviations:

AP	acute pancreatitis
aPFC	acute peripancreatic fluid collection
APR	Acute Pancreatitis Registry
BMI	body mass index
BRCA1	breast cancer type 1 susceptibility protein
BRCA2	breast cancer type 2 susceptibility protein
BUN	blood urea nitrogen
CA 19-9	carbohydrate antigen 19-9
CDKN2A	cyclin-dependent kinase inhibitor 2A
CI	confidence interval
CP	chronic pancreatitis
CT	computed tomography
early CP	early chronic pancreatitis
ERCP	endoscopic retrograde cholangio-pancreatography,
EUS	endoscopic ultrasound
FNA	fine-needle aspiration
HgbA1c	haemoglobin A1c
HHS	hyperosmolar hyperglycemic state
HPSG	Hungarian Pancreatic Study Group
IAP/APA	International Association of Pancreatology/ American Pancreatic Association
IR	incidence rate
IQR	interquartile range
LDH	lactate dehydrogenase
MPD	main pancreatic duct
MRI	magnetic resonance imaging
OGTT	oral glucose tolerance test
OR	odds ratio
PC	pancreatic cancer
PDAC	pancreatic ductal adenocarcinoma
PFCs	peripancreatic fluid collections

PP	pancreatic pseudocyst
RAP	recurrent acute pancreatitis
SIRS	systemic inflammatory response syndrome
STK11	serine/threonine kinase 11
STROBE	strengthening the reporting of observational studies in epidemiology

2. Vision

Our vision is to reduce the incidence and severity of recurrent acute pancreatitis (RAP), chronic pancreatitis (CP) and pancreatic cancer (PC) after an episode of acute pancreatitis (AP) by identifying the underlying mechanisms leading to their development and developing effective patient prevention and treatment strategies.

3. Mission

The aims of our research is to identify the biological and clinical factors contributing to the development of the RAP - early CP - CP axis following an episode of AP and the risk of PC as a continuation of this axis. We also aim to identify factors that directly contribute to the development of PC following AP.

We will achieve it through a comprehensive analysis of a prospectively collected international registry and a review of the current literature using state-of-the-art technologies. Our ultimate goal is to develop evidence-based guidelines that allow for adequate follow-up after the episode of AP.

This can help to prevent the development of CP or even PC, thus improving the outcome and quality of life of affected patients.

4. Specific goals

(1) Investigate the risk factors that increase the likelihood of developing RAP and CP after an AP episode.

(2) Investigate the relationship between AP and PC.

5. Background

5.1. Acute pancreatitis

AP is defined according to the evidence-based guidelines of the IAP/APA and HPSG [1, 2] when at least two of the following three criteria are met: (1) abdominal pain, (2) serum amylase or lipase elevation of at least three times the upper limit of normal, and (3) characteristic abnormalities seen on imaging. AP is a serious disease that affects many people worldwide, with an estimated incidence of 23-49 per 100 000 people per year [3, 4].

The course of the disease is mild in 70-75% of cases, but can be moderate to severe (MSAP) in 25-30%. In some cases, the mortality rate can be as high as 50%. [1, 2]. Clinical risk scores, such as the BISAP score, can help predict outcome. Various factors are taken into account when calculating risk, including age, systemic inflammatory response syndrome (SIRS), mental status deterioration, and elevated BUN (blood urea nitrogen) and serum LDH (lactate dehydrogenase) levels [2].

It should be highlighted that once the AP episode has healed and the patient has been discharged, the case is not considered closed. A previous study has shown that the same number of patients died in the 3 months following hospital discharge as during the hospital stay [5].

In the first 90 days after discharge, 37.5% of all deaths was due to end-stage PC, 22.5% of heart failure and the same proportion of patients died of AP-related sepsis. End-stage cancer was also the leading cause of death (43.2%) in the 3 and 12 month periods following discharge. [5].

This shows that it is very important to follow the patient after the first episode of pancreatitis to reduce the risk of a second episode of AP and to detect and treat other comorbidities early to increase survival.

5.1.1. Complications and comorbidities related to AP

5.1.1.1. Peripancreatic Fluid Collections (PFCs)

Peripancreatic fluid collections (PFCs) are enzyme-rich fluid collections that form due to disruption of pancreatic ducts. This results in pancreatic secretions being released into the retroperitoneum or peripancreatic tissue planes.

5.1.1.1.1 Acute peripancreatic fluid collection (aPFC)

Peripancreatic fluid associated with interstitial oedematous pancreatitis within the first 4 weeks with no associated peripancreatic necrosis. Peripancreatic fluid associated with interstitial oedematous pancreatitis within the first 4 weeks without associated peripancreatic necrosis [6].

5.1.1.1.2. Pancreatic pseudocyst (PP)

Pancreatic pseudocyst is a localised fluid rich in amylase and other pancreatic enzymes. It is surrounded by a fibrous wall of tissue, which is not lined by epithelium [7]. Pseudocysts are associated with the ductal system of the pancreas. They form because the pancreatic ducts rupture due to increased pressure. The increase in pressure can be caused by narrowing of the main pancreatic ducts, calcification or pancreatic necrosis due to AP [8, 9]. Appears 4 weeks after the onset of interstitial oedematous pancreatitis and is not associated with necrosis [6].

5.1.1.1.3. Pancreatic necrosis

Can be divided into acute necrotic collection and walled of necrosis. Acute necrotic collection is a collection containing variable amounts of both fluid and necrosis of the pancreatic and/or peripancreatic tissues associated with necrotising pancreatitis.

Walled-off pancreatic necrosis is a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall usually occurring more than 4 weeks after the onset of necrotising pancreatitis [6].

5.1.1.2. Diabetes mellitus (DM)

DM is a group of metabolic diseases that share the common feature of elevated blood glucose levels, or hyperglycaemia. Severe hyperglycaemia is associated with classic symptoms such as polyuria, polydipsia, fatigue and reduced performance, unexplained weight loss, visual disturbances and susceptibility to infection, up to ketoacidosis or the non-ketoacidotic hyperosmolar hyperglycemic state (HHS) with coma risk [10]. Diabetes is diagnosed on the basis of fasting glucose, casual glucose, oral glucose tolerance test (OGTT) or haemoglobin A1c (HbA1c). Hyperglycaemia develops continuously and the disturbances of fasting and postprandial glycaemia occur at different times [11, 12].

The relationship between DM and AP is twofold. Several studies have shown that diabetes is a risk factor in the development of AP [13, 14, 15]. Among the possible machanisms, oxidative stress caused by hyperglycaemia stimulates the production of inflammatory mediators [16]. Chronic vascular insufficiency caused by high blood glucose impairs pancreatic microcirculation, contributing to the development of ischaemic AP [17, 18]. On the other hand, after an episode of AP, the rate of newly diagnosed diabetes increases, with the proportion of newly diagnosed patients ranging from 11-23% [19, 20]. Causes of the development of DM include islet cell loss due to pancreatic necrosis, disturbances of the insulin-insulin axis and persistent inflammation. [21].

5.2. Recurrent acute pancreatitis

The diagnosis of RAP can only be made after the second episode of AP, so it can be interpreted as a retrospective diagnosis, which can be an intermediate state between AP and CP [22, 23]. Only estimates of the incidence of RAP are available, with an approximate incidence of RAP of ~8-10/100,000/year and a prevalence of ~110-140/100,000 population (~350,000-500,000 cases) based on the recurrence rates after the first AP attack and the possibility of further AP attacks in patients with RAP [24]. A 2024 systematic review and meta-analysis showed that the incidence rate (IR) of RAP after first AP among adults was 5.26 per 100 person-years (95% CI: 3.99-6.94) [25].

5.3. Chronic pancreatitis

CP is characterised by irreversible damage to the pancreas causing endocrine and exocrine dysfunction which results in decreased quality of life and reduced life expectancy [26]. Globally, the incidence of CP is estimated at around ten cases per 100 000 person-years [3]. CP was already present in 5-7% of patients hospitalised because of AP [27, 28]. In terms of clinical presentation, it can be divided into 3 stages. The early stage (stage A) is characterized by recurrent clinical AP. The next stage (stage B) is characterised by persistent pain and local complications with preserved endocrine and exocrine function. In the final stage of the disease (stage C), endocrine and/or exocrine function is lost and pancreatic fibrosis dominates the symptoms. [29].

5.4. Pancreatic cancer

PC remains one of the deadliest malignancies, with poor prognosis largely due to late-stage diagnosis. Despite advancements in imaging and treatment, early detection of PC is still unresolved, and the current screening programs are not effective in identifying resectable tumors at an early stage [30].

The carbohydrate antigen 19-9 (CA 19-9) cannot be used as a screening test because some people do not express it, so it is not helpful in that population for diagnostic and therapeutic measures. [31]. In general, we can say that no effective laboratory screening test is currently available [32]. According to recent studies, only 15-20% of patients are candidates for surgical resection at the time of diagnosis [33], thus, identifying high-risk populations who may benefit from enhanced screening and early intervention is crucial.

The risk factors for PC can broadly be categorized into two major groups: (1) non-modifiable factors and (2) modifiable factors [34]. However, some factors, such as DM, are harder to classify due to their complex relationship with cancer risk [35]. Among the non-modifiable risk factors, genetic predisposition plays a significant role in PC risk. For instance, carriers of BRCA1 and BRCA2 mutations have a 3-5% lifetime risk of developing PC [36]. Other mutations, such as those in the STK11 (associated with Peutz-Jeghers syndrome) and CDKN2A genes, also significantly elevate risk [37]. Individuals with hereditary pancreatic cancer syndrome such as Lynch syndrome have up to a 10-

20% increased lifetime risk. Age and family history are also part of the non-modifiable risk factor. The risk of PC increases significantly with age, with most cases occurring in individuals over 60 years old [37], whereas, individuals with a first-degree relative who has had PC have a 2-3 times higher risk of developing the disease [38]. Tobacco use is one of the most well-established modifiable risk factors, contributing to approximately 25% of PC cases [39]. Smokers have a 2-3 times higher risk compared to non-smokers [40]. Obesity increases the risk of PC by about 20-50%, with higher risks associated with a body mass index (BMI) above 30 [41]. Physical inactivity and poor dietary habits also contribute to increased risk [42]. Chronic heavy drinking is associated with CP, which can increase the risk of PC [40]. Diabetes is a unique risk factor, as it is both a consequence and a potential cause of PC [43]. Long-standing type 2 diabetes is associated with a 1.5-2-fold increase in PC risk. However, new-onset diabetes may be an early indicator of undiagnosed PC, complicating its classification as a modifiable or non-modifiable risk factor [44]. Importantly, on average, PC is diagnosed within 1-3 years after the onset of new diabetes [35]. This has led to speculation about the underlying relationship between these two conditions. Diabetes indeed could serve as an early marker of undiagnosed PC [34]. PC also impairs exocrine function and can cause AP by tumoural obstruction of the pancreatic duct and release of digestive enzymes into the interstitial space [45].

It is known that PC can act as an etiological factor for AP [46]. Earlier studies also showed that PC risk increases after AP [28, 47].

The aims of our research is to identify the biological and clinical factors contributing to the development of the RAP - early CP - CP axis following an episode of AP and the risk of PC as a continuation of this axis. We also aim to identify factors that directly contribute to the development of PC following AP.

6. Dose-dependent and synergistic effects of alcohol consumption and smoking on local pancreatic damage

6.1. Aims

The aim of our study was to investigate the effects of alcohol consumption and smoking on pancreatic tissue, and to determine whether alcohol and smoking doses are associated with the extent of pancreatic tissue damage. We also examined whether the combined effects of alcohol consumption and smoking increase pancreatic tissue damage, thus increasing the likelihood of RAP and CP.

6.2. Background

CP is characterised by irreversible damage to the pancreas causing endocrine and exocrine dysfunction which results in decreased quality of life and reduced life expectancy [26]. Adam et al recently published an interesting study on a possible diagnostic tool for CP based on metabolomic profiles of patients and controls [48].

The rate of development of CP is associated with the number of episodes of acute pencreatitis, as seen in our previous international cohort study [27, 48]. For this reason, early diagnosis of CP has become more important, along with preventive interventions. It is important to prevent irreversible pancreatic tissue damage.

Alcohol is known to be a major etiological factor in CP. Smoking, often associated with alcohol consumption, increases the risk of recurrent AP and increases the likelihood of developing CP.

Smoking was the main risk factor for RAP in a follow-up study of 669 patients with AP, and the combination of alcohol consumption and smoking was the main factor for CP development. [50].

Therefore, patient education and cessation programs are very important in reducing the development of AP and reducing progression to CP [51, 52].

Unfortunately, smoking cessation and alcohol abstinence seem to be unachievable for most patients and in many cases are not even attempted. As a consequence, it is

questionable whether reducing the amount consumed can prevent relapse and progression of inflammation.

Smoking and alcohol consumption increase each other's harmful effects, as is clearly shown in the basic research results [53, 54].

However, large cohorts are not available to determine whether alcohol consumption and smoking increase pancreatic tissue damage in a dose-dependent manner or by potentiating each other.

6.3. Methods

For our analysis, we used the international cohort of the Acute Pancreatitis Registry initiated by the Hungarian Pancreas Study Group. We analysed 2441 cases, with data collected from 13 countries and 30 health centres (Table 1.). Further characteristics of the cohort are presented in Table 2.

Institute	City	Country	Number of cases
First Department of Medicine, University of Pécs	Pécs	Hungary	877
Department of Medicine, University of Szeged	Szeged	Hungary	423
Szent György University Teaching Hospital of County Fejér	Székesfehérvár	Hungary	395
Department of Internal Medicine, University of Debrecen	Debrecen	Hungary	169
Bajcsy-Zsilinszky Hospital	Budapest	Hungary	152
Dr. Réthy Pál Hospital of County Békés	Békéscsaba	Hungary	67
County Emergency Clinical Hospital - Gastroenterology and University of Medicine, Pharmacy, Sciences and Technology	Tragu Mures	Romania	57
Pándy Kálmán Hospital of County Békés	Gyula	Hungary	31
Vilnius University Hospital Santariskiu Klinikos	Vilnius	Lithuania	31
General Surgery, Consorci Sanitari del Garraf, Sant Pere de Ribes	Barcelona	Spain	28
Saint Luke Clinical Hospital	St. Petersburg	Russia	28
Helsinki University Central Hospital	Helsinki	Finland	25
Dr. Bugyi István Hospital	Szentes	Hungary	23
Hospital of Bezmialem Vakif University, School of Medicine	Istanbul	Turkey	20
Markusovszky University Teaching Hospital	Szombathely	Hungary	18
Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital	Miskolc	Hungary	14
Bács-Kiskun County Hospital	Kecskemét	Hungary	11
Centrum péče o zažívací trakt, Vítkovická nemocnice a.s.	Ostrava	Czech Republic	11
Clinical Hospital Center Rijeka	Rijeka	Croatia	11
Csongrád County Health Center	Makó	Hungary	10
Gomel Regional Clinical Hospital	Gomel	Belarus	8
Bogomolets National Medical University	Kiev	Ukraine	8
Department of Surgery, University of Debrecen	Debrecen	Hungary	7
Gastroenterology, Hepatology and Nutrition Centre, Pauls Stradins Clinical University Hospital	Riga	Latvia	6
Polyclinic of Hospitaller Brothers of Saint John of God	Budapest	Hungary	4
Second Department of Medicine, Semmelweis University	Budapest	Hungary	2
Keio University	Tokyo	Japan	2
Central Military Emergency Hospital "Dr Carol Davila"	Bucharest	Romania	1
Heim Pál National Pediatric Institute	Budapest	Hungary	1
Medical Centre, Hungarian Defence Forces	Budapest	Hungary	1
Total			**2 441**

Table 1. Centre distribution.

Variable	Value (n=2441)
Age in years, median (IQR)	57 (44–69)
Male, n (%)	1 395 (57.1%)
Etiology, n (%)	
Biliary	972 (39.8%)
Alcoholic	475 (19.5%)
Alcoholic and hypertriglyceridaemia	57 (2.3%)
Hypertriglyceridaemia	77 (3.2%)
Post-ERCP	68 (2.8%)
Idiopathic	442 (18.1%)
Combined	89 (3.6%)
Other	261 (10.7%)
Revised Atlanta classification	
Mild, n (%)	1 738 (71.2%)
Moderate, n (%)	579 (23.7%)
Severe, n (%)	124 (5.1%)
Mortality, n (%)	67 (2.7%)
Length of stay in days, median (IQR)	8 (6–12)
Patients with local complication, n (%)	654 (26.8%)
Acute pancreatic fluid collection, n (%)	545 (22.4%)
Pseudocyst, n (%)	191 (7.8%)
Acute necrotic collection, n (%)	218 (8.9%)
Patients with systemic complication, n (%)	205 (8.4%)
Respiratory failure, n (%)	140 (5.7%)
Heart failure, n (%)	52 (2.1%)
Renal failure, n (%)	87 (3.6%)
New-onset diabetes, n (%)	77 (3.2%)

Table 2. General characteristics of the total analysed cohort. ERCP: endoscopic retrograde cholangiopancreatography, IQR: interquartile range.

The patient population was divided into groups according to current amounts of smoking and alcohol consumption (Figure 1.).

SMOKING	N
Non-smoker	1 691
Light smoker	358
Heavy smoker	358
Total	2 407

ALCOHOL	N
Non-drinker	1 255
Light drinker	194
Heavy drinker	328
Total	1 777

Light smoker = <20 cigarettes/day
Heavy smoker = ≥20 cigarettes/day
Light drinker = <200 g per week
Heavy drinker = ≥200 g per week

Figure 1. Light and heavy alcohol consumption and smoking groups and definitions.

General characteristics of the smoking and drinking groups, including amylase and lipase levels, RAP, CP and local complications are shown in Table 3.

SMOKING DOSE DEPENDENCY	NON-SMOKER	LIGHT SMOKER	HEAVY SMOKER	p*
AMYLASE (N=2237)				
N	1 571	332	334	<0.001
Mean (SD)	1 206 (1 188)	851 (952)	692 (788)	
Median (IQR)	831 (343, 1 681)	496 (240, 1 112)	398 (195, 808)	
Minimum; Maximum	13; 8 544	30; 7 532	32; 4 852	
LIPASE (N=1705)				
N	1 149	274	282	<0.001
Mean (SD)	2 916 (3 523)	1 962 (2 398)	1 587 (2 459)	
Median (IQR)	1 675 (635, 3 846)	1 027 (499, 2 508)	822 (376, 1 692)	
Minimum; Maximum	10; 24 940	14; 13 398	31; 20 569	
RAP AND CP (N=2407)				
RAP, n (%)	321 (19%)	94 (26%)	105 (29%)	<0.001
CP, n (%)	46 (2.7%)	41 (11%)	50 (14%)	<0.001
LOCAL COMPLICATIONS (N=2386)	438 (26%)	92 (26%)	109 (31%)	0.200

Table 3a. General characteristics of smoking groups.
SD: standard deviation; IQR: interquartile range; RAP: recurrent acute pancreatitis; CP: chronic pancreatitis
*Kruskal-Wallis rank sum test; Pearson's Chi-squared test.

ALCOHOL DOSE DEPENDENCY	NON-DRINKER	LIGHT DRINKER	HEAVY DRINKER	p*
AMYLASE (N=1649)				
N	1 158	186	305	<0.001
Mean (SD)	1 247 (1 216)	821 (892)	663 (846)	
Median (IQR)	863 (366, 1 719)	522 (230, 1 016)	379 (180, 782)	
Minimum; Maximum	13; 8 544	28; 5 283	30; 7 000	
LIPASE (N=1231)				
N	845	153	233	<0.001
Mean (SD)	2 864 (3580)	2 155 (2 575)	1 723 (2 862)	
Median (IQR)	1 571 (572, 3 756)	1 276 (570, 2 681)	736 (353, 1 730)	
Minimum; Maximum	10; 24 940	110; 17 904	19; 20 569	
RAP AND CP (N=1777)				
RAP, n (%)	239 (19%)	50 (26%)	98 (30%)	<0.001
CP, n (%)	47 (3.7%)	16 (8.2%)	36 (11%)	<0.001
LOCAL COMPLICATIONS (N=1762)	301 (24%)	51 (26%)	109 (34%)	0.003

Table 3b. General characteristics of alcohol consumption groups.
SD: standard deviation; IQR: interquartile range; RAP: recurrent acute pancreatitis; CP: chronic pancreatitis
*Kruskal-Wallis rank sum test; Pearson's Chi-squared test.

Patients with acute AP were divided into the following four groups based on smoking and alcohol consumption. (1) non-smoking– non-drinking (NS-ND) group, (2) non-smoking– drinking (NS-D) group, (3) smoking– non-drinking (S-ND) and (4) smoking– drinking (S-D) group (Figure 2.). The summary of the combined alcohol consumption and smoking groups are presented in Table 4.

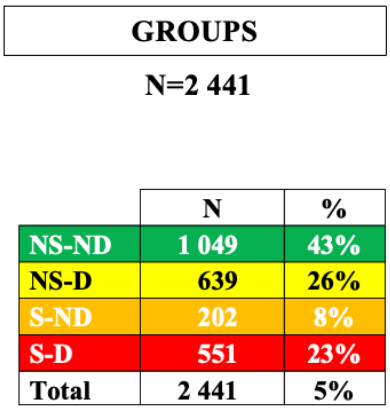


Figure 2. Summary of combined alcohol consumption and smoking groups in AP. AP, acute pancreatitis; NS–D: non-smoking– drinking; NS–ND: non-smoking– non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

SYNERGISTIC EFFECT	NS-ND	NS-D	S-ND	S-D	p*
AGE (N=2441)					
N	1 049	639	202	551	<0.001
Mean (SD)	62 (18)	57 (15)	51 (14)	47 (12)	
Median (IQR)	64 (50, 76)	59 (45, 69)	52 (42, 60)	47 (38,56)	
Minimum;Maximum	18; 95	19; 95	18; 91	18; 82	
SEX (N=2441)					
Male, n (%)	356 (34%)	470 (74%)	102 (50%)	467 (85%)	<0.001
Female, n (%)	693 (66%)	169 (26%)	100 (50%)	84 (15%)	
SEVERITY (N=2441)					
Moderately severe, **n (%)**	225 (21%)	153 (24%)	39 (19%)	162 (29%)	0.002
Severe, n (%)	61 (5.8%)	40 (6.3%)	5 (2.5%)	18 (3.3%)	0.022
Mortality, n (%)	32 (3.1%)	23 (3.6%)	2 (1.0%)	10 (1.8%)	0.100
AMYLASE (N=2266)					
N	967	601	188	510	<0.001
Mean (SD)	1 285 (1 233)	1 079 (1 101)	1 056 (1 117)	692 (764)	
Median (IQR)	918 (381, 1 751)	705 (298, 1 537)	652 (309, 1 428)	414 (197, 844)	
Minimum; Maximum	13; 8 544	28; 7 750	33; 7 532	23; 4 852	
LIPASE (N=1732)					
N	690	458	152	432	<0.001
Mean (SD)	2 999 (3 684)	2 788 (3 268)	2 244 (3 024)	1 637 (2 191)	
Median (IQR)	1 690 (623, 3 964)	1 624 (678, 3 537)	1 213 (426, 2 524)	914 (454, 1 924)	
Minimum; Maximum	10; 24 940	19; 18 380	14; 17 450	22; 20 569	
RAP AND CP (N=2441)					
RAP, n (%)	183 (17%)	137 (21%)	56 (28%)	151 (27%)	<0.001
CP, n (%)	28 (2.7%)	18 (2.8%)	19 (9.4%)	76 (14%)	<0.001

Table 4. General characteristics of smoking/alcohol groups.
NS–D: non-smoking– drinking; NS–ND: non-smoking– non-drinking;
S–D: smoking–drinking; S-ND: smoking–non-drinking.
*Kruskal-Wallis rank sum test; Pearson' s Chi-squared test.

6.4. Results

6.4.1. Dose dependency of alcohol consumption and smoking

We found a dose-dependent correlation in amylase and lipase levels for both smoking and alcohol consumption (Figure 3a., Figure 3b.). Among AP patients, a dose-dependent correlation was also found in the prevalence of RAP and CP (Figure 4.). Higher prevalence of local complications was associated with alcohol consumption (Figure 5). We use Pearson's $\chi 2$ test and Kruskal-Wallis rank sum test.

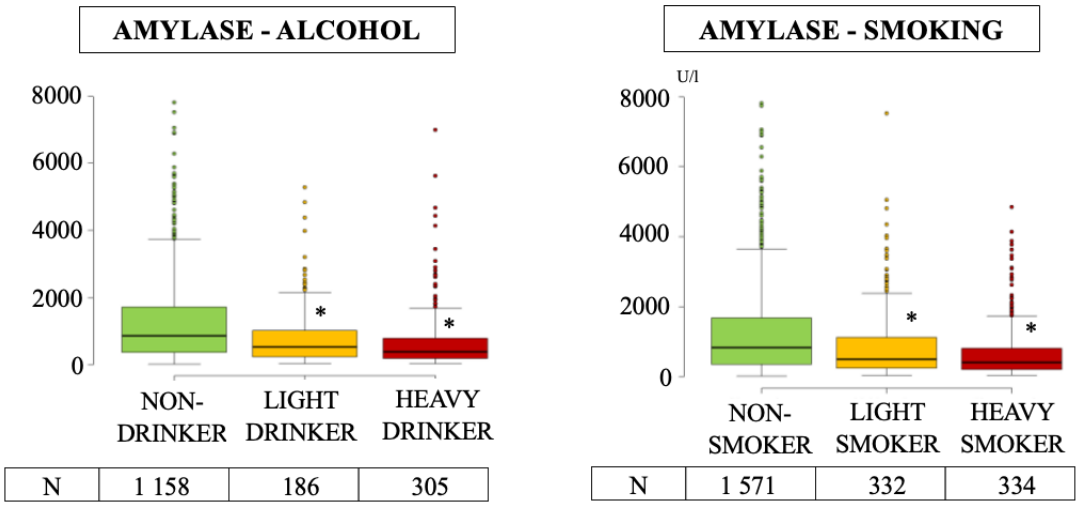


Figure 3a. Amylase levels on admission. *P<0.001.

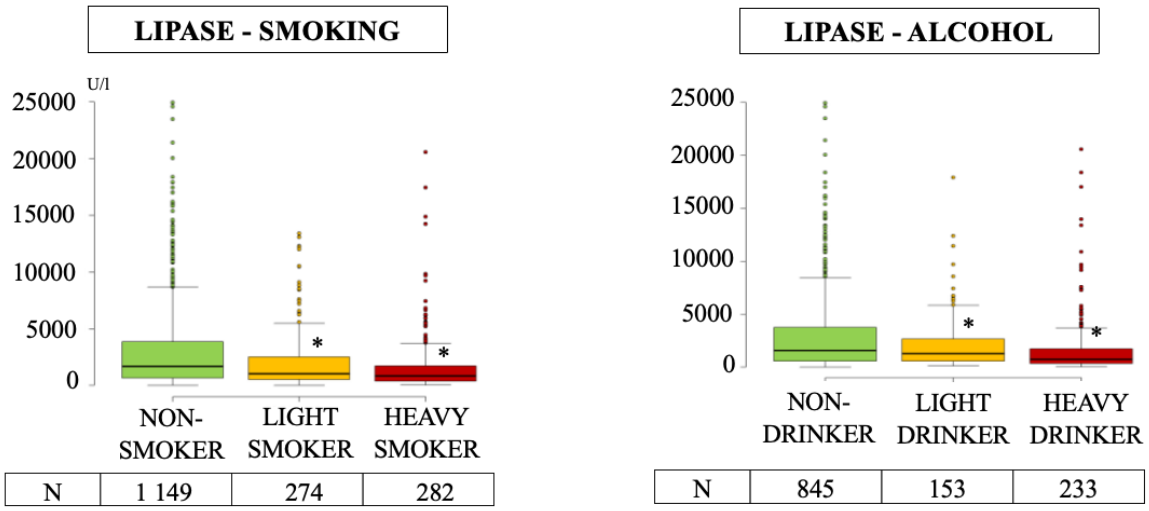


Figure 3b. Lipase levels on admission. *P<0.001.

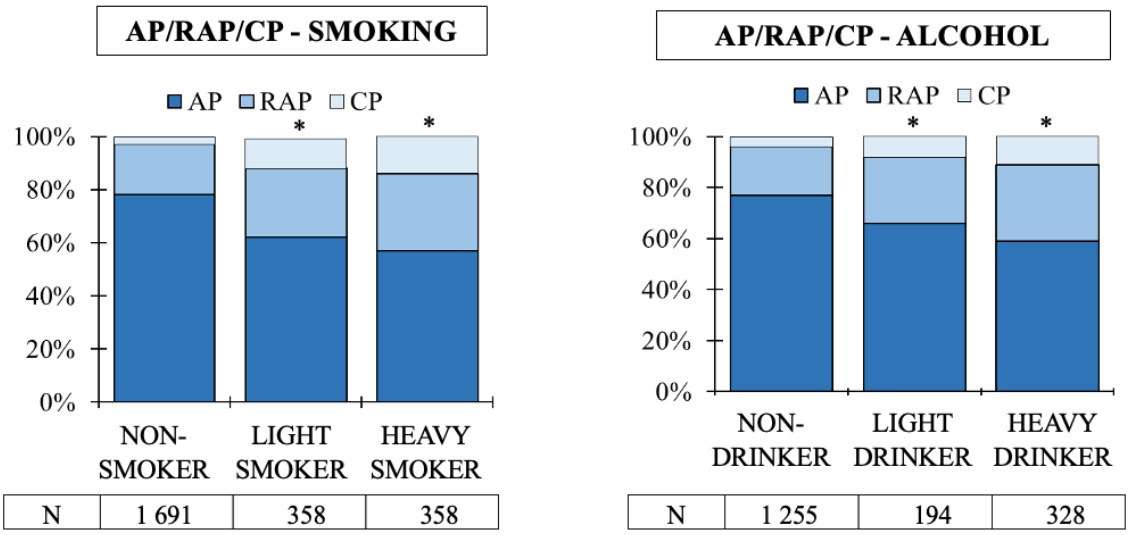


Figure 4. Prevalence of RAP and CP (%). AP: acute pancreatitis, RAP: recurrent acute pancreatitis, CP: chronic pancreatitis

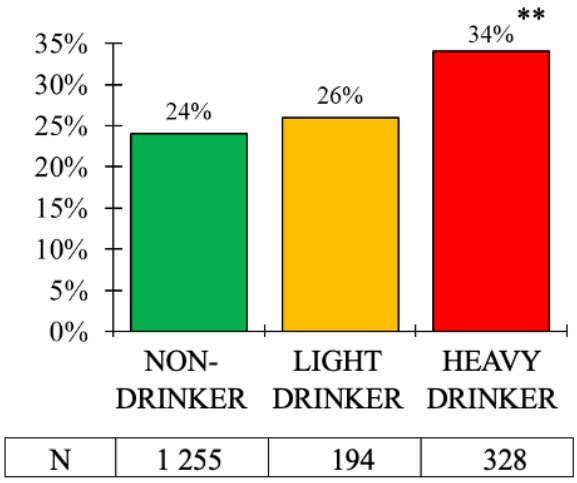


Figure 5. Proportion of local complications (%), **p=0.003.

6.4.2. Synergistic effect of alcohol consumption and smoking

We also examined the possible synergistic effects of alcohol consumption and smoking. As described in Methods, we divided the cohort population into 4 groups based on smoking and alcohol consumption status. Within each group, the gender distribution, age distribution and AP severity were presented in Figure 6a., 6b. and 6c.

Also in this case, Pearson's $\chi 2$ test and Kruskal-Wallis rank sum test were used..

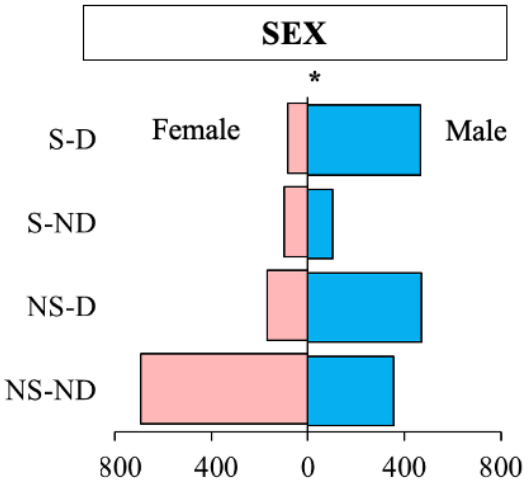


Figure 6a. Sex in combined alcohol consumption and smoking groups. *P<0.001 in all comparisons. AP, acute pancreatitis; NS–D: non-smoking– drinking; NS–ND: non-smoking– non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

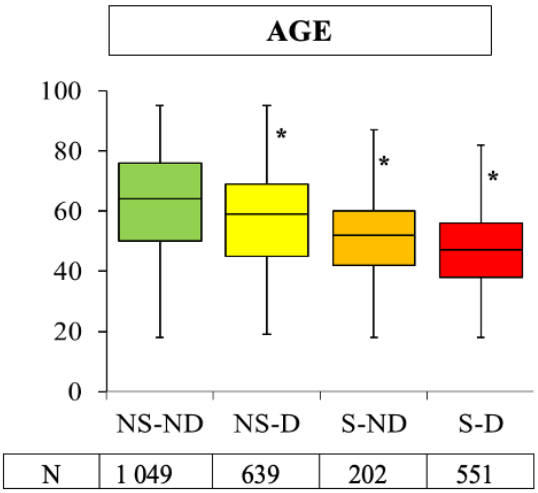


Figure 6b. Age in combined alcohol consumption and smoking groups. *P<0.001 or p=0.001 in all comparisons. AP, acute pancreatitis; NS–D: non-smoking– drinking; NS–

ND: non-smoking– non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

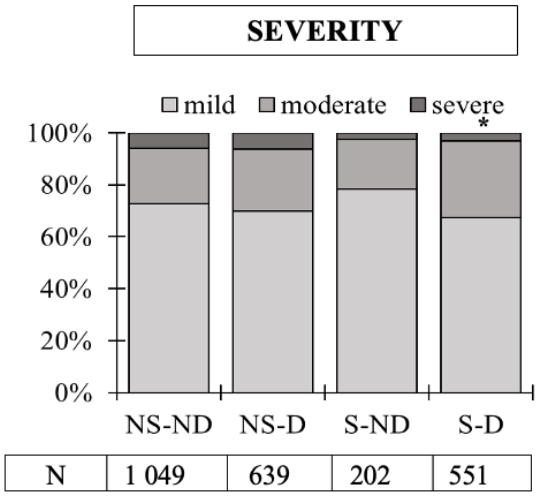


Figure 6c. AP severity in combined alcohol consumption and smoking groups Moderately severe *p=0.003 vs NS–ND. P=0.022 vs S–ND. AP: acute pancreatitis; NS–D: non-smoking– drinking; NS–ND: non-smoking– non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

Both alcohol consumption and smoking are associated with the male sex. The first AP episode occurs 15 years earlier than in case of non-drinkers and non-smokers.

Analysing the on admission and outcome parameters, we found that the lowest levels of amylase, lipase and the highest moderate AP cases were in the smoking-drinking group, indicating that this group had the highest levels of pancreatic tissue damage and local complications (Figures 7a, 7b).

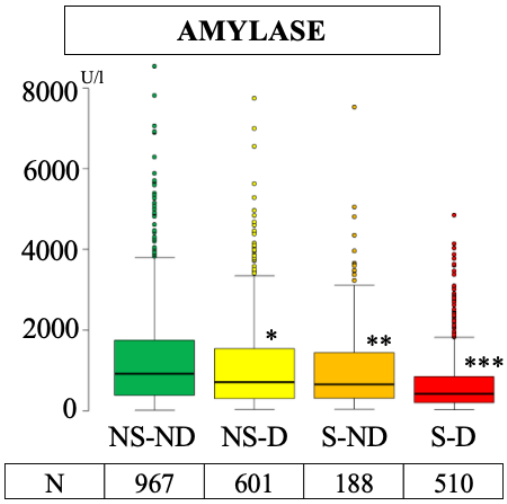


Figure 7a. On admission amylase level, *P<0.001 vs NS–ND. **P<0.003 vs NS–ND. ***p<0.001 vs NS–ND, NS–D and S–ND. NS–D: non-smoking– drinking; NS–ND: non-smoking– non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

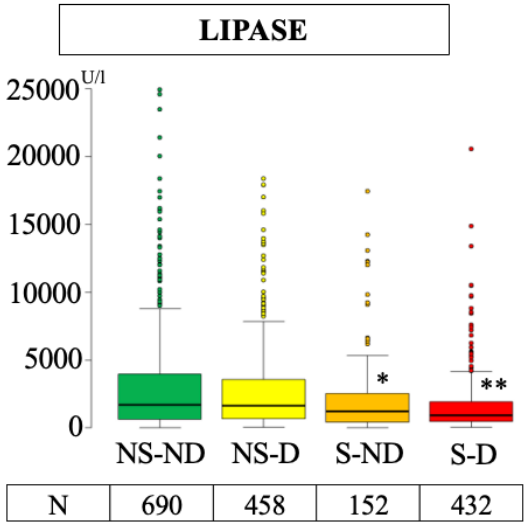


Figure 7b. On-admission lipase level, *P<0.003 vs NS–ND, p<0.006 vs NS D. **P<0.001 vs NS–ND and NS–D. NS–D: non-smoking– drinking; NS–ND: non-smoking– non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

The smoking groups had elevated rates of RAP. The smoking-drinking group had the highest percentage of patients with CP. This suggests the syndromic effect of smoking and alcohol consumption and the prominent role of smoking in progression (Figures 8a., 8b.).

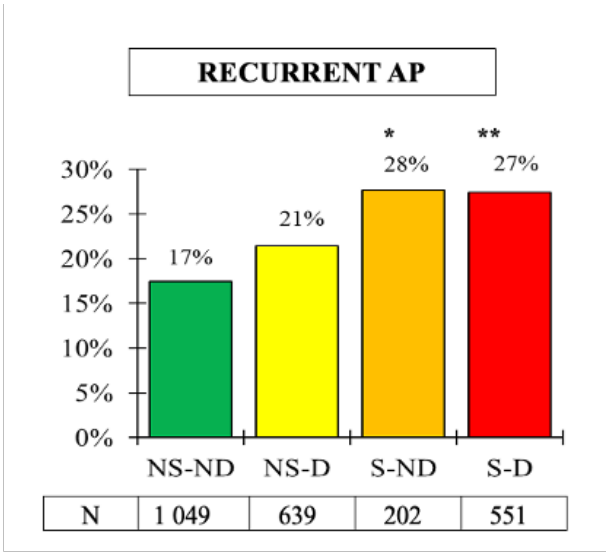


Figure 8a. Prevalence of recurrent AP. *P=0.003 vs NS ND. **p=0.04 vs NS–D. p<0.001 vs NS–ND. NS–D: non-smoking– drinking; NS–ND: non-smoking– non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking. Recurrent AP: recurrent acute pancreatitis.

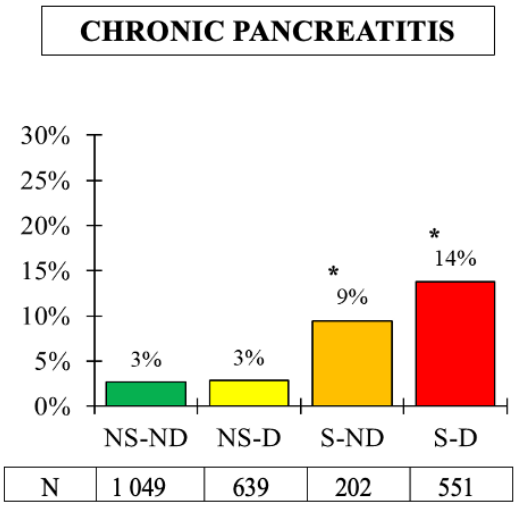


Figure 8b. Prevalence of chronic pancreatitis. *P<0.001 vs NS–ND, NS–D. NS–D: non-smoking– drinking; NS–ND: non-smoking– non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

7. Investigating the incidence of pancreatic cancer before and after an acute pancreatitis episode

7.1. Aims

The aim of the study was to explore the link between AP and PC and to assess the risk factors that may predispose patients with AP to developing PC. This multicenter cohort study investigated the incidence of PC before and after an AP episode, focusing on idiopathic AP and the role of pancreatic pseudocysts (PP) as potential early markers for PC development.

7.2. Methods

7.2.1. Study type and preliminary settings

This study is a post hoc analysis of prospectively collected data from AP patients in the Acute Pancreatitis Registry (APR) following the STROBE guidelines for cohort studies.

The APR is maintained by the Hungarian Pancreatic Study Group (HPSG). The HPSG (https://tm-centre.org/en/research/study-groups/hungarian-pancreatic-study-group) was established in 2011 to improve patient care for pancreatic diseases. The registry received ethical permission from the Scientific and Research Ethics Committee of the Medical Research Council (22254–1/ 2012/EKU, 17787–8/2020/EÜIG), and all the patients provided written informed consent to participate. The study protocol conforms to the Declaration of Helsinki ethical guidelines.

7.2.2. Data collection

Data was collected by trained clinical research administrators, and a four-checkpoint electronic clinical data management system was set up to ensure data quality.

Altogether 2356 well-characterized patients from 25 centers were included and followed by the Hungarian Pancreatic Study Group (HPSG) between 2012 and 2021. The total cohort was screened for PC, and we analyzed all cases with data on the presence or

absence of PC during the 4.1 (Q1: 1.6y, Q3: 6.8y) years median follow-up after AP. Paper-based and electronic medical records were reviewed.

7.2.3. Definitions

According to the IAP/APA and HPSG evidence-based guidelines [1, 2] AP is diagnosed when at least two out of the following three criteria are met: (1) abdominal pain, (2) serum amylase or lipase elevation of at least three times the upper limit of normal, and (3) characteristic abnormalities seen on imaging. Severity and local and systemic complications were defined based on the modified Atlanta classification [6].

In our study, PC was defined as pancreatic ductal adenocarcinoma (PDAC) and/or adenocarcinoma of the Ampulla of Vater or pancreatic functioning and nonfunctioning neuroendocrine tumour. It should be noted, that most of the cases were PDAC.

Cases were considered to have cancer (1) if they had a histological diagnosis, (2) if imaging, clinical presentation, and tumor markers confirmed the presence of cancer, or (3) if there was documented chemotherapy treatment for PC.

We formed groups of patients with PC (PC group) and without PC (Control group) and further divided the PC group into 'PC before AP' and 'PC after AP' groups.

The 'PC before AP' subgroup included patients who were diagnosed with PC (1) before AP episode, (2) during the hospitalization of the index AP episode or (3) within one months after AP. The 'PC after AP' group included patients who were diagnosed with PC more than 30 days following AP.

7.2.4. Statistical analysis

To assess idiopathic etiology as a risk factor for pancreas cancer after AP, we calculated the crude odds ratio and the adjusted odds ratio as well in the total cohort, controlling for age, sex and AP severity as possible confounders.

For the case-control part of the study, to have similar distributions in the 'PC after AP' and their controls in terms of age, sex, etiology and AP severity, we used the nearest neighbor matching method with 1:3 allocation ratio, which resulted in a sample of 35 'PC after AP' patients (cases) and 105 controls. The matching was very precise and produced almost identical distributions regarding the 4 matched variables. To compare the PC and

the control group in terms of the investigated exposures, we fit a logistic regression model including the 4 matched variables as covariates and using cluster-robust standard error to account for pair membership. Based on the output of the logistic regression models, we used the odds ratio (OR) and its 95% confidence interval to assess the associations between the investigated exposures and pancreas cancer.

We used the R program v4.2.0.for all computations and the MatchIt package v4.5.4. for the matching and for estimating effects after matching.

7.3. Results

7.3.1. General characteristics

In the total cohort of 2,356 patients, the average age was 55.03±17.53 years, and the proportion of male patients was 55.09%. A 67.40% (n=1,588) of the cases were mild, 24.10% (n=568) moderately severe, and 8.48% (n=200) were severe AP suggesting a general AP cohort.

7.3.2. PC is highly associated with AP

Sixty-nine patients (2.9%) had PC in the total cohort. Thirty-four (1.4%) of them were diagnosed before, whereas 35 (1.5%) were after the AP episode (Table 5.).

	n	%
Total AP cohort	**2356**	100,0%
Non-PC	2287	97,1%
PC	69	2,9%
Before AP	34	1,4%
After AP	35	1,5%

Table 5. Summary of the pancreatic cancer and control group. PC is highly associated with AP. PC: pancreatic cancer, AP: acute pancreatitis.

Detailed PC diagnosis and AP time of the 'PC before AP' and 'PC after AP' group are shown in Figure 9.

For patients who had PC diagnosis after AP, the median time to PC diagnosis was approximately one year (375 days) (Figure 10.).

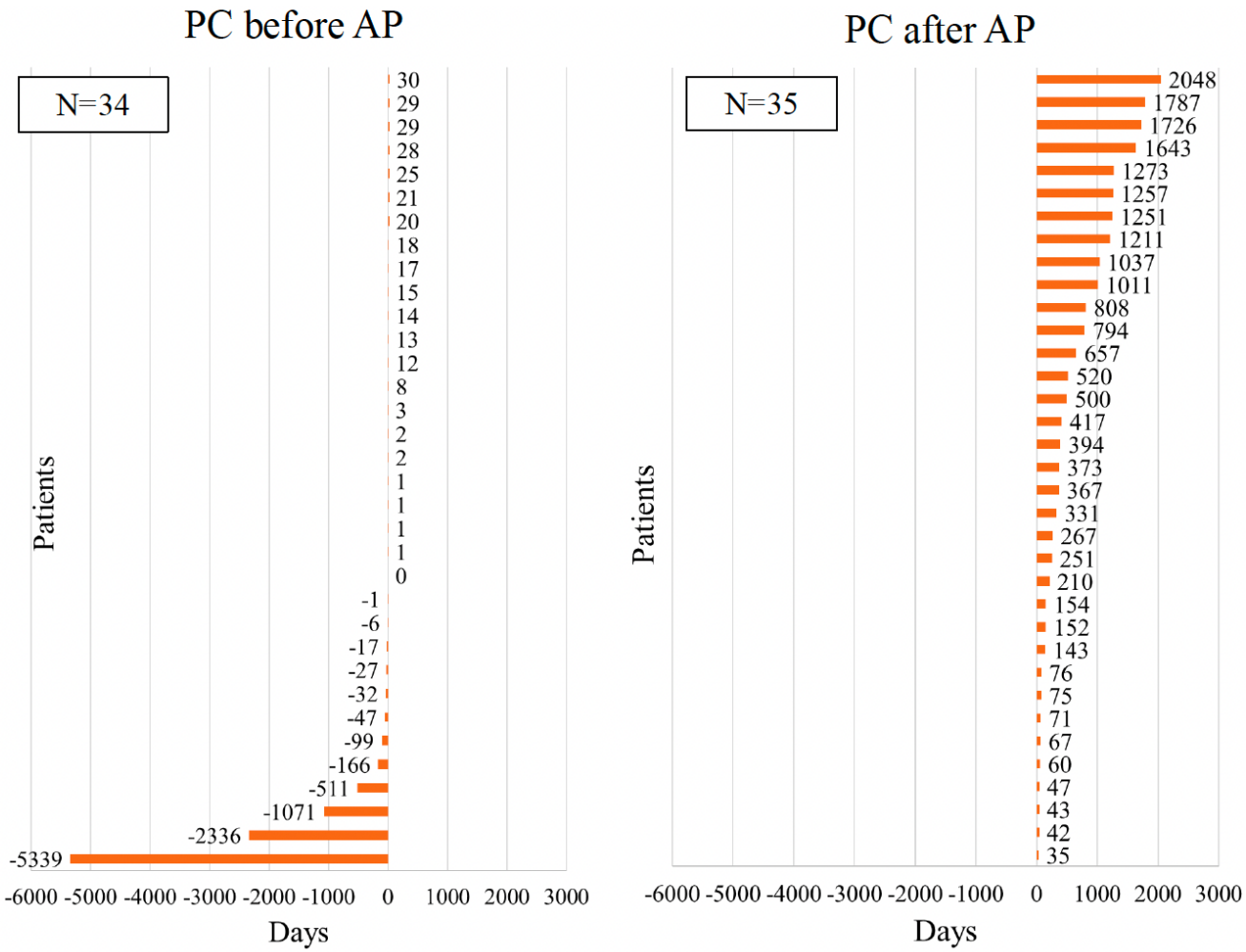
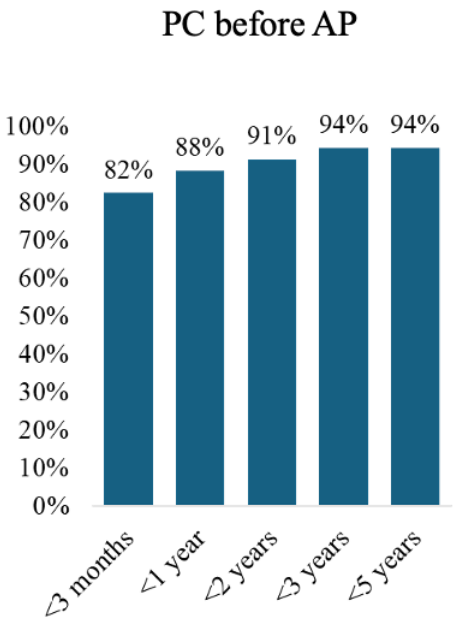
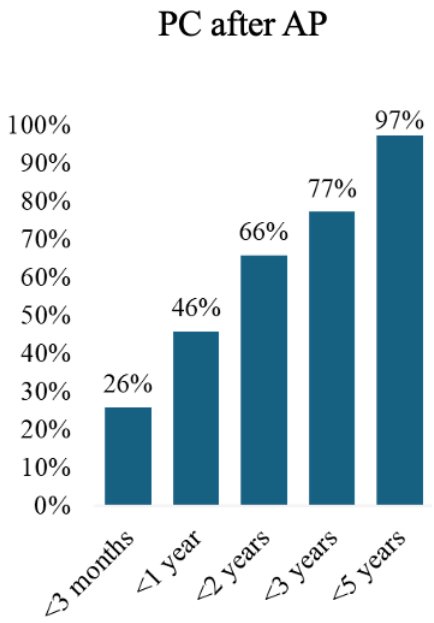


Figure 9. Pancreatic cancer (PC) diagnosis time by patients, in 'PC before AP' and 'PC after AP' subgroups.





N	34
Min	-5339
Q1	-24.5
Median	1.5
Q3	16.5
Max	30
IQR	41
>5 years	2

N	35
Min	35
Q1	109.5
Median	373
Q3	1024
Max	2048
IQR	914.5
>5 years	1

Figure 10. Cummulative diagnosis time in 'PC before AP' and 'PC after AP' subgroups.

7.3.3. Idiopathic etiology is associated with PC development

The proportion of idiopathic cases was twice as high in patients diagnosed with PC after AP compared to the Non-PC group (51% vs. 25%, $p<0.001$) (Figure 11.).

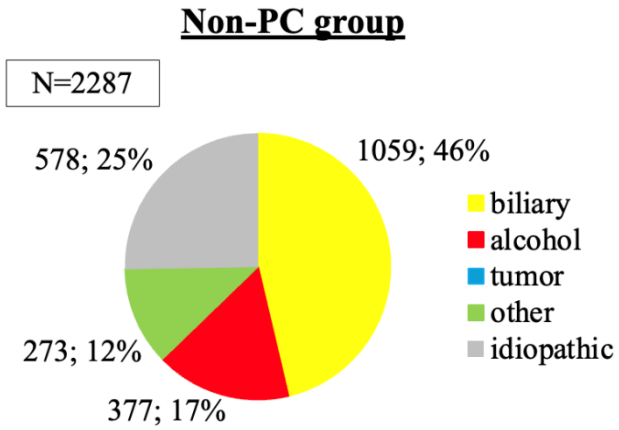


Figure 11a. Distribution of AP etiology in the Non-PC (control) group.

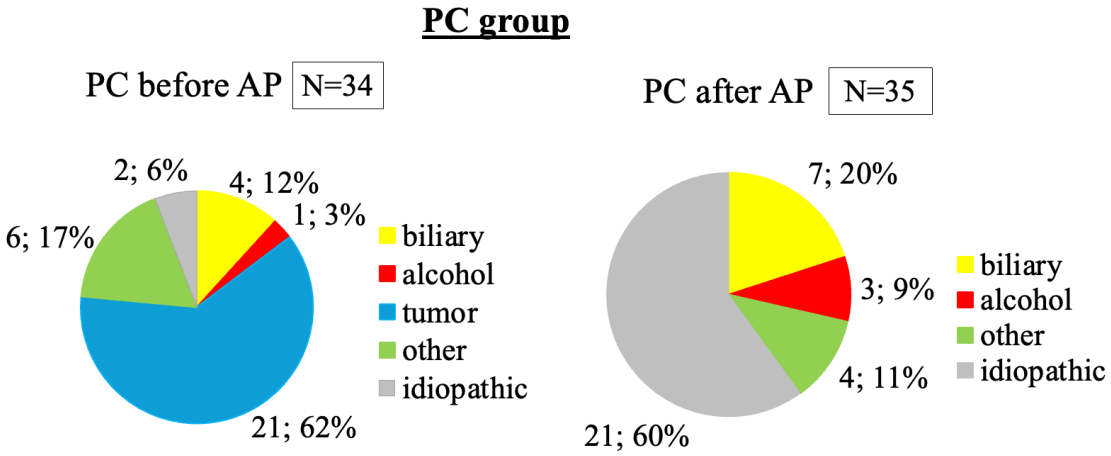


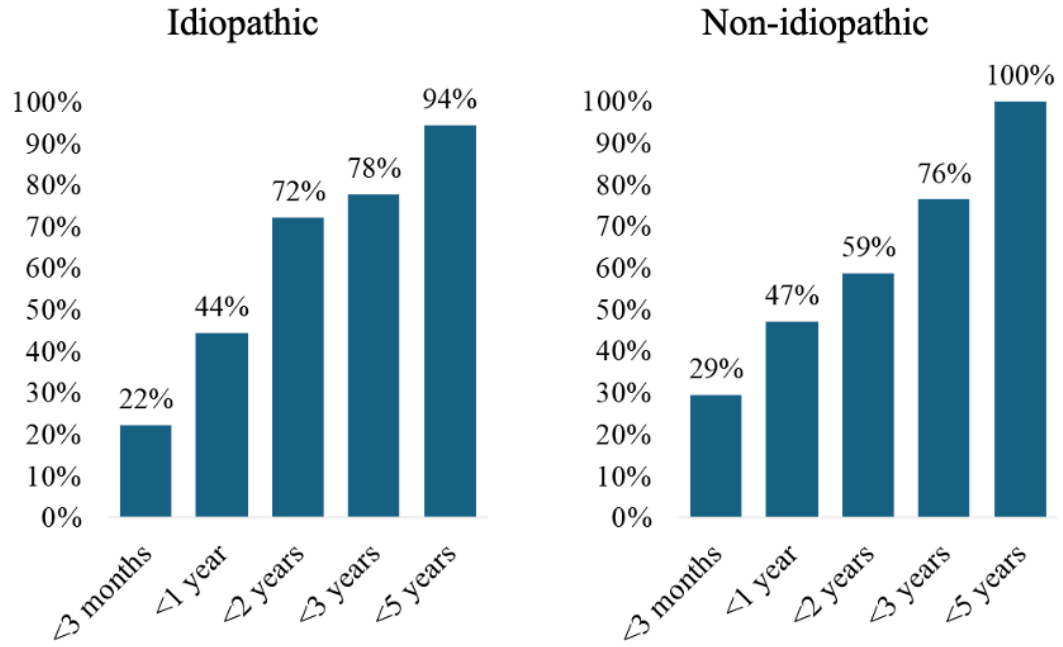
Figure 11b. Distribution of AP etiology in the PC group ('PC before AP' and 'PC after AP' subgroups)

In idiopathic cases, PC was diagnosed in 3% of patients after AP during a median follow-up of 4.1 years, while in non-idiopathic cases, only 1.0% was diagnosed with PC (OR = 4.44, [CI: 2.24-8.77]) (Table 6.). This association remained significant even after adjusting for age, sex and AP severity as possible confounders (OR = 4.46, [CI: 2.25-8.85]).

	Total cohort	PC before AP (n)	PC before AP (%)	PC after AP (n)	PC after AP (%)
Idiopathic	595	2	0,3%	18	3,0%
Non-idiopathic	1761	32	1,8%	17	1,0%
Total	**2356**	**34**	**1,4%**	**35**	**1,5%**

Table 6. PC and idiopathic etiology; PC: pancreatic cancer, AP: acute pancreatitis.

There was no difference in the median cumulative time to PC diagnosis after AP in idiopathic and non-idiopathic cases (370 days vs. 394 days, respectively) (Figure 12.).



N	18
Average	598.5
SD	599.6
Median	370
Q1	145.2
Q3	922.5
Min	35
Max	2048

N	17
Average	607.4
SD	601.5
Median	394
Q1	71
Q3	1037
Min	42
Max	1787

Figure 12. Cumulative diagnosis time in 'PC after AP' subgroup (idiopathic – non idipoathic AP etiology)

7.3.4. Risk factors associated with PC development

7.3.4.1. Comorbidities

We also compared the prevalence of pre-existing and later developed RAP, CP, and diabetes in the PC and Control groups conducting a matched case-control analysis. Both pre-existing and newly developing RAP were similar in the two groups (20% vs. 14%, OR = 2.13 [CI: 0.74-6.13]) and 29% vs. 17%, OR = 1.86, [CI: 0.78-4.43]), respectively) (Figure 13.).

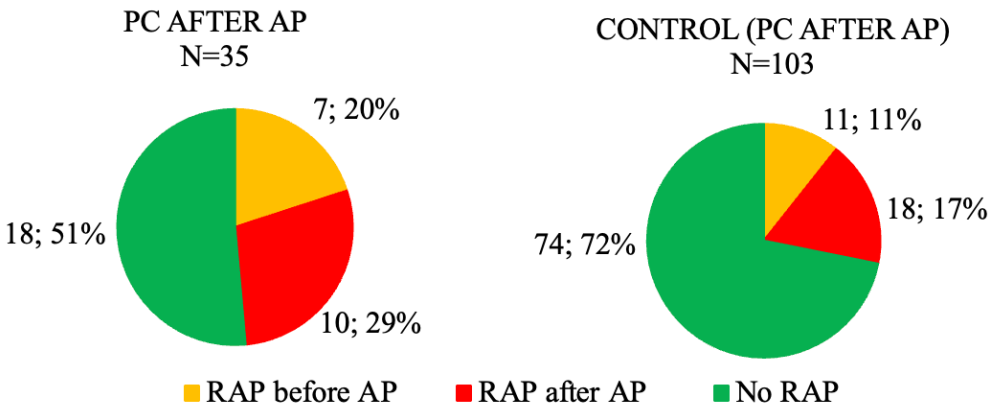


Figure 13. RAP in patients with pancreatic cancer ('PC after AP' subgroup); RAP: recurrent acute pancreatitis, PC: pancreatic cancer, AP: acute pancreatitis.

Pre-existing CP was similar (6% vs. 8%, OR = 0.73, [CI: 0.16-3.45]), whereas newly developing CP was more frequent in the cancer group 16% vs. 6%, OR = 2.75 [CI: 1.03-7.32]) (Figure 14.).

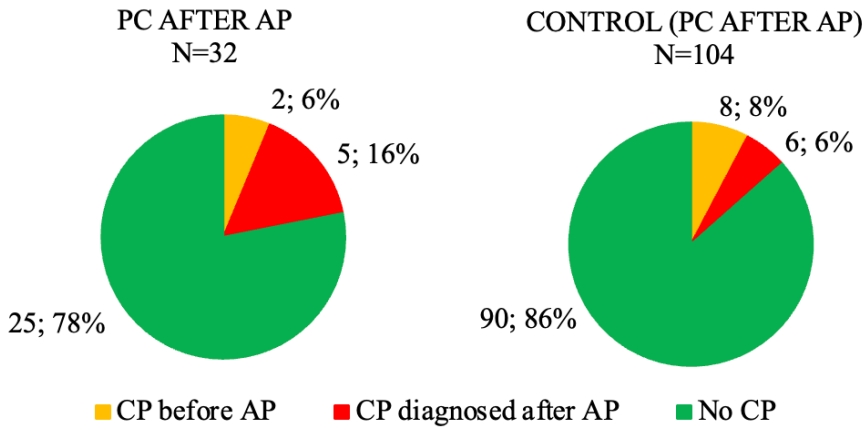


Figure 14. CP in patients with pancreatic cancer ('PC after AP' subgroup); CP: chronic pancreatitis, PC: pancreatic cancer, AP: acute pancreatitis.

Pre-existing DM was less frequent (14% vs. 32%, OR = 0.35, [CI: 0.13-1.00]), however newly developing DM showed no significant difference (12% vs. 8%, OR = 1.56, [CI: 0.59-4.11]) in the cancer group (Figure 15.).

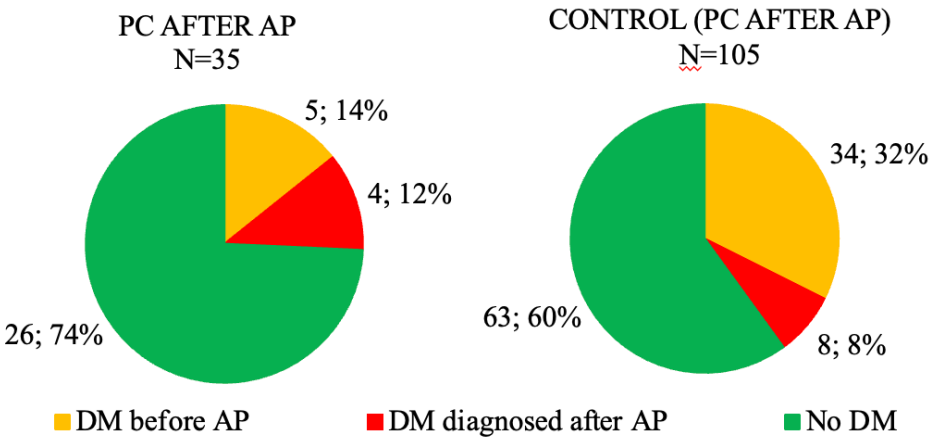


Figure 15. DM in patients with pancreatic cancer ('PC after AP' subgroup). DM: diabetes mellitus, PC: pancreatic cancer, AP: acute pancreatitis.

7.3.4.2. AP complications

Investigating the AP complications as possible risk factors, we found that organ failure was less frequent in the cancer group (3% vs. 7%, OR = 0.36, [CI: 0.29-0.45]) (Figure 16.), while occurrence of local complications was similar (20% vs. 17%, OR = 1.23, [CI: 0.94-1.61]) (Figure 17.).

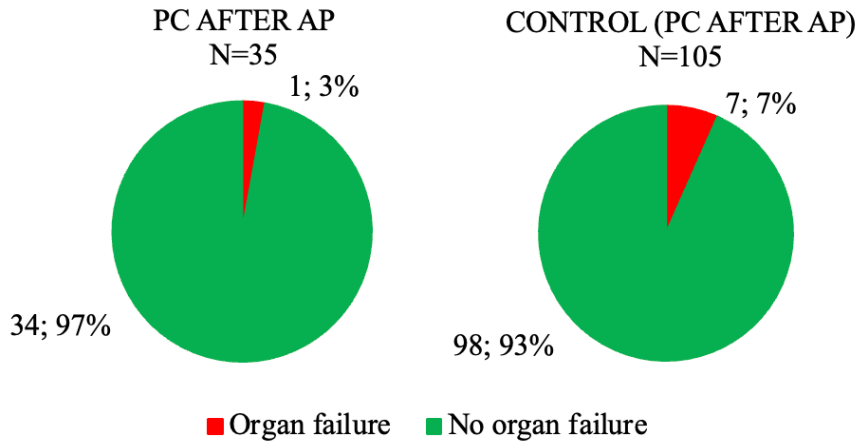


Figure 16. Organ failure in patients with pancreatic cancer ('PC after AP' subgroup); PC: pancreatic cancer, AP: acute pancreatitis.

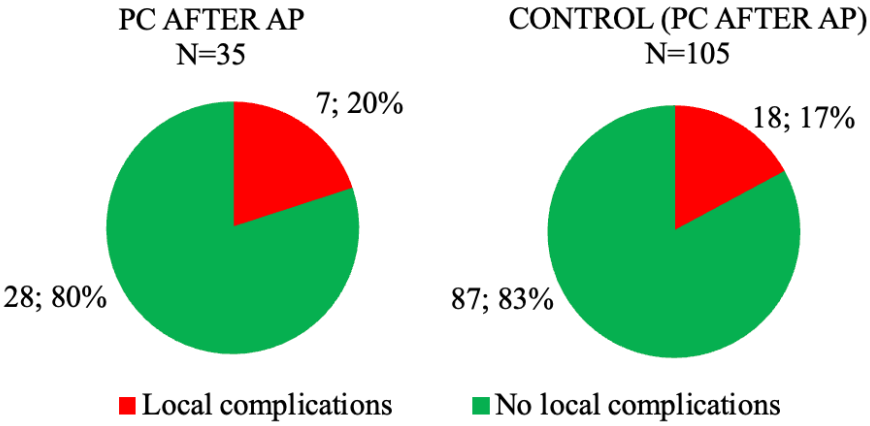


Figure 17. Local complications in patients with pancreatic cancer ('PC after AP' subgroup); PC: pancreatic cancer, AP: acute pancreatitis.

While development of peripancreatic fluid collections were similar (11% vs. 14%, OR = 0.78, [CI: 0.33-1.85]), incidence of necrosis was less frequent in the cancer group (0% vs. 7%, OR = 3.41, [CI: 1.37-8.48]) (Figure 18., Figure 19.).

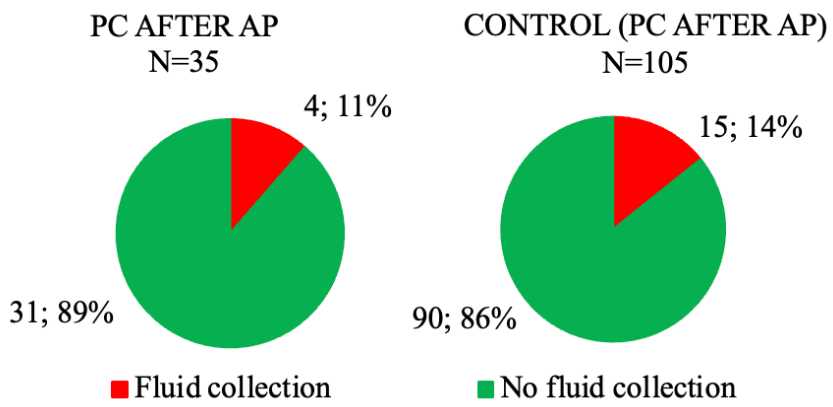


Figure 18. Fluid collection in patients with pancreatic cancer ('PC after AP' subgroup); PC: pancreatic cancer, AP: acute pancreatitis.

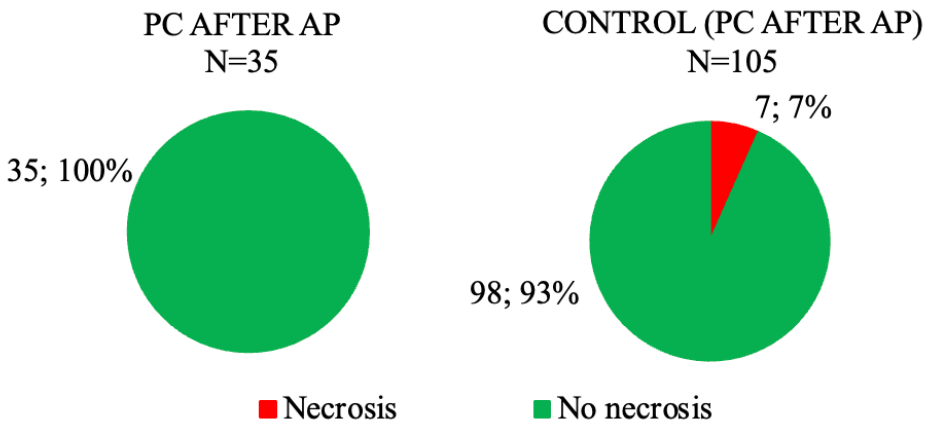


Figure 19. Necrosis in patients with pancreatic cancer ('PC after AP' subgroup); PC: pancreatic cancer, AP: acute pancreatitis.

Most importantly, the proportion of pancreatic pseudocyst (PP) formation was about five times higher in the cancer than in the control group (14% vs. 3%, OR = 5.66, [CI: 1.65-19.4]) (Figure 20.). Four out of the 5 cases, the pseudocyst and the tumor were in the same location within the pancreas.

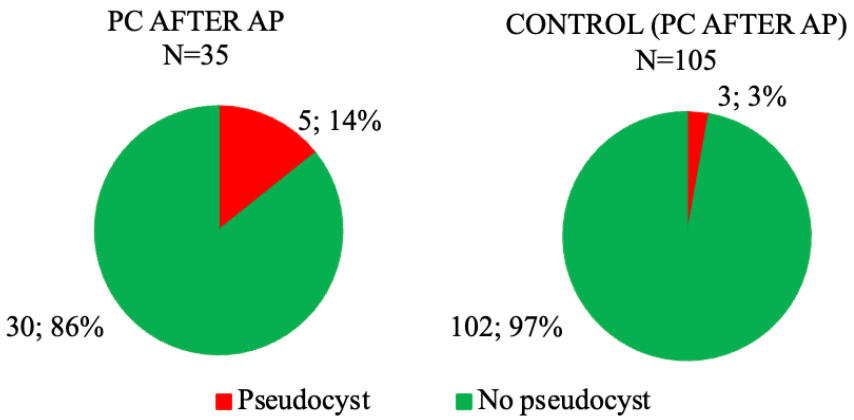


Figure 20. Pancreatic Pseudocyst (PP) in patients with pancreatic cancer ('PC after AP' subgroup); PC: pancreatic cancer, AP: acute pancreatitis.

7.3.4.3. Body Mass Index

Concerning the on-admission body mass index (BMI) we found no significant difference in the 'PC after AP' group than in the 'Control' group (56% vs. 71%, OR = 0.76, [CI: 0.37-1.57]) (Figure 21.).

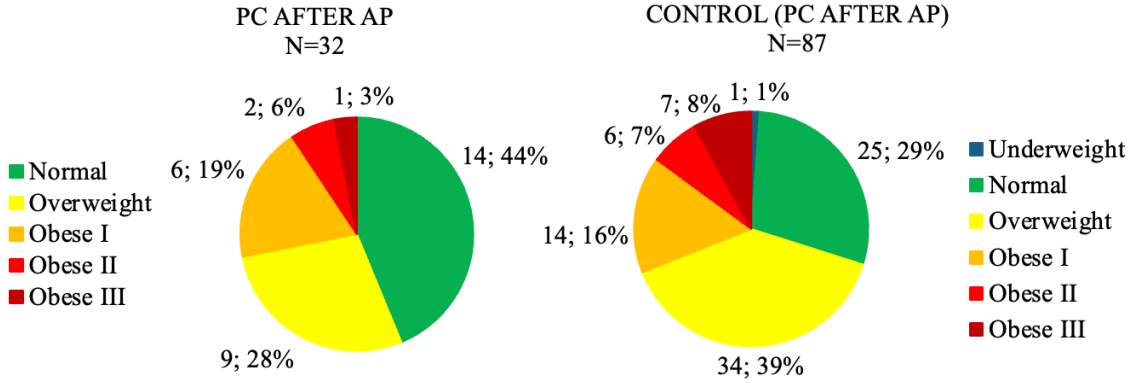


Figure 21. Body mass index in patients with pancreatic cancer ('PC after AP' subgroup); PC: pancreatic cancer, AP: acute pancreatitis.

A summary table of the comorbidities and complications of AP as risk factors of PC can be found in Table 7.

Category	PC After AP (n=35)	Control (n=105)	OR [CI]
RAP before AP	20% (7)	11% (11)	2.13, [0,74-6.13]
RAP after AP	29% (10)	17% (18)	1.86, [0.77-4.43]
CP before AP	6% (2)	8% (8)	0.73, [0.15-3.45]
CP after AP	16% (5)	6% (6)	2.75, [1.03-7.32]
DM before AP	14% (5)	32% (34)	0.35, [0.12-1]
DM after AP	12% (4)	8% (8)	1.56, [0.59-4.11]
Organ Failure	3% (1)	7% (7)	0.35, [0.28-0.44]
Local Complications	20% (7)	17% (18)	1.23, [0.94-1.61]
Peripancreatic Fluid Collections	11% (4)	14%(15)	0.77, [0.32-1.85]
Necrosis	0% (0)	7% (7)	3.41, [1.37-8.48]
Pseudocyst	**14% (5)**	**3% (3)**	**5.66, [1.65-19.4]**
Overweight and obese	56% (18)	70% (61)	0.76, [0.36-1.57]

Table 7. Summary of the comorbidities and complications of acute pancreatitis (AP) as risk factors of pancreatic cancer (PC). RAP: recurrent acute pancreatitis, CP: chronic pancreatitis, DM: diabetes mellitus, OR: odds ratio, CI: confidence interval.

7.4. Strength and limitations

The use of a well-characterized, multicenter cohort from the Hungarian Pancreatic Study Group (HPSG) provided a robust dataset for analysis. The study utilized long-term follow-up data (up to 10 years) with using a multicenter cohort of 2,356 patients, allowing for a comprehensive evaluation of PC development following AP.

However, the study has limitations as well. The study's reliance on post hoc analysis of prospectively collected data may introduce selection biases. While we identified a statistically significant link between idiopathic AP and PC, the sample size of PC cases and event numbers such as organ failure or pseudocyst was relatively small. The lack of standardized follow-up protocols for idiopathic AP patients may have impacted the uniformity of cancer detection in the cohort. The determination of PC onset is also challenging. Although PC could have been present at the time of the AP episode without diagnosis, we defined the PC patient groups based on the time of diagnosis.

7.5. Implications for practice

Translating scientific information to patients benefit has crucial importance [55, 56, 57]. The findings of our study underscore the importance of careful monitoring and follow-up for patients presenting with idiopathic AP. Given the elevated risk of PC especially within the first two years, enhanced screening measures, including imaging modalities such as MRI and CT, should be considered for these patients. In cases of idiopathic AP where pseudocyst formation is present, it may also be beneficial to perform EUS-guided fine-needle aspiration (FNA) for biopsy and further assessment. Early detection could improve resectability and, consequently, survival outcomes for PC patients.

7.6. Implications for research

Further research is needed to investigate the mechanisms underlying the association between idiopathic AP and PC. Identifying specific biomarkers or mechanical/chemical factors that signal early-stage PC could revolutionize screening protocols and potentially lead to earlier diagnosis, improving treatment options and prognosis. Future studies should also focus on refining imaging techniques to detect early tumor formation, even when current modalities cannot visualize it.

8. Discussion of the investigations results and conclusion

8.1. Discussion

AP is the most common gastrointestinal inflammatory disease requiring hospitalisation [58, 59] and the severe, complicated cases can be fatal [58, 59, 60]. Several risk factors contribute to its development and recovery after an AP episode cannot be considered definitive. Various risk factors, such as alcohol consumption and smoking, as well as post-inflammatory complications, all play a role in the development of the RAP-CP-PC axis. In our work, we investigated the role of these factors.

A previous study found that alcohol was the second most common etiological factor in AP, with a prevalence four times higher in men than in women. [60], and the main trigger for CP [61]. The mechanisms of alcohol's adverse effects on the pancreas are poorly understood, but the direct toxicity of alcohol metabolites to pancreatic acinar cells by increasing oxidative stress is important [51, 62, 63]. Alcohol consumption itself not only contributes to the development of pancreatitis, but studys show that also has a dose-dependent carcinogenic effect. Drinking >15-30-60 g alcohol per day, increases the risk of developing cancer by 1.36 fold [64, 65, 66, 67]. Acetaldehyde, which is a metabolite of alcohol, and ethanol can also cause differentiation defects in stem cells and promote inflammatory lesions and carcinogenesis by inhibiting DNA repair proteins [68, 69, 70].

In pancreatitis, the acinar cells secreting the digestive enzyme may undergo metaplasia due to inflammation, which is a precursor of PC. Inflammatory molecules may also promote tumour growth through paracrine and autocrine effects. In this way CP itself can cause PC [71]. Previous meta-analysis has shown that CP increases the risk of developing pancreatic ducatl adenocarcinoma (PDAC) [72].

Smoking is an independent risk factor for CP [73], and can lead to PC through cumulative exposure to smoking-related carcinogens (heterocyclic amines and polycyclic aromatic hydrocarbons). Consequently, mutations in proto-oncogenes, mutations in tumour suppressor genes and smoke-induced chronic inflammation all contribute to the development of PC [68].

The first part of our study looked at the effects of smoking and alcohol on the pancreas. In our analysis, in a clinical setting, we found that both smoking and alcohol consumption damage pancreatic tissue in a dose-dependent manner. This was supported by the inverse correlation observed at baseline between alcohol/tobacco consumption and serum amylase and lipase levels, suggesting that higher consumption is associated with greater pancreatic damage.

In addition, it contributes to an increase in the incidence of RAP and CP. Alcohol use correlates with a higher frequency of local complications, suggesting it exacerbates the severity and complications of pancreatitis.

Our analysis showed that both risk factors were more common among men. The first AP episode began 15 years earlier in the smoking-alcohol (SD – smoking-drinking) group than in the non-smoking-non-alcohol (NS-ND – non-smoking, non-drinking) group. It is also noteworthy that members of the smoking-alcohol group had the lowest enzyme levels (amylase/lipase) at baseline and the highest rate of moderate AP, indicating greater pancreatic necrosis and tissue damage.

Smoking, especially in combination with alcohol, was associated with higher rates of AP and CP, suggesting a synergistic and additive effect. This supports the concept that smoking is an associated factor in both the development and progression of pancreatitis.

Alcohol and smoking independently and synergistically worsen the clinical course of AP. Smoking plays a dominant role in the transition of the disease to chronic forms. The combination of these two behaviors leads to earlier onset of the disease, more severe symptoms, and poorer outcomes.

Pancreatitis may not only be a cause of PC, but AP can also be an early sign of PC [28, 47]. A possible mechanism of PC-induced AP is that a pancreatic tumor obstructs the pancreatic duct, causing obstruction of pancreatic juice flow. Tumor growth can also cause local pancreatic necrosis [74]. In the acute phase of AP, PC often remains hidden. This is because small tumors are difficult to detect with CT. The presence of small PC is particularly likely in cases where, during remission, CT shows mild or subthreshold main pancreatic duct (MPD) dilatation (diameter 2.5 mm) or moderate pancreatitis [75].

In the second part of our study, we identified a high prevalence of PC following idiopathic AP, with most cancer diagnoses occurring within two years of an AP episode.

Compared with previously reported investigations [28, 47], the strength of our study is that AP etiologies were available for patients with AP and complications after AP were well documented. It is notable that the control group also included AP patients who did not develop PC.

Our results provide new insights into the pathogenesis of idiopathic AP and its possible association with PC, adding valuable data to the existing literature. Patients with idiopathic AP had twice the rate of later PC diagnosis compared to those with a known AP cause (3.0% vs. 1.0%). This study highlights idiopathic AP as an important clinical marker of PC and emphasizes the need for targeted screening protocols in this population.

One particularly noteworthy finding of our study was the significant number of pancreatic pseudocysts observed in the PC group, which may indicate the presence of obstructive phenomena, especially since four of the five pseudocysts were associated with tumors. These obstructions could be due to a growing tumor within the pancreatic duct, causing pseudocyst formation and, subsequently, AP. This scenario is strikingly similar to the pathophysiology observed in colorectal cancer and biliary tumors, where tumor-induced obstruction leads to symptoms such as ileus or obstructive jaundice.

The associations we observed between preexisting diabetes, CP, and PC are not surprising. These risk factors have been well-documented in the literature [34, 35, 37] and further confirm their role in the complex interplay between chronic inflammation, metabolic dysregulation, and cancer development. It should be noted that in our results, there was no significant difference in BMI values between the cancer and control groups.

Our results clearly show that, in addition to the development of prognostic and therapeutic measures for PC, further clinical trials are needed on alcohol and smoking cessation programmes and patient education.

There is also a need to identify biomarkers or mechanical/chemical factors that can detect early PC, and imaging studies that detect early-stage cancer could revolutionise screening protocols and potentially lead to earlier diagnosis, improving treatment options and prognosis. The window of opportunity (~1 year) between AP and PC diagnosis should be emphasized, as with appropriate monitoring, they may allow for early detection of cancer.

It is essential to communicate the importance of smoking cessation or reducing smoking and alcohol consumption to all stakeholders. In addition, it is important to emphasise the importance of follow-up after an AP episode to detect a potentially early-stage cancer.

8.2. Conclusion

We found significant association between smoking and alcohol dose and the extent of pancreatic tissue damage. We have shown that smoking and alcohol increase each other's harmful effects.

We found also a significant association between idiopathic AP and PC, particularly within the first two years following an AP episode. The high prevalence of pancreatic cysts in the PC group suggests that early tumor-induced obstruction could play a role in triggering AP.

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9. References

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10. Publications

10.1. Scientific metrics (as of 2025.02.27)

Number of publications **related to the subject of the thesis**: Cumulative impact factor of publications related to the thesis: D1: 1, Q1: 1, Q2: 0, Q3: 0, Q4: 0	2 27.3
Number of **other first or co-author accepted/published** articles: Cumulative impact factor of the published articles: D1: 1, Q1: 13, Q2: 1, Q3: 1, Q4: 0	16 90.7
Number of total citation by **Google Scholar**: https://scholar.google.com/citations?hl=hu&user=ITmYWh0AAAAJ Hirsch Index:	143 7
Number of total citation by **MTMT**: https://m2.mtmt.hu/gui2/?type=authors&mode=browse&sel=10078474 Hirsch Index:	74 5

10.2. Publications related to the subject of the thesis

n=2, cumulative impact factor: 27.3

1. Szentesi A, Farkas N, Sipos Z, Mátrai P, Vincze Á, Izbéki F, Párniczky A, Hegyi P; Hungarian Pancreatic Study Group including Bálint Erőss, Péter Jenő Hegyi, Szilárd Váncsa1, Rita Nagy, Katalin Márta, Klementina Ocskay, Márk Félix Juhász, Marcell Imrei, Mária Földi, Szabolcs Kiss, Balázs Csaba Németh, Tamás Takács, László Czakó, Szilárd Gódi, Judit Bajor, Patrícia Sarlós, László Gajdán, Mária Papp, József Hamvas, Márta Varga, Melania Macarie, Imola Török, János Novák, Artautas Mickevicius, Elena Ramirez Maldonado, Shamil Galeev, Ville Sallinen, Barnabás Bod, Ali Tüzün Ince, Tamás Nagy, Nándor Faluhelyi, Noémi Gede, Stefania Bunduc, **Tamás Hussein**, Mónika Lipp, Anna Németh, Orsolya Urbán, Dorottya Tarján, Simon Tóth, Dániel Pécsi, Péter Varjú, Noémi Zádori.

Alcohol consumption and smoking dose-dependently and synergistically worsen local pancreas damage. Gut. 2022 Dec;71(12):2601-2602. doi: 10.1136/gutjnl-2021-326853. Epub 2022 Jan 19. PMID: 35046088; PMCID: PMC9664132. (**D1, IF: 24,5**)

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11. List of conference presentations

11.1. Conference presentations related to the subject of the thesis

11.1.1. Oral presentation

• Title: “High prevalence of pancreatic cancer after acute pancreatitis”

2024, november – Hungary

13th Conference ot the Hungarian Pancreatic Study Group (HPSG-XIII)

11.1.2. Poster presentation

• Title: “Strong association between acute pancreatitis and pancreatic cancer”

2023, june - Spain

56th European Pancreatic Club (EPC) meeting

11.2. Other conference presentations

11.2.1. Oral presentations

• Title: „Renin és aldosteron vizsgálata hypertoniásokon” [Renin and aldosterone investigation on hypertension patients]

2014, September – Hungary

22th Congress of the Hungarian Society of Hypertension

• Title: „A primer aldosteronizmus szűrésével szerzett tapasztalataink.” [Our experience with the screening of primary aldosteronism.]

2017, June – Hungary

52th Congress of the Hungarian Society of Internal Medicine

• Title: „Magyar akromegália regiszter” [Hungarian acromegaly registry]

2018, May – Hungary

27th Congress of the Hungarian Society for Endocrinology and Metabolism

• Title: „AcroR”
2018 November - Hungary
7th Conference of Translational Medicine

• Title: „Multidisciplinary approeach in pancreatology – first experiencing and potentials”
2022, February – Hungary
10th Conference ot the Hungarian Pancreatic Study Group (HPSG-X)

• Title: „A jelenlegi egycentrumos útvonal” [The current single-centre route]
2022, June – Hungary
64th Conference of the Hungarian Socitey of Gastroenterology

• Title: „Pancreas betegségek multidiszciplináris kezelés” [Multidisciplinary approach in pancreatic disorders]
2022, September – Hungary
48th Assembly of the Hungarian Society of Internal Medicine

• Title: „Pancreatic Solid Tumor Registry”
2022, November – Hungary
11th Conference ot the Hungarian Pancreatic Study Group (HPSG-XI)

• Title: „Betegtámogatást nyújtó onkoteam tagok” [Patient supporting oncoteam members]
2023, June – Hungary
65th Conference of the Hungarian Socitey of Gastroenterology

Letters

Alcohol consumption and smoking dose-dependently and synergistically worsen local pancreas damage

Chronic pancreatitis (CP) is characterised by irreversible damage to the pancreas causing endocrine and exocrine dysfunction which results in decreased quality of life and reduced life expectancy.[1]

Adam *et al* recently published an interesting study on a possible diagnostic tool for CP based on metabolomic profiles of patients and controls.[2]

Our previous international cohort analysis showed that the proportion of patients developing CP is exponentially and directly associated with the number of acute pancreatitis (AP) episodes, thus strengthening the focus on the challenging task of diagnosing CP early.[3 4] However, in addition to diagnosing early, we should also focus on preventive interventions, before the damage becomes irreversible.

Alcohol is the main aetiological factor for CP and both alcohol consumption and smoking increase the risk for recurrence of AP and the development of CP. According to Ahmed Ali *et al*, in a follow-up study of 669 AP patients, smoking represented the dominant risk factor for recurrent AP (RAP) and a combination of alcohol consumption and smoking was the main risk factor for the progression to CP.[5] Therefore, cessation programmes and patient education are extremely important means to intervening and lowering the recurrence of AP and the progression to CP.[6 7] However, total cessation and abstinence often seems impossible for patients and they do not even try. Is it also possible to reduce recurrence and progression by decreasing the amount consumed?

Basic research evidence clearly suggests that alcohol and smoking amplify each other's harmful effects.[8 9] However, large cohorts are lacking to determine whether smoking and alcohol consumption dose-dependently, mutually exacerbate the damage to the pancreas caused by each.

We have used the international cohort in the Acute Pancreatitis Registry initiated by the Hungarian Pancreatic Study Group. Data were collected from 13 countries and 30 medical centres, with 2441 cases included in the analysis. Further characteristics of the cohort and information on methods are available in online supplemental file 1.

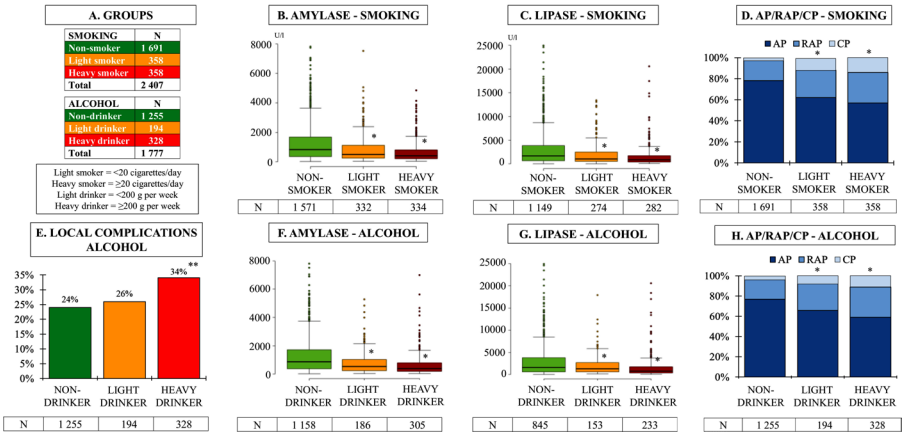

Figure 1 Dose dependency in alcohol consumption and smoking in AP. (A) Light and heavy alcohol consumption and smoking groups and definitions. (B, C) Amylase and lipase levels on admission. (D) Prevalence of RAP and CP (%). (E) Proportion of local complications (%). (F, G) Amylase and lipase levels on admission. (H) Prevalence of RAP and CP (%). *P<0.001, **p=0.003. Pearson's χ^2 test and the Kruskal-Wallis rank sum tests were used. AP, acute pancreatitis; CP, chronic pancreatitis; RAP, recurrent AP.

The patient population was divided into groups according to current amounts of smoking and alcohol consumption. We found that both smoking and alcohol consumption are dose-dependently associated with amylase and lipase levels and with the prevalence of RAP and CP among AP patients. Alcohol consumption was also linked to a higher rate of local complications (figure 1).

Second, we examined the possible synergistic effect of these two risk factors. We arranged the cohort population into four groups based on current smoking and alcohol consumption status (figure 2). Smoking and drinking together are associated with the male sex and linked to the first AP episode 15 years earlier than non-smoking and non-drinking are. Analysing on-admission and outcome parameters between groups, we found that amylase and lipase levels are the lowest and the proportion of moderately severe cases are the highest in the smoking–drinking group, suggesting the most pancreatic tissue damage and local complications here. The highest proportion of patients with RAP was found in both smoking groups, and the largest percentage of CP patients was observed in the smoking–drinking population, suggesting a clear synergising effect of alcohol consumption and smoking and

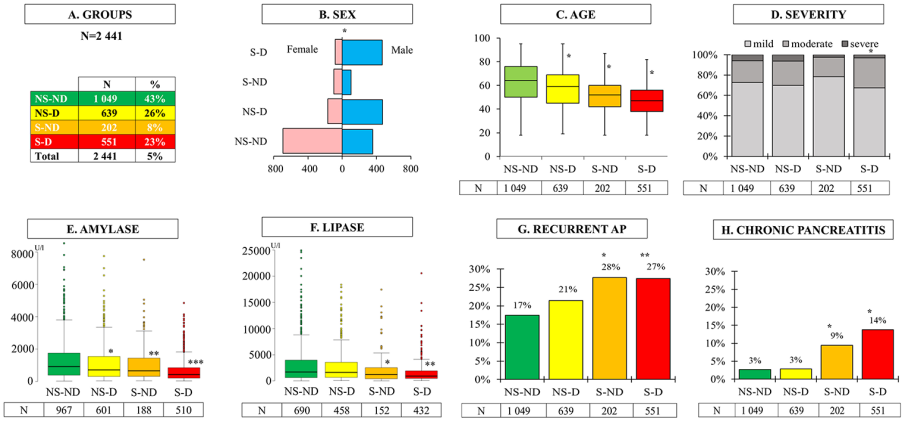

Figure 2 Combined alcohol consumption and smoking groups in AP. (A) Groups. (B) Sex. *P<0.001 in all comparisons. (C) Age. *P<0.001 or p=0.001 in all comparisons. (D) Severity. Moderately severe *p=0.003 vs NS–ND. P=0.022 vs S–ND. (E) On admission amylase level. *P<0.001 vs NS–ND. **P<0.003 vs NS–ND. ***p<0.001 vs NS–ND, NS–D and S–ND. (F) On-admission lipase level. *P<0.003 vs NS–ND, p<0.006 vs NS–D. **P<0.001 vs NS–ND and NS–D. (G) Prevalence of recurrent AP. *P=0.003 vs NS–ND. **p=0.04 vs NS–D. p<0.001 vs NS–ND. (H) Prevalence of chronic pancreatitis. *P<0.001 vs NS–ND, NS–D. Pearson's χ^2 test and the Kruskal-Wallis rank sum tests were used. AP, acute pancreatitis; NS–D: non-smoking–drinking; NS–ND: non-smoking–non-drinking; S–D: smoking–drinking; S-ND: smoking–non-drinking.

a highlighted importance of smoking in progression.

Our analysis confirms in a clinical setting that both smoking and alcohol are dose-dependently associated with pancreatic tissue damage and the prevalence of RAP and CP. Moreover, they mutually exacerbate each other's harmful effect. In addition to the development of prognostic and therapeutic measures, further clinical trials on cessation programmes and patient education are needed. Communication to all stakeholders of the importance of at least quitting smoking or cutting the amount of smoking and alcohol consumption is crucial.

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Contributors PH conceptualised the study. ÁV, FI, AS and AP contributed to the data collection and quality assurance. AS, ZS, PM and NF extracted and analysed the data. PH, AS, AP and NF interpreted the data. AS and PH wrote the manuscript. All the authors reviewed and contributed to the manuscript before finalisation and submission. Hungarian Pancreatic Study Group (full names are available in the Contributors section and affiliations are detailed in online supplemental file 1: BE, PJH, SV, RN, KM, KO, FJ, MF, SK, BN, TT, LC, SG, JB, PS, LG, MP, JH, MV, MM, IT, JN, AM, ERM, SG, VS, BB, ATI contributed to the data collection. TN, NF contributed to the interdisciplinary evaluation of the cases. NG conducted preliminary analyses. BE, PJH, SV, RN, KM, KO, FJ, MI, MF, SK, NG, SB, TH, ML, AN, OU, DT, ST, DP, PV and NZ ensured professional data quality control.

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Data availability statement Original raw data are available from the corresponding author on reasonable request.

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Alcohol consumption and smoking dose dependently and synergistically worsen local pancreas damage

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Supplementary file 1 2

Supplementary Table 1. CENTRE DISTRIBUTION

Institute	**City**	**Country**	**Number of cases**
First Department of Medicine, University of Pécs	Pécs	Hungary	877
Department of Medicine, University of Szeged	Szeged	Hungary	423
Szent György University Teaching Hospital of County Fejér	Székesfehérvár	Hungary	395
Department of Internal Medicine, University of Debrecen	Debrecen	Hungary	169
Bajcsy-Zsilinszky Hospital	Budapest	Hungary	152
Dr. Réthy Pál Hospital of County Békés	Békéscsaba	Hungary	67
County Emergency Clinical Hospital - Gastroenterology and University of Medicine, Pharmacy, Sciences and Technology	Tragu Mures	Romania	57
Pándy Kálmán Hospital of County Békés	Gyula	Hungary	31
Vilnius University Hospital Santariskiu Klinikos	Vilnius	Lithuania	31
General Surgery, Consorci Sanitari del Garraf, Sant Pere de Ribes	Barcelona	Spain	28
Saint Luke Clinical Hospital	St. Petersburg	Russia	28
Helsinki University Central Hospital	Helsinki	Finland	25
Dr. Bugyi István Hospital	Szentes	Hungary	23
Hospital of Bezmialem Vakif University, School of Medicine	Istanbul	Turkey	20
Markusovszky University Teaching Hospital	Szombathely	Hungary	18
Borsod-Abaúj-Zemplén County Hospital and University Teaching Hospital	Miskolc	Hungary	14
Bács-Kiskun County Hospital	Kecskemét	Hungary	11
Centrum péče o zažívací trakt, Vítkovická nemocnice a.s.	Ostrava	Czech Republic	11
Clinical Hospital Center Rijeka	Rijeka	Croatia	11
Csongrád County Health Center	Makó	Hungary	10
Gomel Regional Clinical Hospital	Gomel	Belarus	8
Bogomolets National Medical University	Kiev	Ukraine	8
Department of Surgery, University of Debrecen	Debrecen	Hungary	7
Gastroenterology, Hepatology and Nutrition Centre, Pauls Stradins Clinical University Hospital	Riga	Latvia	6
Polyclinic of Hospitaller Brothers of Saint John of God	Budapest	Hungary	4
Second Department of Medicine, Semmelweis University	Budapest	Hungary	2
Keio University	Tokyo	Japan	2
Central Military Emergency Hospital "Dr Carol Davila"	Bucharest	Romania	1
Heim Pál National Pediatric Institute	Budapest	Hungary	1
Medical Centre, Hungarian Defence Forces	Budapest	Hungary	1
Total			**2 441**

Supplementary Table 2. CHARACTERISTICS OF THE ANALYSED COHORT

Variable	**Value (n=2441)**
Age in years, median (IQR)	57 (44–69)
Male, n (%)	1 395 (57.1%)
Etiology, n (%)	
Biliary	972 (39.8%)
Alcoholic	475 (19.5%)
Alcoholic and hypertriglyceridaemia	57 (2.3%)
Hypertriglyceridaemia	77 (3.2%)
Post-ERCP	68 (2.8%)
Idiopathic	442 (18.1%)
Combined	89 (3.6%)
Other	261 (10.7%)
Revised Atlanta classification	
Mild, n (%)	1 738 (71.2%)
Moderate, n (%)	579 (23.7%)
Severe, n (%)	124 (5.1%)
Mortality, n (%)	67 (2.7%)
Length of stay in days, median (IQR)	8 (6–12)
Patients with local complication, n (%)	654 (26.8%)
Acute pancreatic fluid collection, n (%)	545 (22.4%)
Pseudocyst, n (%)	191 (7.8%)
Acute necrotic collection, n (%)	218 (8.9%)
Patients with systemic complication, n (%)	205 (8.4%)
Respiratory failure, n (%)	140 (5.7%)
Heart failure, n (%)	52 (2.1%)
Renal failure, n (%)	87 (3.6%)
New-onset diabetes, n (%)	77 (3.2%)

ERCP: endoscopic retrograde cholangiopancreatography
IQR: interquartile range

Supplementary Table 3. DATA QUALITY OF THE ANALYSED COHORT

Synergistic effect	**Total cohort**	**Uploaded data**	**%**
Age	2 441	2 441	**100.0%**
Sex	2 441	2 441	**100.0%**
Etiology	2 441	2 441	**100.0%**
Severity (mild/moderate/severe)	2 441	2 441	**100.0%**
Mortality	2 441	2 441	**100.0%**
Local complications	2 441	2 421	**99.2%**
Fluid collection	2 441	2 422	**99.2%**
Pseudocyst	2 441	2 422	**99.2%**
Necrosis	2 441	2 421	**99.2%**
Diabetes as complication	2 441	2 441	**100.0%**
Systemic complications	2 441	2 433	**99.7%**
Respiratory failure	2 441	2 432	**99.6%**
Heart failure	2 441	2 433	**99.7%**
Renal failure	2 441	2 433	**99.7%**
Smoking status	2 441	2 441	**100.0%**
Alcohol consumption status	2 441	2 410	**98.7%**
Smoking amount	2 441	2 407	**98.6%**
Alcohol consumption amount	2 441	1 777	**72.8%**
Amylase	2 441	2 266	**92.8%**
Lipase	2 441	1 732	**71.0%**
RAP	2 441	2 441	**100.0%**
CP	2 441	2 441	**100.0%**
Overall	**53 702**	**51 978**	**96.8%**

Smoking dose dependency	**Total cohort**	**Uploaded data**	**%**
Local complications	2 407	2 386	**99.1%**
Amylase	2 407	2 237	**92.9%**
Lipase	2 407	1 705	**70.8%**
RAP	2 407	2 407	**100.0%**
CP	2 407	2 407	**100.0%**
Overall	**12 035**	**11 142**	**92.6%**

Alcohol dose dependency	**Total cohort**	**Uploaded data**	**%**
Local complications	1 777	1 762	**99.2%**
Amylase	1 777	1 649	**92.8%**
Lipase	1 777	1 231	**69.3%**
RAP	1 777	1 777	**100.0%**
CP	1 777	1 777	**100.0%**
Overall	**8 885**	**8 196**	**92.2%**

RAP: recurrent acute pancreatitis, CP: chronic pancreatitis

Supplementary Table 4. STATISTICAL RESULTS – DOSE DEPENDENCY

SMOKING DOSE DEPENDENCY	NON-SMOKER	LIGHT SMOKER	HEAVY SMOKER	p*
AMYLASE (N=2237)				
N	1 571	332	334	<0.001
Mean (SD)	1 206 (1 188)	851 (952)	692 (788)	
Median (IQR)	831 (343, 1 681)	496 (240, 1 112)	398 (195, 808)	
Minimum; Maximum	13; 8 544	30; 7 532	32; 4 852	
LIPASE (N=1705)				
N	1 149	274	282	<0.001
Mean (SD)	2 916 (3 523)	1 962 (2 398)	1 587 (2 459)	
Median (IQR)	1 675 (635, 3 846)	1 027 (499, 2 508)	822 (376, 1 692)	
Minimum; Maximum	10; 24 940	14; 13 398	31; 20 569	
RAP AND CP (N=2407)				
RAP, n (%)	321 (19%)	94 (26%)	105 (29%)	<0.001
CP, n (%)	46 (2.7%)	41 (11%)	50 (14%)	<0.001
LOCAL COMPLICATIONS (N=2386)	438 (26%)	92 (26%)	109 (31%)	0.200

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test

ALCOHOL DOSE DEPENDENCY	NON-DRINKER	LIGHT DRINKER	HEAVY DRINKER	p*
AMYLASE (N=1649)				
N	1 158	186	305	<0.001
Mean (SD)	1 247 (1 216)	821 (892)	663 (846)	
Median (IQR)	863 (366, 1 719)	522 (230, 1 016)	379 (180, 782)	
Minimum; Maximum	13; 8 544	28; 5 283	30; 7 000	
LIPASE (N=1231)				
N	845	153	233	<0.001
Mean (SD)	2 864 (3580)	2 155 (2 575)	1 723 (2 862)	
Median (IQR)	1 571 (572, 3 756)	1 276 (570, 2 681)	736 (353, 1 730)	
Minimum; Maximum	10; 24 940	110; 17 904	19; 20 569	
RAP AND CP (N=1777)				
RAP, n (%)	239 (19%)	50 (26%)	98 (30%)	<0.001
CP, n (%)	47 (3.7%)	16 (8.2%)	36 (11%)	<0.001
LOCAL COMPLICATIONS (N=1762)	301 (24%)	51 (26%)	109 (34%)	0.003

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test

SD: standard deviation, IQR: interquartile range, RAP: recurrent acute pancreatitis, CP: chronic pancreatitis.

Supplementary Table 5. STATISTICAL RESULTS – SYNERGISTIC EFFECT

SYNERGISTIC EFFECT	NS-ND	NS-D	S-ND	S-D	p*
AGE (N=2441)					
N	1 049	639	202	551	<0.001
Mean (SD)	62 (18)	57 (15)	51 (14)	47 (12)	
Median (IQR)	64 (50, 76)	59 (45, 69)	52 (42, 60)	47 (38,56)	
Minimum;Maximum	18; 95	19; 95	18; 91	18; 82	
SEX (N=2441)					
Male, n (%)	356 (34%)	470 (74%)	102 (50%)	467 (85%)	<0.001
Female, n (%)	693 (66%)	169 (26%)	100 (50%)	84 (15%)	
SEVERITY (N=2441)					
Moderately severe, **n (%)**	225 (21%)	153 (24%)	39 (19%)	162 (29%)	0.002
Severe, n (%)	61 (5.8%)	40 (6.3%)	5 (2.5%)	18 (3.3%)	0.022
Mortality, n (%)	32 (3.1%)	23 (3.6%)	2 (1.0%)	10 (1.8%)	0.100
AMYLASE (N=2266)					
N	967	601	188	510	<0.001
Mean (SD)	1 285 (1 233)	1 079 (1 101)	1 056 (1 117)	692 (764)	
Median (IQR)	918 (381, 1 751)	705 (298, 1 537)	652 (309, 1 428)	414 (197, 844)	
Minimum; Maximum	13; 8 544	28; 7 750	33; 7 532	23; 4 852	
LIPASE (N=1732)					
N	690	458	152	432	<0.001
Mean (SD)	2 999 (3 684)	2 788 (3 268)	2 244 (3 024)	1 637 (2 191)	
Median (IQR)	1 690 (623, 3 964)	1 624 (678, 3 537)	1 213 (426, 2 524)	914 (454, 1 924)	
Minimum; Maximum	10; 24 940	19; 18 380	14; 17 450	22; 20 569	
RAP AND CP (N=2441)					
RAP, n (%)	183 (17%)	137 (21%)	56 (28%)	151 (27%)	<0.001
CP, n (%)	28 (2.7%)	18 (2.8%)	19 (9.4%)	76 (14%)	<0.001

* Kruskal-Wallis rank sum test; Pearson's Chi-squared test

NS–ND: non-smoking–non-drinking; NS–D: non-smoking–drinking; S–ND: smoking–non-drinking; S–D: smoking–drinking, SD: standard deviation, IQR: interquartile range, RAP: recurrent acute pancreatitis, CP: chronic pancreatitis.

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Onset of pancreatic cancer before and after acute pancreatitis: A multicenter longitudinal cohort study

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ABSTRACT

Background: Pancreatic cancer (PC) is a leading cause of cancer mortality, often diagnosed at advanced stages. Acute pancreatitis (AP), particularly idiopathic cases, may serve as an early indicator of PC.
Objective: This multicenter cohort study investigated the incidence of PC before and after an AP episode, focusing on idiopathic AP and the role of pseudocysts as potential early markers for PC development.
Methods: We analyzed data from 2356 AP patients across 25 centers, with a median follow-up of 4.1 years (IQR: 1.6–6.8 years). Patients were categorized into 'PC before AP' and 'PC after AP' groups, and relative risk (RR) and adjusted odds ratios (OR) were calculated for idiopathic AP cases to quantify PC risk.
Results: Among all cases, 69 patients (2.9 %) developed PC: 1.4 % (n = 34) before and 1.5 % (n = 35) after AP. Idiopathic AP cases had a fourfold higher risk of PC (OR = 4.46, [2.25–8.85]). Notably, pseudocysts were five times more prevalent in the PC group (14 %) compared to controls (3 %) (RR = 5.66; $p < 0.01$), often located at the tumor site. PC developed in 3 % of idiopathic AP cases versus 1.0 % in non-idiopathic cases. The median time to PC diagnosis post-AP was 373 days.
Conclusion: Idiopathic AP and pseudocyst formation significantly elevate the risk of PC, particularly within two years. These findings underscore the need for structured follow-up and early screening in idiopathic AP cases to improve PC detection and survival outcomes.

1. Introduction

Pancreatic cancer (PC) remains one of the deadliest malignancies, with poor prognosis largely due to late-stage diagnosis. Despite advancements in imaging and treatment, early detection of pancreatic cancer is still unresolved, and the current screening programs are not effective in identifying resectable tumors at an early stage [1]. According to recent studies, only 15–20 % of patients are candidates for surgical resection at the time of diagnosis [2], thus, identifying high-risk populations who may benefit from enhanced screening and early intervention is crucial. The risk factors for pancreatic cancer can broadly be categorized into two major groups: (1) non-modifiable factors and (2) modifiable factors [3]. However, some factors, such as diabetes mellitus, are harder to classify due to their complex relationship with cancer risk [4]. Among the non-modifiable risk factors, genetic predisposition plays a significant role in pancreatic cancer risk. For instance, carriers of BRCA1 and BRCA2 mutations have a 3–5% lifetime risk of developing PC [5]. Other mutations, such as those in the STK11 (associated with Peutz-Jeghers syndrome) and CDKN2A genes, also significantly elevate risk [6]. Individuals with Lynch syndrome and familial pancreatic cancer syndromes have up to a 10–20 % increased lifetime risk. Age and family history are also part of the non-modifiable risk factor. The risk of pancreatic cancer increases significantly with age, with most cases occurring in individuals over

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1424-3903/

60 years old [6], whereas, Individuals with a first-degree relative who has had pancreatic cancer have a 2–3 times higher risk of developing the disease [7]. Tobacco use is one of the most well-established modifiable risk factors, contributing to approximately 25 % of pancreatic cancer cases [8]. Smokers have a 2–3 times higher risk compared to non-smokers [9]. Obesity increases the risk of pancreatic cancer by about 20–50 %, with higher risks associated with a body mass index (BMI) above 30 [10]. Physical inactivity and poor dietary habits also contribute to increased risk [11]. Chronic heavy drinking is associated with chronic pancreatitis, which can increase the risk of pancreatic cancer [9]. Diabetes is a unique risk factor, as it is both a consequence and a potential cause of pancreatic cancer [12]. Long-standing type 2 diabetes is associated with a 1.5-2-fold increase in pancreatic cancer risk. However, new-onset diabetes may be an early indicator of undiagnosed pancreatic cancer, complicating its classification as a modifiable or non-modifiable risk factor [13]. Importantly, on average, pancreatic cancer is diagnosed within 1–3 years after the onset of new diabetes [4]. This has led to speculation about the underlying relationship between these two conditions. Diabetes indeed could serve as an early marker of undiagnosed pancreatic cancer. In addition to its effects on the endocrine pancreas, pancreatic cancer may also compromise the exocrine function, leading to disorders such as acute pancreatitis (AP).

It is known that pancreatic cancer can act as an etiological factor for acute pancreatitis (AP) [14]. Earlier studies also showed that PC risk increases after AP [15,16]. However, a detailed analysis of this association has not yet been conducted. This study aims to explore this link and assess the risk factors that may predispose patients with AP to develop PC.

2. Methods

2.1. Study type and preliminary settings

This study is a post hoc analysis of prospectively collected data from AP patients in the Acute Pancreatitis Registry (APR) following the STROBE guidelines for cohort studies.

The APR is maintained by the Hungarian Pancreatic Study Group (HPSG). The HPSG (https://tm-centre.org/en/research/study-groups/hungarian-pancreatic-study-group) was established in 2011 to improve patient care for pancreatic diseases. The registry received ethical permission from the Scientific and Research Ethics Committee of the Medical Research Council (22254–1/2012/EKU, 17787–8/2020/EÜIG), and all the patients provided written informed consent to participate. The study protocol conforms to the Declaration of Helsinki ethical guidelines.

2.2. Data collection

Data was collected by trained clinical research administrators, and a four-checkpoint electronic clinical data management system was set up to ensure data quality.

Altogether 2356 well-characterized patients from 25 centers were included and followed by the Hungarian Pancreatic Study Group (HPSG) between 2012 and 2021. The total cohort was screened for PC, and we analyzed all cases with data on the presence or absence of PC during the 4.1 (Q1: 1.6y, Q3: 6.8y) years median follow-up after AP. Paper-based and electronic medical records were reviewed.

2.3. Definitions

According to the IAP/APA and HPSG evidence-based guidelines [17,18] AP is diagnosed when at least two out of the following three criteria are met: (1) abdominal pain, (2) serum amylase or lipase elevation of at least three times the upper limit of normal, and (3) characteristic abnormalities seen on imaging. Severity and local and systemic complications were defined based on the modified Atlanta classification [19].

In our study, pancreatic cancer (PC) was defined as pancreatic ductal adenocarcinoma and/or adenocarcinoma of the Ampulla of Vater or pancreatic functioning and nonfunctioning neuroendocrine tumour. Cases were considered to have cancer (1) if they had a histological diagnosis, (2) if imaging, clinical presentation, and tumor markers confirmed the presence of cancer, or (3) if there was documented chemotherapy treatment for pancreatic cancer. We formed groups of patients with PC (PC group) and without PC (Control group) and further divided the PC group into 'PC before AP' and 'PC after AP' groups.

The 'PC before AP' subgroup included patients who were diagnosed with pancreatic cancer (1) before AP episode, (2) during the hospitalization of the index AP episode or (3) within one months after AP. The 'PC after AP' group included patients who were diagnosed with PC more than 30 days following AP.

2.4. Statistical analysis

To assess idiopathic etiology as a risk factor for pancreas cancer after AP, we calculated the crude odds ratio and the adjusted odds ratio as well in the total cohort, controlling for age, sex and AP severity as possible confounders.

For the case-control part of the study, to have similar distributions in the 'PC after AP' and their controls in terms of age, sex, etiology and AP severity, we used the nearest neighbor matching method with 1:3 allocation ratio, which resulted in a sample of 35 'PC after AP' patients (cases) and 105 controls. The matching was very precise and produced almost identical distributions regarding the 4 matched variables. To compare the PC and the control group in terms of the investigated exposures, we fit a logistic regression model including the 4 matched variables as covariates and using cluster-robust standard error to account for pair membership. Based on the output of the logistic regression models, we used the odds ratio (OR) and its 95 % confidence interval to assess the associations between the investigated exposures and pancreas cancer.

We used the R program v4.2.0.for all computations and the MatchIt package v4.5.4. for the matching and for estimating effects after matching.

3. Results

In the total cohort of 2356 patients, the average age was 55.03 ± 17.53 years, and the proportion of male patients was 55.09 %. A 67.40 % (n = 1588) of the cases were mild, 24.10 % (n = 568) moderately severe, and 8.48 % (n = 200) were severe AP suggesting a general AP cohort.

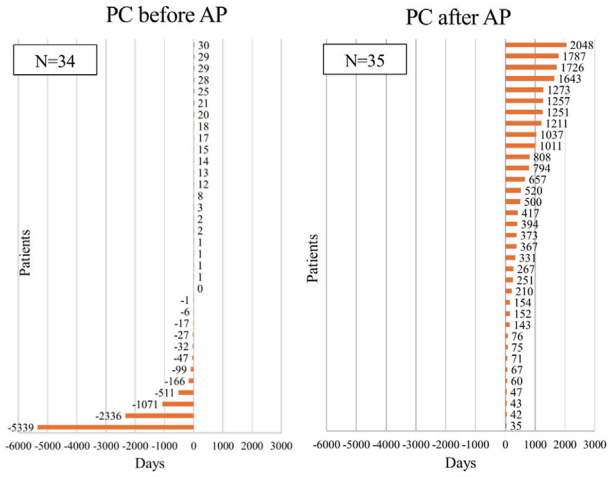
Sixty-nine patients (2.9 %) had PC in the total cohort. Thirty-four (1.4 %) of them were diagnosed before, whereas 35 (1.5 %) were after the AP episode (Fig. 1A). For patients who had PC diagnosis after AP, the median time to PC diagnosis was approximately one year (375 days) (Fig. 1B and C).

The proportion of idiopathic cases was twice as high in patients diagnosed with PC after AP compared to those diagnosed with PC before or during AP (51 % vs. 25 %, $p < 0.001$, Fig. 1D). In idiopathic cases, PC was diagnosed in 3 % of patients after AP during a median follow-up of 4.1 years, while in non-idiopathic cases, only 1.0 % was diagnosed with PC (OR = 4.44, [2.24–8.77]), Fig. 1E). This association remained significant even after adjusting for age, sex and AP severity as possible confounders (OR = 4.46, [2.25–8.85]).

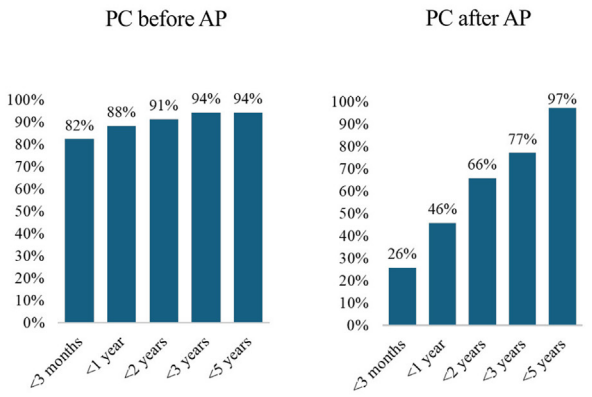
A) PC is highly associated with AP

	n	%
Total AP cohort	**2356**	100.0%
Non-PC	2287	97.1%
PC	69	2.9%
Before AP	34	1.4%
After AP	35	1.5%

B) Diagnosis time by patients



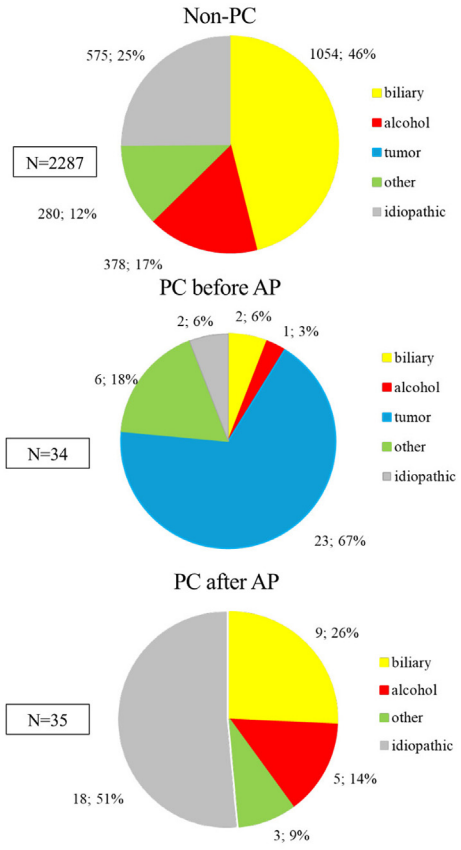
C) Cumulative diagnosis time



N	34
Min	-5339
Q1	-24.5
Median	1.5
Q3	16.5
Max	30
IQR	41
>5 years	2

N	35
Min	35
Q1	109.5
Median	373
Q3	1024
Max	2048
IQR	914.5
>5 years	1

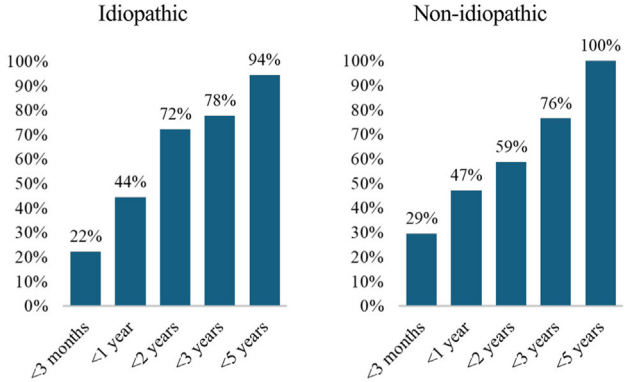
D) Etiology



E) PC and idiopathic etiology

	Total cohort	PC before AP (n)	PC before AP (%)	PC after AP (n)	PC after AP (%)
Idiopathic	595	2	0.3%	18	3.0%
Non-idiopathic	1761	32	1.8%	17	1.0%
Total	**2356**	**34**	**1.4%**	**35**	**1.5%**

F) Cumulative diagnosis time – PC after AP



N	18
Average	598.5
SD	599.6
Median	370
Q1	145.2
Q3	922.5
Min	35
Max	2048

N	17
Average	607.4
SD	601.5
Median	394
Q1	71
Q3	1037
Min	42
Max	1787

Fig. 1. Association between acute pancreatitis (AP) and pancreatic cancer (PC). (A) Summary of the pancreatic cancer and control group. (B) Diagnosis time of PC and (C) cummulative diagnosis time of PC. (D) Etiologies of AP. (E) Idiopathic AP relation to PC and (F) cummulative diagnosis time of cancer in case of idiopathic AP.

There was no difference in the median cumulative time to PC diagnosis after AP in idiopathic and non-idiopathic cases (370 days vs. 394 days, respectively) (Fig. 1F).

We also compared the prevalence of pre-existing and later developed recurrent AP (RAP), chronic pancreatitis (CP), and diabetes in the PC and Control groups conducting a matched case-control analysis. Both pre-existing and newly developing RAP were similar in the two groups (20 % vs. 14 %, OR = 2.13 [0.74–6.13]) and 29 % vs. 17 %, OR = 1.86, [0.78–4.43]), respectively) (Fig. 2A). Pre-existing CP was similar (6 % vs. 8 %, OR = 0.73, [0.16–3.45]), whereas newly developing CP was more frequent in the cancer group 16 % vs. 6 %, OR = 2.75 [1.03–7.32]) (Fig. 2B). Pre-existing diabetes mellitus (DM) was less frequent (14 % vs. 32 %, OR = 0.35, [0.13–1.00]), however newly developing DM showed no significant difference (12 % vs. 8 %, OR = 1.56, [0.59–4.11]) in the cancer group (Fig. 2C).

Investigating the AP complications as possible risk factors, we found that organ failure was less frequent in the cancer group (3 % vs. 7 %, OR = 0.36, [0.29–0.45]) (Fig. 2D), while occurrence of local complications was similar (20 % vs. 17 %, OR = 1.23, [0.94–1.61]) (Fig. 2E). While development of peripancreatic fluid collections were similar (11 % vs. 14 %, OR = 0.78, [0.33–1.85]), incidence of necrosis was less frequent in the cancer group (0 % vs. 7 %, OR = 3.41, [1.37–8.48]) (Fig. 2F,G). Most importantly, the proportion of pseudocyst formation was about five times higher in the cancer than in the control group (14 % vs. 3 %, OR = 5.66, [1.65–19.4]) (Fig. 2H). Four out of the 5 cases, the pseudocyst and the tumor were in the same location within the pancreas.

Concerning the on-admission body mass index (BMI) we found no significant difference in the 'PC after AP' group than in the 'Control' group (56 % vs. 71 %, OR = 0.76, [0.37–1.57]) (Fig. 2I). A summary table of the comorbidities and complications of acute pancreatitis (AP) as risk factors of pancreatic cancer (PC) can be found in Table 1.

4. Discussion

We identified a high prevalence of PC following idiopathic AP, with most cancer diagnoses occurring within two years of an AP episode. Our findings offer new insights into the pathogenesis of idiopathic AP and its potential relationship with PC, contributing valuable data to the existing body of literature. This study highlights idiopathic AP as an important clinical marker for PC and underscores the need for targeted screening protocols in this population.

An especially notable finding of our study was the significant occurrence of pancreatic pseudocysts in the PC group, which may indicate the presence of obstructive phenomena. These obstructions could be due to a growing tumor within the pancreatic duct, causing pseudocyst formation and, subsequently, acute pancreatitis. This scenario is strikingly similar to the pathophysiology observed in colorectal cancer and biliary tumors, where tumor-induced obstruction leads to symptoms such as ileus or obstructive jaundice.

The associations we observed between preexisting diabetes, CP, and pancreatic cancer are not surprising. These risk factors have been well-documented in the literature [3,4,6] and further confirm their role in the complex interplay between chronic inflammation, metabolic dysregulation, and cancer development.

4.1. Strength and limitations

The use of a well-characterized, multicenter cohort from the Hungarian Pancreatic Study Group (HPSG) provided a robust dataset for analysis. The study utilized long-term follow-up data (up to 10 years) with using a multicenter cohort of 2356 patients, allowing for a comprehensive evaluation of PC development following AP.

However, the study has limitations as well. The study's reliance on post hoc analysis of prospectively collected data may introduce selection biases. While we identified a statistically significant link between idiopathic AP and PC, the sample size of PC cases and event numbers such as organ failure or pseudocyst was relatively small. The lack of standardized follow-up protocols for idiopathic AP patients may have impacted the uniformity of cancer detection in the cohort. The determination of PC onset is also challenging. Although PC could have been present at the time of the AP episode without diagnosis, we defined the PC patient groups based on the time of diagnosis.

4.2. Implications for practice

Translating scientific information to patients' benefit has crucial importance [20–22]. The findings of our study underscore the importance of careful monitoring and follow-up for patients presenting with idiopathic acute pancreatitis. Given the elevated risk of PC especially within the first two years, enhanced screening measures, including imaging modalities such as MRI and CT, should be considered for these patients. In cases of idiopathic AP where pseudocyst formation is present, it may also be beneficial to perform EUS-guided fine-needle aspiration (FNA) for biopsy and further assessment. Early detection could improve resectability and, consequently, survival outcomes for pancreatic cancer patients.

4.3. Implications for research

Further research is needed to investigate the mechanisms underlying the association between idiopathic AP and PC. Identifying specific biomarkers or mechanical/chemical factors that signal early-stage PC could revolutionize screening protocols and potentially lead to earlier diagnosis, improving treatment options and prognosis. Future studies should also focus on refining imaging techniques to detect early tumor formation, even when current modalities cannot visualize it.

5. Conclusion

In conclusion, we found a significant association between idiopathic AP and PC, particularly within the first two years following an AP episode. The high prevalence of pancreatic cysts in the PC group suggests that early tumor-induced obstruction could play a role in triggering AP.

CRediT authorship contributions

Tamás Hussein, MD (Data curation: Lead; Formal analysis: Lead; Investigation: Equal; Project administration: Lead; Writing – original draft: Equal; Writing – review & editing: Equal).

Péter Mátrai, MSc (Formal analysis: Equal; Methodology: Equal; Writing – review & editing: Supporting).

Vivien Vass, MSc (Data curation: Equal; Methodology: Equal; Visualization: Equal; Writing – review editing: Supporting).

Andrea Szentesi, PhD (Formal analysis: Equal; Methodology: Lead; Resources: Equal; Writing – review & editing: Equal).

Péter Hegyi, DSc (Conceptualization: Lead; Funding acquisition: Lead; Investigation: Lead; Methodology: Lead; Resources: Lead; Writing – original draft: Lead).

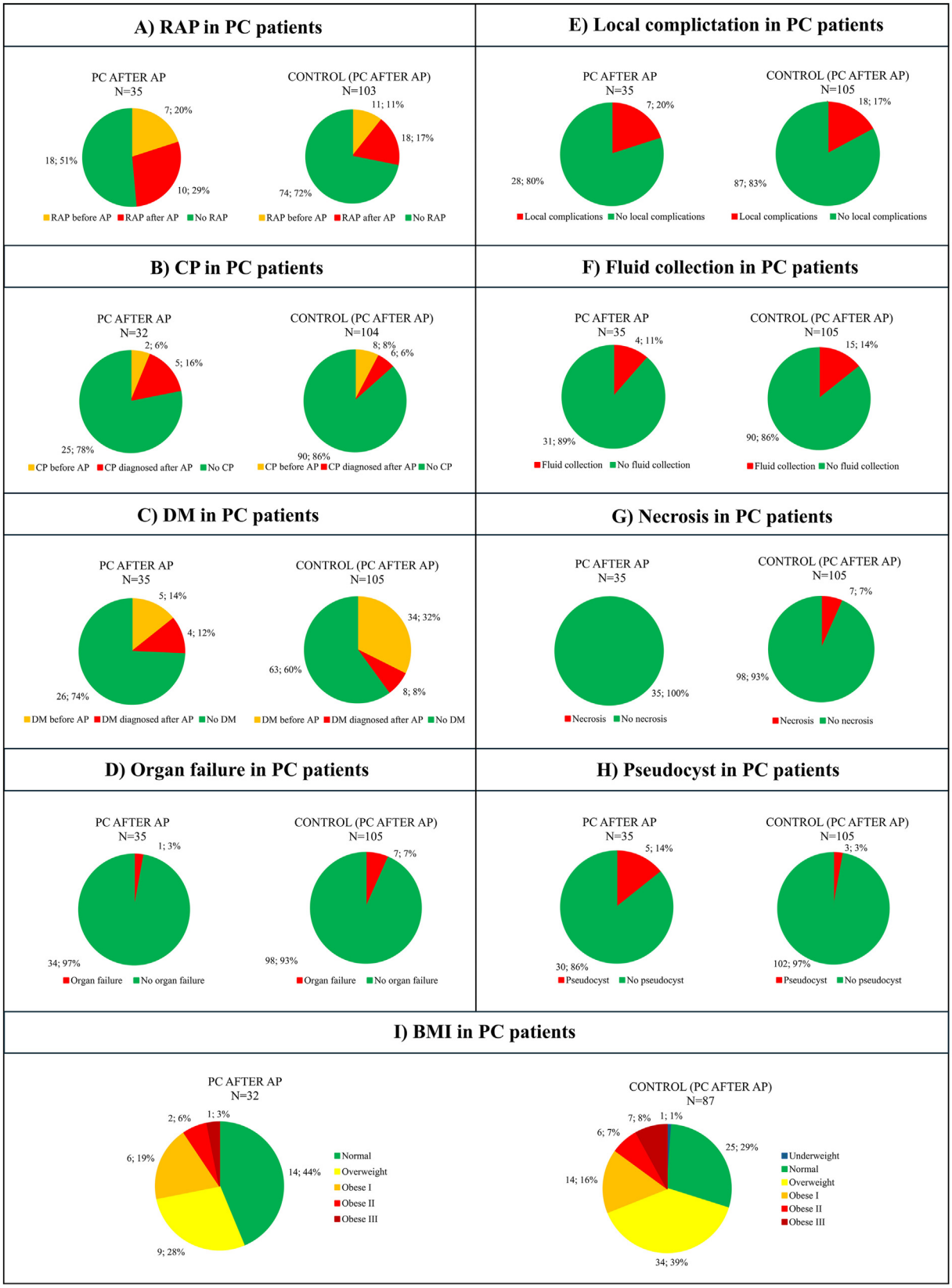


Fig. 2. Comorbidities and complications of acute pancreatitis (AP) as risk factors of pancreatic cancer (PC). (A) Recurrent acute pancreatitis (RAP). (B) Chronic pancreatitis (CP). (C) Diabetes mellitus (DM). (D) Organ failure. (E) Summary of local complications of AP. (F) Fluid collection. (G) Necrosis. (H) Pseudocyst formation. (I) Distribution of Body Mass Index (BMI).

Table 1
Summary of the comorbidities and complications of acute pancreatitis (AP) as risk factors of pancreatic cancer (PC).

Category	PC After AP (n = 35)	Control (n = 105)	OR [CI]
RAP before AP	20 % (7)	11 % (11)	2.13, [0,74–6.13]
RAP after AP	29 % (10)	17 % (18)	1.86, [0.77–4.43]
Chronic Pancreatitis (CP) before AP	6 % (2)	8 % (8)	0.73, [0.15–3.45]
Chronic Pancreatitis (CP) after AP	16 % (5)	6 % (6)	2.75, [1.03–7.32]
Diabetes Mellitus (DM) before AP	14 % (5)	32 % (34)	0.35, [0.12–1]
Diabetes Mellitus (DM) after AP	12 % (4)	8 % (8)	1.56, [0.59–4.11]
Organ Failure	3 % (1)	7 % (7)	0.35, [0.28–0.44]
Local Complications	20 % (7)	17 % (18)	1.23, [0.94–1.61]
Peripancreatic Fluid Collections	11 % (4)	14 % (15)	0.77, [0.32–1.85]
Necrosis	0 % (0)	7 % (7)	3.41, [1.37–8.48]
Pseudocyst	**14 % (5)**	**3 % (3)**	**5.66, [1.65–19.4]**
Overweight and obese	56 % (18)	70 % (61)	0.76, [0.36–1.57]

Data transparency statement

Original raw data is available from the corresponding author upon reasonable request.

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Conflict of interest statement

All authors declare no conflict of interest.

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