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Risk Factors in Pancreatic Adenocarcinoma: the Interrelation with Familial History and Predictive Role on Survival

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ABSTRACT

Background & Aims: Pancreatic cancer is associated with poor survival and quality of life. In Romania the prognostic influence of known risk factors for pancreatic adenocarcinoma, such as age, smoking, chronic pancreatitis, diabetes mellitus, and obesity is little known. Their importance in developing cancer in families with a history of adenocarcinoma is less studied. This study aims to assess the risk factors in pancreatic ductal adenocarcinoma, in familial pancreatic adenocarcinoma, in neuroendocrine tumors and to evaluate their predictive role on survival.

Methods: We performed a prospective bicentric study of patients with pancreatic tumors detected in transabdominal imaging; we assessed the risk factors and their possible association with survival.

Results: 312 pancreatic cancer patients (279 with pancreatic ductal adenocarcinoma and 24 patients with neuroendocrine tumors, and nine patients with other malignant types) and 312 controls were included. The median body mass index was significantly higher in patients with neuroendocrine tumors. Positive family history for pancreatic cancer was found in 4% of patients with pancreatic cancer. The risk for familial pancreatic carcinoma was associated with the presence of new-onset diabetes (OR: 4.64, p=0.018). The multivariate logistic analysis suggested that advanced age (OR: 1.67), smoking (OR: 1.67), low body mass index (OR: 12.07), and diabetes (OR: 3.91) were risk factors for pancreatic cancer. The overall survival analysis after adjustment for age and tumor stage showed only advanced tumoral stage (HR=1.6, p=0.003) and metastasis as independent predicting factors (HR=1.67, p<0.001).

Conclusion: Our study suggests that diabetes, smoking, underweight, and age over 60 years are risk factors for pancreatic cancer. Patients with a family history of pancreatic cancer, especially those with new-onset diabetes, should be followed carefully and considered for screening. Only an advanced tumor stage was associated with poor overall survival for patients with pancreatic ductal adenocarcinoma.

Key words: pancreatic cancer – neuroendocrine tumor – familial pancreatic carcinoma – risk factor – obesity – survival.

Abbreviations: BMI: body mass index; CT: computed tomography; EUS: endoscopic ultrasonography; FNA: fine needle aspiration; HBV: hepatitis B virus; HCV: hepatitis C virus; OS: overall survival; PC: pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma; NET: neuroendocrine tumor; US: ultrasonography.

INTRODUCTION

Pancreatic cancer (PC) has one of the highest mortality rates among malignancies, with only a 5-7% survival at five years, despite advances in surgery, chemotherapy, and radiotherapy [1]. Worldwide, the incidence and mortality have been increasing, especially in developed countries [2, 3]. Pancreatic cancer is the fourth leading cause of cancer death in the United States [4], and the sixth leading cause of cancer death in Europe [5].

Unfortunately, PC is an aggressive type of cancer, and at the time of diagnosis, 80% of patients have locally advanced or metastatic PC [6].

As there are no screening tests for early detection of PC, it is important to explore the risk factors, such as genetic factors (taking into consideration that 5-10% of cases have a familial history of PC [7-10]) and the modifiable risk factors which include smoking, non-hereditary chronic pancreatitis, obesity, long-standing diabetes mellitus [6], alcohol consumption,

decreased physical activity, increased intake of red or processed meat and inadequate intake of fruits and vegetables, certain abdominal surgeries and some infections [11, 12]. For example, survival is negatively associated with smoking [13], and the risk rises when it is associated with familial pancreatitis history [14]. New-onset diabetes may be an early marker of pancreatic cancer [7].

Romania is situated on rank 7, with an incidence of approximately 7.9 cases per 100,000 inhabitants [2] with one of the highest mortality rates in Eastern Europe [15]. The male/female incidence has increased from 5.5/2.92 in 1955 to 8.1/4.2 in 2008 [8] and 9.3/5.1 in 2012 [16]. In the same 2012 year, PC was the third digestive cancer as incidence, and the forth digestive cancer as a cause of mortality in males, meanwhile in females, it was the second digestive cancer as incidence and the third cause of deaths from digestive cancer [17]. It has been estimated by the International Agency of Cancer that the incidence for males reached 8.9 and for females 5.3 per 100,000 inhabitants in 2018 [18]. There are few published data on risk factors in PC in Romania or the frequency on the familial history in this population [19].

The purpose of this study was to assess the risk factors in pancreatic ductal adenocarcinoma (PDAC) and familial pancreatic adenocarcinoma, to assess their presence in the adenocarcinoma patients compared to patients with neuroendocrine tumors and controls and to evaluate their predictive role on survival.

METHODS

Study subjects

For this study, we collected prospective data from patients diagnosed with PC between January 2015 and January 2017, in two Romanian tertiary medical centers. Our hospital-based study assessed the major risk factors of pancreatic cancer.

A total of 624 patients were recruited, including 312 pathologically verified cancer cases and 312 controls selected from other patients who did not have pancreatic cancer. Cases and control were 1:1 matched by gender and age. Inclusion criteria were: patients with solid pancreatic masses on ultrasonography (US) or a computed tomography (CT) scan, with or without hepatic metastases and confirmed histologically by fine needle aspiration (FNA) biopsy during endoscopic ultrasonography (EUS) or surgery. Control subjects had no cancer history and were individually matched to cases with the same gender and age (within five years). Exclusion criteria were solid pancreatic masses with no proven malignancy or cystic pancreatic masses.

All subjects gave informed consent before being included in the study. The study was approved by the Ethics Committee of both hospitals.

Data collection

We collected information regarding demographic data, data on possible risk factors, symptoms, diagnosis, staging, therapy, and survival. Demographic data included age and gender of patients. Information regarding alcohol consumption and smoking (the average number of cigarettes smoked daily; a pack-year was defined as twenty cigarettes smoked daily for one year), body mass index (BMI), history of chronic pancreatitis, diabetes mellitus, B or C viral hepatitis, abdominal surgeries, and familial PC was collected as possible risk factors. Based on BMI, the patients were classified as underweight (<18.5 kg/m^2), normal (18.5-24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (>30 kg/m^2). Diabetes mellitus was considered as unrelated to the occurrence of PC when it was diagnosed ≥3 years before the diagnosis of PC. Fasting blood samples were collected to determine the levels of glucose, HDL-cholesterol and triglycerides. Diabetes mellitus was diagnosed when fasting glycemia was ≥126 mg/dl. The metabolic syndrome was assessed using the IDF criteria [20]: central obesity (waist circumference > 94 cm in men and > 80 cm in women or BMI >30kg/m^2 no matter the waist circumference [21, 22]), fasting plasma glucose or previously diagnosed type 2 diabetes, high blood pressure or treatment of previously diagnosed hypertension, decreased HDL-cholesterol (< 40 mg/dl in males, <50 mg/dl in females), and increased triglyceride ≥ 150 mg/dl. Using IDF criteria, metabolic syndrome was defined as central obesity plus any two of the other four components listed above [20].

Familial PC was considered when any of the first-degree relatives had PC.

Cancer-related data included the date of diagnosis, staging, localization of the primary tumor, treatment, and the level of CA 19-9 at the time of diagnosis.

Diagnosis and staging of pancreatic cancer were based on imaging techniques CT and/or EUS, which assessed the primary resectable tumor, the locally advanced, and the metastatic disease. The final diagnosis was based on the histologic results from EUS-FNA or surgery. In neuroendocrine tumors (NET) patients, the diagnosis was made on core-histology from EUS-FNA with immunohistochemistry for chromogranin A, synaptophysin and Ki-67. The NET included were non-functioning tumors. The diagnosis of chronic pancreatitis was made by appearance on CT and/or EUS examination as previously described [23].

Survival was defined as the number of months between the date of diagnosis and date of death. The date of diagnosis was defined as the time from the first imaging modality (CT or EUS) giving the diagnosis of pancreatic cancer.

Statistical analyses

Categorical data were presented as count and relative frequencies. Continuous data were presented as means and standard deviations for normally distributed data and as medians with 25% and 75% percentiles, for skewed data.

Potential predictors for PDAC were checked with univariate logistic regression models, followed by a multivariate logistic regression model including all of them. All models were checked for goodness-of-fit with the Hosmer-Lemeshow test. For the multivariate model we checked the multicolinearity with variance inflation factor (and removing redundant variables), misspecification (Stuckel test and Osius-Rojek test). All logistic regression models were presented with odds ratios, 95% confidence intervals and p-values.

Potential predictors for overall survival (OS) were assessed using univariate Cox proportional hazard regression. The same predictors were then analyzed in multivariate models, adjusted

for age (years), T stage (1-2, 3, 4), adenopathy, metastasis. Proportional hazard assumptions were checked using Schoenfeld residuals and a formal test. The multicollinearity assumption was verified with the variance inflation factor for the multivariable models. For continuous variables, the linearity was checked with penalized smoothing splines. All models shown adhere to these assumptions. Hazard ratios and 95% confidence intervals are shown for the models. For all analyses, two-sided p-values were shown, and a 0.05 level of significance was used.

All analyses were performed in R environment for statistical computing and graphics (R Foundation for Statistical Computing, Vienna, Austria), version 3.4.3.

RESULTS

There were 624 patients included in the study, 312 with suspected PC and 312 healthy persons as controls. Mean age of the entire cohort was 63.4 years (SD 12.18, ranging from 16 to 91 years). There were more males than females (n=183, 59% vs. n=129, 41%) in patients with suspected PC and also in control group (n= 193, 62% vs n=119, 38%). Mean age of patients with PDAC was 64.88 ±10.74 years old compared to 62.42 ±13.29 years old (p>0.05). The most frequent symptoms in patients suspected of PC were abdominal pain and weight loss, which were present in 83% and 68% of all patients. Jaundice was found in 38%. Diarrhea was recorded in 18% of the patients, 29% had constipation.

The characteristics of PDAC and NET patients are displayed in Table I. In 90% of patients we identified histologically PDAC and in 8% NET. There were 3 cases (1%) of adeno-squamous carcinoma of pancreas, 2 cases (1%) of mucinous adenocarcinoma of the pancreas, and one case each of solid pseudopapillary neoplasm, signet ring cell carcinoma, undifferentiated carcinoma with osteoclast-like cells, and one of pancreatic metastases of squamous carcinoma. The age, gender, and size of the tumor were similar in the two categories of patients. The high level of CA 19-9 was more frequent in PDAC than in NET (p<0.001). The presence of metabolic syndrome was noted in 4.3% of patients with PDAC and in 16.7% of patients with NET.

Univariate analysis showed that age over 60 years (OR: 1.7, 95%CI: 1.22-2.38), cigarette smoking (OR: 1.49, 95%CI: 1.07-2.08), low BMI (OR: 10.67, 95%CI: 4.74-28.61) and high BMI (OR: 2.12, 95%CI: 1.18-3.86), diabetes (OR: 4.1, 95%CI: 2.59-6.61), and the presence of new-onset diabetes (OR: 11.78, 95%CI: 5.28-31.42) were associated with an increased risk of pancreatic cancer. In multivariate analyses, after adjusting for age >60 years, smoking, alcohol and coffee consumption, weight status, diabetes and new-onset diabetes, hepatitis B virus (HBV), hepatitis C virus (HCV), cholecystectomy and biliary lithiasis, we found that advanced age (OR: 1.67), smoking (OR: 1.67), low body mass index (OR: 12.07), and diabetes (OR: 3.91) with the presence of new-onset diabetes (OR: 12.97) were associated with elevated risk (Table II).

No differences for the frequency of risk factors (smoking, alcohol consumption, diabetes and familial history of pancreatic cancer) was found between PDAC and NET, except for the median BMI (24.24 kg/m^2 in PDAC vs 27.55 kg/m^2 in NET, p=0.013). Also, the association with the presence of HCV was significantly higher in patients with NET (12.5% in NET vs 7.53% in PDAC, p=0.027). The rate of diabetes (41.2% in PDAC and 37.5% in NET, p=0.72) was similar. There was no difference regarding smoking in the 2 groups (43.37% in PDAC and 29.17% in NET) (p=0.176).

More than 40% of patients with PDAC had metastases, compared to 20% of patients with NET (p=0.037).

Positive family history for pancreatic adenocarcinoma was found in 13 patients (4%) with PC (12 patients with PDAC and one patient with NET). For the analysis of the influence of familial history, the NET patient was excluded (Table III). The presence of new-onset diabetes was associated with an elevated risk of familial PC (OR: 4.64, p=0.018).

At 38 months of follow up, almost 73% of patients with PDAC had died. The median overall OS was 9 months for the 279 patients with PDAC. This was significantly different in relation to the advanced tumor stage (p=0.001) and the presence of metastases (p<0.001) in a Kaplan-Meier analysis.

There was no association between risk factors (obesity, history of chronic pancreatitis, diabetes, smoking, familial pancreatic cancer, etc.) and OS.

In a multivariate Cox- proportional survival analysis, we assessed several variables after adjustment for T stage (1-2, 3, 4), malignant lymph nodes, and metastasis. Still, only advanced tumoral stage (HR=1.6, p=0.003) was identified as an independent predictor for OS (Table IV).

DISCUSSION

The mortality rate of PC in Central Europe is one of the highest in the world [15] and decreases in the immediate vicinity in Eastern Europe countries, such as Romania [2]. There is no explanation for this difference, and it is very important to know which are the factors involved in the development of the disease. This work brings together and assesses two groups of the PC population from the north-western part and the eastern part of Romania. Less than 10% were NET and from all the population included, only 4% recognized history of pancreatic cancer in this bi-centric study, which is consistent with the literature data showing that the familial history of PC increases risk and accounts for 4–16% of cases [24]. A previous retrospective study made on a Romanian population in one tertiary medical center of 148 patients found 1% history of PC in the population over 45 years old [19], which is consistent with 4% in our group with a median age of 61 years old.

Several studies revealed that smoking [9] and the recent onset of diabetes [10] are supplementary risk factors for familial PC. Consistent with these results, we found that there was a significantly elevated risk of familial PC for patients with new-onset diabetes (OR: 4.64). Moreover, in patients with familial PC 50% of patients were smokers, and 33% of them drank alcohol, but the difference was not significant compared to non-familial PC. The age of these patients was similar compared to patients with no family history of PC (61.08 vs. 64.61).

Pancreatic cancer is predominantly a disease of older individuals and almost 90% of patients with PC are diagnosed

Table I. Demographic characteristic of patients with pancreatic adenocarcinoma and pancreatic neuroendocrine tumors

Characteristic	PDAC patients (n=279)	NET patients (n=24)	p
Age (years), mean (SD) [range]	64.88 (10.74) [35 – 89]	62.04 (10.51) [27-82]	0.21
Age >60 years, n (%)	187 (67.03)	15 (62.5)	0.65
Gender (female), n (%)	114 (40.86)	12 (50)	0.383
Triglycerides (mg/dL), median (IQR) [range]	127 (93-191) [42-535]	117.5 (74-153) [52-245]	0.22
HDL-cholesterol (mg/dL), median (IQR) [range]	29 (20-44) [5-81]	17.5 [15-20]	0.28
BMI, median (IQR)	24.24 (21.66 - 26.72)	27.55 (23.43 - 30.62)	0.014
Normal weight, n (%)	121 (43)	8 (33)	0.4
Underweight, n (%)	44 (15.3)	1 (4.2)	0.22
Overweight, n (%)	116 (40.3)	16 (66.7)	0.06
Obese, n (%)	32 (11.5)	7 (29.2)	0.043
Fasting blood glucose (mg/dL), mean (SD) [range]	149.18 (60.1) [58-473]	130.3 (53.5) [80-292]	0.08
Arterial hypertension, n (%)	124 (44.4)	24 (58.3)	0.2
Metabolic syndrome, n (%)	12 (4.3)	4 (16.7)	0.029
CA 19-9 (U/ml)>37 UI/l, median (IQR) [range]	191 (45 – 400) [1-400]	16 (8.21 – 72.95) [1-400]	< 0.001
Tumor size >=3cm, n (%)	231 (82.8)	18 (75)	0.401
T stage, n (%)			
T1-2	26 (9.3)	4 (16.7)	0.08
T3	100 (35.8)	12 (50)	0.2
T4	153 (54.8)	8 (33.33)	0.043
Stage III-IV, n (%)	168 (60.2)	9 (37.5)	0.04
Pancreatic cancer location			
Head + uncinated process + isthmus, n (%)	183 (65.6)	13 (54.2)	0.367
Body + tail, n (%)	96 (34.4)	11(45.8)	
Histological grade, n (%)			
G1	9/77 (11.84)	2/4 (50)	
G2	39/77 (51.32)	2/4 (50)	0.085
G3	28/77 (36.84)	0/4 (0)	
N stage n (%)	230 (82.44)	16 (66.67)	0.097
Metastasis, n (%)	119 (42.65)	5 (20.83)	0.037
Chemotherapy, n (%)	163 (77.25)	17 (89.47)	0.381
Endoscopic palliative biliary drainage:			
biliary plastic stents, n (%)	56 (20)	4 (17)	0.336
metal stents, n (%)	37 (13)	2 (8)	
External biliary drainage	4 (1)		
Palliative surgical drainage (enteral and biliary bypass)	43 (15)	3 (12.5)	

PDAC: pancreatic adenocarcinoma; NET: neuroendocrine tumors; CA 19-9: Carbohydrate antigen 19-9; SD: standard deviation; IQR: interquartile range; BMI: body mass index; HDL: high density lipids

after the age of 55 years [1, 25], as in our study, although 33% of patients were younger than this cut-off age. Also, the mortality in both genders increases with age, especially after the age of 55 years [2, 26]. In our study, mortality was higher in patients over 60 years, although its independent role in predicting survival was not proved, results similar to those in the literature [27] (Table IV).

Many studies have confirmed that smoking increases the risk of PC up to 6 times [28]. A meta-analysis reported that smokers were at twice the risk of PC compared to non-smokers, and the number of cigarettes smoked and the duration of smoking were associated with an increasing trend of elevated risk [29, 30]. The cessation of cigarette smoking for less than five years and the exposure to tobacco smoke during childhood or at home or work are associated with PC. Still, it was reduced in non-smokers within five years of quitting [30]. The association of coffee consumption found no additional risk [31]. According to the latest Eurobarometer survey, 31% of the Romanian population regularly smokes (33% of men and 22% women) [32, 33]. In our study, we found a higher percentage of smokers (43% of patients with PDAC, 29% of patients with NET and 34% in controls) significantly associated with PC risk (OR: 1.67) (Table III). Smoking did not influence the survival in pancreatic cancer, as in the literature [34].

Table II. Frequency of possible risk factors for patients with pancreatic ductal adenocarcinoma

Risk factors	PDAC (n=279)	Controls (n=312)	p	OR adjusted (95% CI)
Age >60 years	187 (67)	170 (54.2)	0.002	1.67 (1.13 – 2.48)
Smoking, n (%)	121 (43.37)	106 (34)	0.02	
>20 pack-year	74 (27)	53 (17)	0.005	1.67 (1.09 – 2.59)
Alcohol consumption, n (%)	128 (45.88)	138 (44.2)	0.688	0.92 (0.62 – 1.38)
Coffee consumption, n (%)				
Moderate	141 (50.57)	179 (57)	0.09	0.65 (0.44 – 0.97)
Excessive	7 (2.51)	5 (1.6)		
None	131 (46.95)	128 (41)		
Weight status, n (%)				
Normal weight	121 (43)	173 (56)		
Underweight	44 (15.3)	6 (1.9)		
Overweight	116 (40.3)	130 (41.7)	<0.001*	12.07 (5.03 – 34.32)
Obese	32 (11.5)	22 (7.1)	0.253**	1.49 (0.75 – 2.95)
Metabolic syndrome, n (%)	12 (4.3)	12 (3.8)	0.8	1.02 (0.43-2.38)
Chronic pancreatitis, n (%)	37 (13.26)	35 (1.2)	0.7	
Alcoholic etiology, n (%)	22 (7.97)	22 (7.1)	0.13	0.77 (0.42 – 1.41)
Diabetes, n (%)	115 (41.22)	36 (11.5)	0.001	3.91 (2.38 – 6.54)
Insulin treatment	44 (16)	11 (4)		
Oral antidiabetics	62 (22)	22 (7)		
New-onset diabetes, n (%)	42 (15)	6 (1.9)	<0.001	12.97 (5.54 – 35.92)
Familial PDAC history, n (%)	12 (4.3)	0 (0)	≤0.001	NA
HCV, n (%)	6 (2.15)	13 (4.2)	0.17	0.31 (0.09 – 0.93)
HBV, n (%)	2 (0.72)	9 (2.9)	0.06	0.24 (0.03 – 1.16)
Cholecystectomy, n (%)	48 (17.2)	40 (12.8)	0.214	1.15 (0.68 – 1.96)
Biliary lithiasis, n (%)	21 (7.53)	31 (9.9)	0.39	0.62 (0.32 – 1.19)

* p between underweight vs normal weight; ** p between obese vs normal Weight; PDAC: pancreatic ductal adenocarcinoma; HCV: hepatitis C virus; HBV: hepatitis B virus; BMI: body mass index; CI: confidence; OR: odds ratio..

Epidemiological studies showed that the alcohol-abusing group has a higher PC incidence and mortality than non-drinkers and heavy alcohol drinkers had a relative risk of 1.36 compared to light drinkers and 1.29 compared to non-drinkers [35], with chronic pancreatitis being one carcinogenic pathway. In our studied population, regular consumption of alcohol was reported in almost 46% of the PDAC patients, among which 8% (n=22) had chronic alcoholic pancreatitis, and this is higher than in the published literature where it was stated that 5% of patients with chronic pancreatitis developed PC [36]. Statistical analysis proved that alcohol consumption represented no risk factor for PDAC or NET.

The association between diabetes and PDAC is well-known [37] and new-onset diabetes proved the strongest association with this disease [38]; this was confirmed both in patients with a familial history of PC as well in sporadic PDAC. Overall, 41% of our patients with PDAC had diabetes, compared to 50% in other published data [39]. Almost 15% of patients had new-onset diabetes, which was an important risk factor for PDAC (OR: 12.97). However, long-standing diabetes, accepted as a risk factor in other reports [40], was not confirmed in our group.

In addition to diabetes, obesity, and overweight patients were considered at risk for PC [41-44]. Overweight and obese people had a 10%, respectively 20% increased risk of PC compared with people of normal weight [45]. There are many possible mechanisms by which obesity can lead to PC, including insulin resistance with resulting hyperinsulinemia and inflammation [41]. In our study, BMI< 18.5 kg/m2, but not obesity, was a risk factor for PDAC in the multivariate analysis (OR: 12.07), a fact reported also by another study [42]. This may be explained by the advanced tumor stages of patients included (60% stage III and IV tumors), associated with underweight and cachexia. Furthermore, the BMI was significantly higher in patients with NET vs. PDAC (29% vs. 11%, p=0.043). This is similar to the results of a meta-analysis [46], although contradictory findings exist [47]. However, we found no association of obesity with survival in PC, contrary to other studies that showed that obesity is associated with poorer survival [43, 44, 48]. Previous reports proved a 31-47% increased risk of PC patients with metabolic syndrome [21, 49, 50], but this was not confirmed in our study. The prevalence of the metabolic syndrome in population with cardiovascular diseases in Romania is up to 40% [51], but recent data in general population are lacking. In our patients with pancreatic adenocarcinoma we found the association with metabolic syndrome in 4.3%, which is lower than in other studies (8.46%) with the same criteria for defining the metabolic syndrome

Table III. Characteristics of patients with familial pancreatic cancer

Familial pancreatic cancer	Yes (n=12)	No (n=300)	p	OR (95%CI)
Age (years), mean (SD)*	61.08 (11.59)	64.61 (10.80)	0.3	
Age ≤ 60 years (yes), n (%)	6 (50)	98 (32.78)	0.224	2.06 (0.64-6.55)
Gender (female), n (%)	8 (66.7)	121 (40.3)	0.08	2.35 (0.75-7.36)
BMI (kg/cm2), median (IQR)	23.8 (21.67 – 25.39)	24.4 (21.77 – 27.15)	0.824	
Localization				
Head + isthmus + uncinate process, n (%)	7 (58.3)	189 (64.9)	0.759	1.14 (0.35-3.69)
Body + tail, n (%)	5 (41.7)	102 (35.1)		
Smoking, n (%)	6 (50)	129 (43)	0.63	1.32 (0.41-4.2)
Alcohol, n (%)	4 (33.3)	141 (47)	0.35	0.56 (0.16-1.91)
New-onset diabetes, n (%)	5 (41.7)	40 (13.3)	0.018	4.64 (1.4-15.33)
Long-standing diabetes, n (%)	1 (8.3)	80 (26.7)	0.19	0.25 (0.03-1.96)
Metabolic syndrome, n (%)	1 (8.3)	11 (4.1)	0.41	1.35 (0.15-11.9)

SD: standard deviation; IQR: interquartile range; BMI: body mass index; OR: odds ratio.

[52], but the difference compared to the control group was not significant.

The presence of metabolic syndrome in patients with NET was significantly higher than in PDAC (16.7% vs 4.3%, p=0.029) explained by the fact that BMI was significantly higher in patients with NET, as previously described [53].

Surprisingly, we found the frequency of HCV infection higher in NET cases compared to PDAC, but this is most likely to be an incidentaloma rather than the pancreatic disease itself.

The assessment of OS revealed the median OS for patients with PDAC was nine months and the advanced tumor stage was correlated with poorer survival. In the literature, at the

Table IV. Univariate and multivariate analysis to predict overall survival for patients with pancreatic ductal adenocarcinoma

	Univariate analyses		Multivariate analyses	
	HR unadjusted (95% CI)	p	HR adjusted (95% CI)	p
Age (years)	1.02 (0.9 - 1.04)	0.2	1.01 (0.99- 1.02)	0.06
Age >60 years	1.3 (0.96 - 1.75)	0.089	1.28 (0.95 - 1.73)	0.09
Gender	1 (0.76 - 1.33)	0.979	1.01 (0.76 - 1.34)	0.938
Tumor stage T3 vs. T1-2	1.06 (0.71 - 1.58)	0.775	1.04 (0.7 - 1.55)	0.836
Tumor stage T4 vs. T1-2	1.19 (0.9 - 1.57)	0.211	0.64 (0.39 - 1.05)	0.078
Stage IV	1.66 (1.22 - 2.25)	0.001	1.6 (1.17 - 2.18)	0.003
Lymph nodes N1	1.14 (0.78 - 1.65)	0.494	0.87 (0.58 - 1.31)	0.506
Tumor size >=3cm	1.32 (0.9 - 1.93)	0.157	1.21 (0.82 - 1.78)	0.336
Metastases	1.67 (1.27 - 2.2)	< 0.001	1.79 (0.64 - 5.03)	0.269
Obesity	0.81 (0.52 - 1.28)	0.374	0.89 (0.56 - 1.4)	0.605
Smoking	0.83 (0.62 - 1.09)	0.18	0.87 (0.65 - 1.15)	0.328
Alcohol	1.16 (0.88 - 1.52)	0.299	1.11 (0.84 - 1.46)	0.46
Coffee consumption	1.29 (0.57 - 2.96)	0.54	1.13 (0.49 - 2.6)	0.767
Diabetes	0.89 (0.67 - 1.17)	0.395	0.87 (0.66 - 1.16)	0.345
Metabolic syndrome	0.72 (0.45 – 1.6)	0.39	0.83 (0.54 – 1.28)	0.41
HCV	0.69 (0.26 - 1.87)	0.471	0.75 (0.27 - 2.03)	0.567
HBV	2.06 (0.51 - 8.34)	0.311	1.84 (0.45 - 7.49)	0.392
Genetic factors	1.03 (0.54 - 1.94)	0.939	1.03 (0.54 - 1.96)	0.926
Blood group A2	1.62 (0.88–3.00)	0.11	1.58 (0.87 - 2.86)	0.13
Cholecystectomy	0.89 (0.61 - 1.28)	0.522	0.9 (0.62 - 1.31)	0.588
History of chronic pancreatitis	1.03 (0.69 - 1.53)	0.891	1.12 (0.74 - 1.67)	0.597
Chemotherapy	0.9 (0.62 - 1.3)	0.577	0.75 (0.5 - 1.12)	0.162

HR: hazard ratio; CI: confidence interval; all variables were adjusted in the multivariable analysis for age (years), T stage (1-2, 3, 4), adenopathy, and metastasis. For abbreviations see Table II

time of diagnosis, only approximately 20% of patients with PC have a resectable disease [54, 55]. Still, in our group, only 9% were resectable, and this may explain the low survival duration. More than 40% of PDAC patients had metastasis compared to only 20% in the NET patients. However, because the number of patients with NET was low, we refrained from evaluating the predictive factors for survival in these patients.

Although the study was prospective, there are several limitations to our results. First of all, the group included was a hospital population where the patients addressed obtained a pathological diagnosis, and this could explain the low rate of resectability. Secondly, the patients were included from only two regions of the country and may not be representative for the entire population of Romania. Thirdly, the number of patients included was small (n=312), and a larger cohort would have been helpful to obtain good epidemiological data in Romania. Moreover, the number of patients with NET was relatively small, so we had insufficient data for survival analysis in this subgroup.

Although in our study we did not find any correlation between risk factors and survival in PC, the recognition and control of risk factors can provide opportunities to improve prognosis.

CONCLUSIONS

Our data suggest that diabetes, smoking, underweight, and age over 60 years are risk factors for PDAC. Besides the known risk factors for PC, a family history of PC is an important risk factor to consider for screening. Patients with a family history of PC, especially those with new-onset diabetes, should be followed carefully and considered for screening studies in order to detect early PC. There was no association between gender, smoking, alcohol consumption, diabetes, presence of overweight or obesity, chronic pancreatitis and OS. Advanced tumor stage was identified as an independent predictor for OS.

Conflicts of interests: None to declare.

Authors' contribution: L.P., A.S. designed the study and drafted the manuscript. L.P., M.B., V.D., A.S. collected the data. D.C.L performed data analyses. A.S. performed the endoscopic procedures. V.D., D.C.L, C.C, R.S, A.S. critically revised the manuscript. All authors approved the final version to be published, and agree to be accountable for all aspects of the work.

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