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RESEARCH ARTICLE

Prevalence of Pancreatic Intraepithelial Neoplasia among Resectable Pancreatic Specimens in a Private Tertiary Care Setting in Taiwan

Marissa Krizelda D Santos, MD[1*], Ren Chin Wu, MD[2], Shih Chiang Huang, MD[2], Kwai Fong Ng, MD[2] and Tse Ching Chen, MD[2]

[1]*Institute of Pathology, Chinese General Hospital and Medical Center, Santa Cruz, Metro Manila, Philippines*

[2]*Department of Pathology, Chang Gung Memorial Hospital, Chang Gung University School of Medicine, Guishan, Taoyuan, Taiwan*

***Corresponding author:** *Marissa Krizelda D Santos, MD, Institute of Pathology, Chinese General Hospital and Medical Center, Santa Cruz, #9 Minnesota St. Greenland Newtown Subd. Banaba San Mateo Rizal, Philippines, Tel: +63-9228196043*

Abstract

Objectives: Pancreatic adenocarcinoma remains as the seventh most common cause of mortality in Taiwan (5-year survival rate of 5.2%). Pancreatic intraepithelial neoplasia is an established precursor of pancreatic adenocarcinoma. This study aims to investigate the prevalence, age distribution and variables associated with the presence of pancreatic intraepithelial neoplasia.

Method: This is a retrospective cohort review of 1242 pancreatic specimens at Chang Gung Memorial Hospital, Linkou from 2007 to 2022.

Results: Of the total 1242 specimens, pancreatic intraepithelial neoplasia is identified in 729 cases with overall prevalence of 58.7%. The frequency is highest among males (52%) with median age of 64-years-old and diagnosis of ductal adenocarcinoma (90.7%). It is determined in 57% of smokers, 59% of drinkers of alcoholic beverage and 71% of those with diabetes mellitus. Of these, only a history of diabetes mellitus is found to have a statistical difference ($p < 0.0001$) between the two groups in a univariate analysis.

Conclusion: Pancreatic intraepithelial neoplasia has a frequency of 58.7% with the highest frequency among those diagnosed with ductal adenocarcinoma. The median age of patients is significantly higher than those without ($p < 0.00001$). Using univariate analysis, age, diagnosis and history of diabetes mellitus are significantly associated with pancreatic intraepithelial neoplasia.

Keywords

Pancreas, Pancreatic intraepithelial neoplasia, Pan IN, Pancreatic neoplasm, Ductal adenocarcinoma

Introduction

According to the 2022 statistical report of the Ministry of Health and Welfare [1], carcinoma remained the most common cause of mortality in Taiwan, with lung and liver as the main primary origins. On the other hand, pancreatic ductal adenocarcinoma ranks as the seventh most common cause of mortality[1]which is similar to the data of cancer-related deaths worldwide [2]. In 2018, a study by Chang, et al. noted that the 5-year survival rate of patients with pancreatic ductal adenocarcinoma in Taiwan is 5.2% [3]. In comparison to the global data, the 5-year survival rate of pancreatic ductal adenocarcinoma is also low at about 9% [4]. An epidemiologic study has also predicted that the global incidence of pancreatic ductal adenocarcinoma will increase to 15.1 and 18.6 per 100,000 in 2030 and 2050, respectively. In the same study, it is noted that the age group more than 65-years-old will have the highest incidence of about 31.9 per 100,000 in 2050 and with an average annual growth of 1.3% and 0.9% in males and females, respectively [5].

The dismal figure of the survival rate can be due to the fact that majority (80%) of cases present as an unresectable tumor with metastasis at the time of diagnosis [6]. The apparent delay in the diagnosis can be attributed to different factors. For example, in terms of anatomic location, the pancreas is not easily and readily

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accessible with imaging modalities and conventional diagnostic tools unlike other organs such as the breast and gastrointestinal tract. Likewise, the initial symptoms of pancreatic adenocarcinoma can be unremarkable and non-specific [7].

The National Cancer Institute Working Group [8] defined a carcinoma precursor as follows: 1) The precursor to invasive cancer must be associated with an increased risk of the cancer; 2) When a precursor to invasive cancer progresses to cancer, the resulting cancer arises from cells within the precancer; 3) A precursor to invasive cancer should differ from the normal tissue from which it arises; 4) A precursor to invasive cancer should differ from the cancer into which it develops; 5) There should be a method by which the precursor to invasive cancer can be diagnosed. The pancreatic intraepithelial neoplasia fulfills the five criteria hence it is established as one of the precursor lesions of pancreatic ductal adenocarcinoma [9].

However, in contrast to the cystic precursor lesions such as intraductal papillary mucinous neoplasm and mucinous cystic neoplasm, the pancreatic intraepithelial neoplasia can only be currently diagnosed microscopically in a biopsy or resection specimen. The World Health Organization Classification of tumors [10] defined pancreatic intraepithelial neoplasia (Pan IN) as a microscopic, non-invasive epithelial neoplasm which is confined to the pancreatic ducts. At present, it is classified using a two-tiered grading system namely, low-grade and high-grade. The former encompasses the previous grades PanIN-1a, PanIN-1b and PanIN-2 while the latter consists of the PanIN-3. Histologically, pancreatic intraepithelial neoplasia is a microscopic lesion measuring < 0.5 cm and is characterized by the presence of mucin-producing cuboidal to columnar cells [10]. In terms of molecular histogenesis, the progression of pancreatic intraepithelial neoplasia to pancreatic ductal adenocarcinoma occurs in a stepwise sequence which is similar to that of the colorectal carcinoma. Molecular studies have shown that low-grade pancreatic intraepithelial neoplasia harbors KRAS mutation and telomere shortening while high-grade pancreatic intraepithelial neoplasiais found to have p16, SMAD4 loss and TP53 mutations [11]. It is notable that the same genetic mutations in high-grade pancreatic intraepithelial neoplasia are seen in pancreatic ductal adenocarcinoma.

Since pancreatic intraepithelial neoplasia is a precursor lesion only identified incidentally in a biopsy or resection specimen, a limited number of literatures have characterized this precursor lesion.

This study aims to determine the prevalence of pancreatic intraepithelial neoplasia in resected pancreatic specimens for various indications in a tertiary clinical setting in Taiwan and to identify the clinicopathologic characteristics associated with pancreatic intraepithelial neoplasia

Methods

This is a retrospective cohort review of 1242 resected pancreatic specimens at Chang Gung Memorial Hospital, Linkou Branch from 2007 to 2022. The cases are identified and retrieved from the digital pathology archives cases and are then categorized into pancreatic ductal carcinoma, intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), neuroendocrine neoplasm, non-ductal carcinoma, non-pancreatic carcinoma, and non-tumoral cases.

For all the cases, the histopathology report, demographics (age and gender), and if available, clinical data (history of diabetes mellitus, alcohol intake and smoking) are extracted from the medical records database.

Study design and data collection

The available slides of the cases are evaluated by two pathologists (TCC and MDS) for the presence and grade of pancreatic intraepithelial neoplasia lesions using the two-tiered grading system of the World Health Organization. The slides are initially screened at 40x magnification to detect the presence of pancreatic intraepithelial neoplasia. Lesions of interest are then examined at higher magnification (100X or 400X). Slides of the representative foci of low grade (Figure 1A, Figure 1B and Figure 1C) and high-grade (Figure 1D and Figure 1E) pancreatic intraepithelial neoplasia lesions are scanned and the photomicrographs are taken using a digital pathology system. All the photomicrographs are taken from formalin-fixed paraffin embedded sections which are stained with Hematoxylin and Eosin (H&E) stain.

Definition of PanIN

A low-grade Pan IN is characterized by flat or papillary architecture with basally located or pseudo stratified nuclei and mild to moderate nuclear atypia. On the other hand, high-grade PanIN exhibits marked architectural abnormalities (cribriforming, micropapillae and budding) as well as severe nuclear atypia.

To differentiate pancreatic intraepithelial neoplasia from the common mimickers, the following criteria are used:

1. **Invasive ductal adenocarcinoma**

   Pancreatic intraepithelial neoplasia retains the lobular architecture even in the presence of significant fibrosis. On the other hand, the hallmarks of ductal carcinoma include the haphazard arrangement of glands, close association of glands with nerves, adipose tissue and muscular vessels.

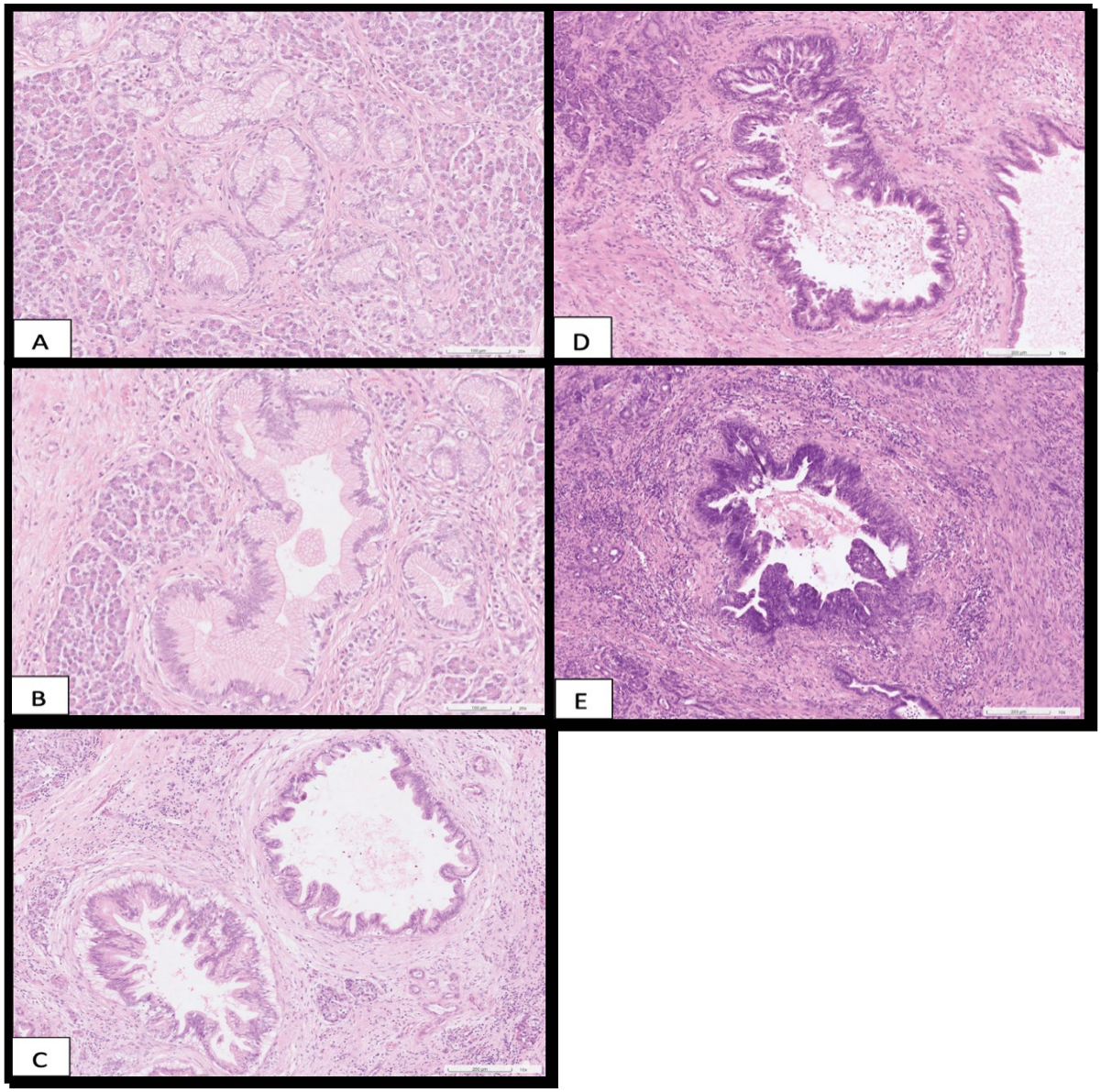

Figure 1: Representative photomicrographs of low-grade and high-grade PanIN. a) Shows the small ducts are lined by tall, mucin-producing columnar cells with bland and basally located nuclei; b) Shows the lesion exhibits the same cytology as in image (a) but with papillary architecture. Representative photomicrographs of Low-grade PanIN as shown in image (c) with nuclear pseudostratification, loss of cellular polarity, mild to moderate nuclear atypia, hyperchromasia and prominent papillary architecture are evident. Representative photomicrographs of High-grade PanIN as shown on image (d) and image (e), with high-grade PanIN. Micropapillary architecture, budding of small clusters, intraglandular necrosis and severe atypia are noted.

2. **Cancerization of benign pancreatic ducts**

   Cancerization is considered if there is abrupt transition between normal duct to highly dysplastic epithelium. The presence of invasive ductal adenocarcinoma nearby also favors the process of cancerization.

3. **Intraductal papillary mucinous neoplasm (IPMN)**

   IMPNs are grossly identifiable as cysts in comparison to pancreatic intraepithelial neoplasia which is only seen microscopically. In terms of size, IPMNs measure more than 1 cm while PanINs measure less than 0.5 cm. The latter also tend to have shorter and less complex papillary structures than IPMNs.

Assessment and histopathologic review of the specimen for presence of PanIN lesions

The PanIN grade is noted for each case and for the final grading, the highest grade is recorded. For cases of pancreatic ductal carcinoma and intraductal papillary mucinous neoplasm, the PanIN lesions are separately evaluated in the tumoral and non-tumoral areas. In cases of pancreatic ductal adenocarcinoma, only the high-grade PanIN lesions that are located distantly from the invasive carcinoma or surrounded by pancreatic parenchyma are recorded.

The PanIN lesions are further categorized into three different morphologic phenotypes namely intestinal, gastric and pancreaticobiliary types. The intestinal

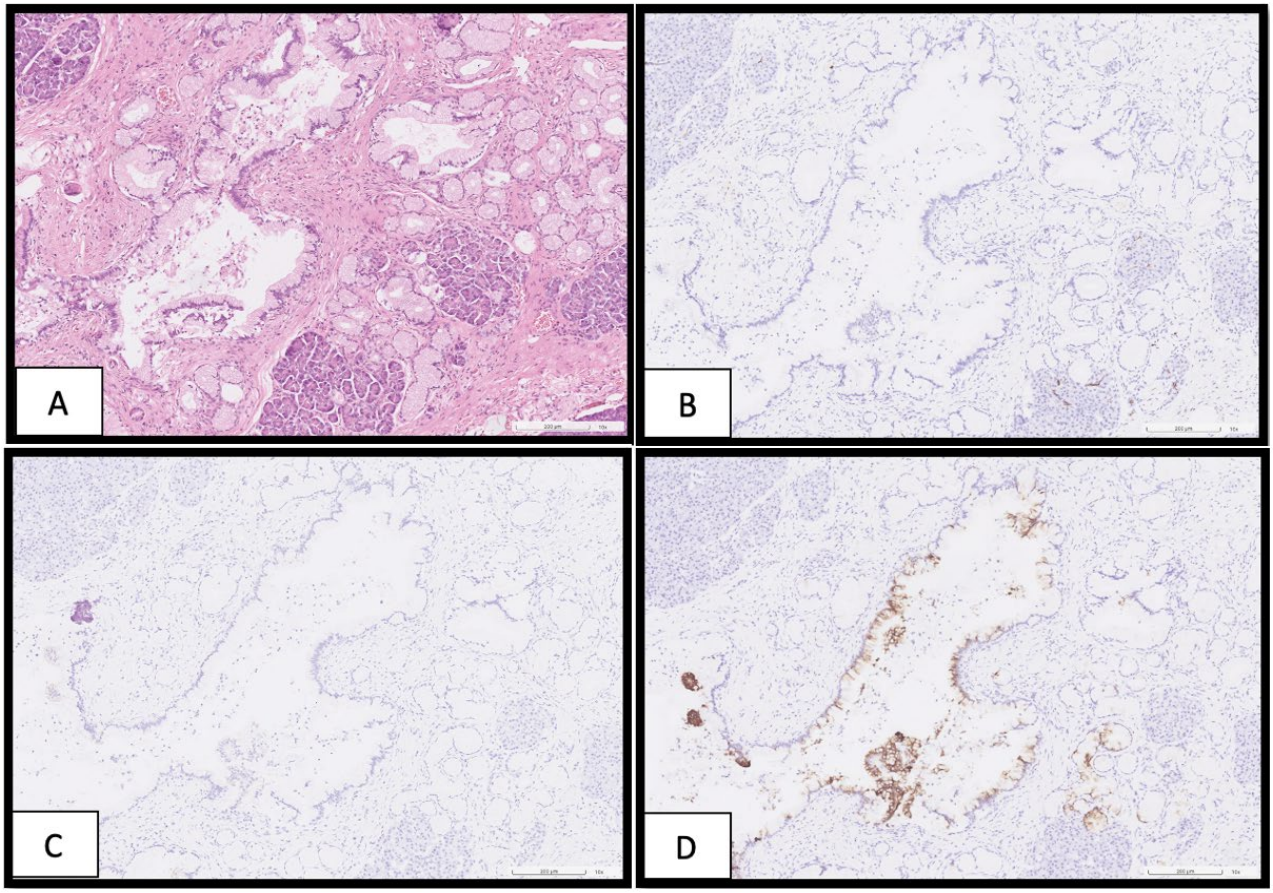

Figure 2: Representative photomicrographs of gastric-type morphology of PanIN.

Image (a) shows representative photomicrograph of gastric-type morphology of PanIN. The following images shows MUC1 (b), MUC2 (c), and MUC5AC (d).

type is characterized by its resemblance to colonic adenoma which has a pseudo stratified, elongated and hyperchromatic nuclei. Morphologically, the gastric type is similar to the gastric foveolar epithelium which as basally located nuclei and apical mucin. The pancreaticobiliary type has cuboidal epithelium and rounded nuclei. Immunohistochemical staining with MUC1, MUC2 and MUC5AC is performed in cases in which the histomorphology cannot be ascertained. The representative H&E and immunohistochemical stain slides of the gastric-type and pancreaticobiliary-type morphology of PanIN are shown in Figure 2 and Figure 3, respectively.

Data analysis and statistical methods

Data is encoded in MS Excel version 16.75.2 by the researcher. Stata MP version 17 software is used for data processing and analysis. Continuous variables are presented as median (interquartile range/IQR) due to the non-normal distribution based on the Shapiro Wilk's test. Categorical variables are expressed as frequencies and percentages. Comparison of continuous variables is performed using Mann Whitney U test, while Chi square test and Fisher's exact test are used for categorical variables. P values ≤ 0.05 are considered statistically significant.

Results

Demographics and characteristics of the study cohort

A total of 1242 pancreatic resection specimens are included in the study cohort from the year 2007 to 2022.

The mean age of patients in the study cohort is 59.68 ± 15.0 years-old with a median age of 62-years-old, ranging from 2 to 90-years-old.

Among the 1242 cases who underwent pancreatic resection, the most common diagnosis is non-pancreatic carcinoma (34%), followed by pancreatic ductal adenocarcinoma (28%).

Of the 1242 patients, there are 578 (47%) females and 664 (53%) males. There are 225 (18%) patients with history of alcohol intake while the remaining 999 (82%) reported no history of alcohol intake. Two hundred fifty-two (21%) are smokers while 974 (79%) are non-smokers. Nine hundred thirty-five (76%) had no reported history of diabetes mellitus and the remaining 24% had diabetes mellitus.

Demographics and characteristics of patients with PanIN lesions

Pancreatic intraepithelial neoplasia is identified in

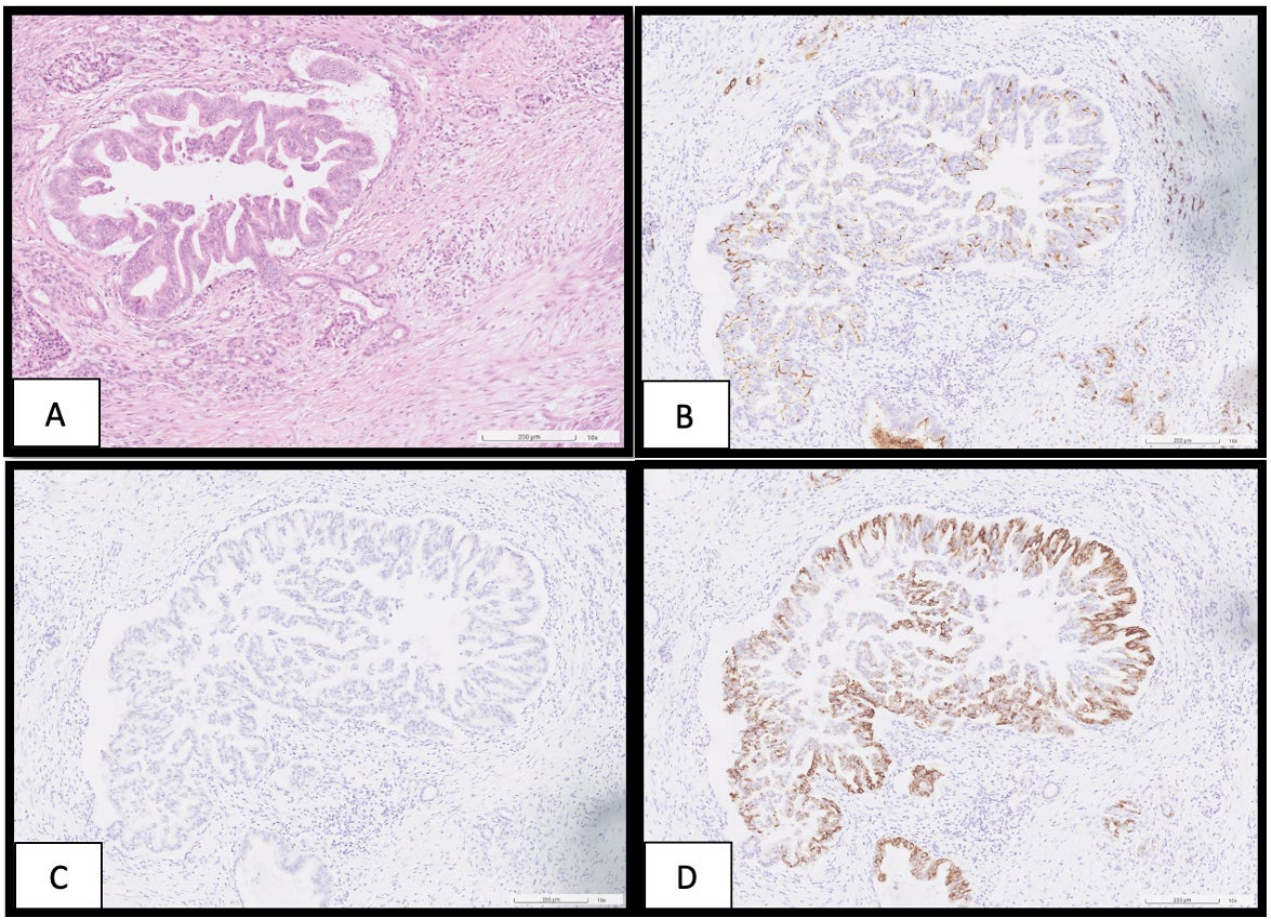

Figure 3: Representative photomicrographs of pancreaticobiliary-type morphology of PanIN.
Image (a) shows photomicrograph of pancreaticobiliary type morphology of PanIN, while the following images show MUC1 (b), MUC2 (c) and MUC5AC (d).

729 of the 1242 cases included in this study with an overall prevalence of 58.7%.

Clinical features and risk factors of patients with PanIN lesions: Among the patients found to have PanIN, the median age is significantly higher in comparison to those without PanIN (64-years-old versus 58-years-old, respectively, $p < 0.00001$).

Three hundred-forty eight (60%) of the 578 female and 380 (57%) of the 664 male patients are found to have PanIN. Among the 729 cases found to have PanIN, more than half (52%) are males. However, the difference is statistically not significant ($p = 0.261$).

Pancreatic intraepithelial neoplasia is identified in 145 (57%) of 252 smokers and 133 (59%) of the 225 patients with history of alcohol intake. There is no statistically significant correlation between the presence of PanIN and history of smoking and alcohol intake. Of the 291 patients with diabetes mellitus, there are 207 (71%) cases in which PanIN is determined. There is a statistical difference ($p < 0.0001$) between the occurrence of PanIN in patients with diabetes mellitus and patients without diabetes mellitus.

The frequency of PanIN is highest among patients diagnosed with pancreatic ductal adenocarcinoma (90.7%), followed by intraductal papillary mucinous neoplasm (78.5%), and mucinous cystic neoplasm (65.7%). There is statistically significant difference in PanIN frequency noted among patients with pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasm, mucinous cystic neoplasm, non-ductal carcinoma, non-pancreatic carcinoma, and non-tumoral cases.

Table 1 shows the comparison of the clinicopathologic characteristics by presence or absence of pancreatic intraepithelial neoplasia.

Association between patient clinical features and PanIN: Only 1224 patients with complete data for all variables are included in the analysis. Based on the univariable analysis (i.e., crude OR), the variables associated with the presence of PanIN are the following: age, histopathologic diagnosis and history of diabetes mellitus. In terms of age, the odds of PanIN increase by 4% for every year increase in age. In comparison to patients with pancreatic ductal adenocarcinoma, the odds of PanIN is about 3 times lower among those with intraductal papillary mucinous neoplasm, 5 times lower among those with mucinous cystic neoplasm, 13 times lower among those with non-pancreatic carcinoma and 13 times lower among those with non-tumoral

Table 1: Comparison of characteristics by presence of PanIN (n = 1242).

Characteristics	All patients (n = 1242) n (%)	PanIN		
		With (n = 729) n (%)	Without (n = 513) n (%)	P value
Age (in years), median	62 [IQR: 52-70]	64 [IQR: 56-72]	58 [IQR: 43-68]	< 0.00001*[a]
Gender				
Female	578 (47)	349 (48)	229 (45)	0.261[b]
Male	664 (53)	380 (52)	284 (55)	
Diagnosis				
Pancreatic ductal carcinoma	344 (28)	312 (43)	32 (6)	< 0.0001*[c]
IPMN	79 (6)	62 (9)	17 (3)	
MCN	35 (3)	23 (3)	12 (2)	
Neuroendocrine Neoplasm	73 (6)	33 (5)	40 (8)	
Non-ductal cancer	39 (3)	6 (1)	33 (6)	
Non-pancreatic cancer	424 (34)	185 (25)	239 (47)	
Non-tumoral	248 (20)	108 (15)	140 (27)	
Smoking history [n = 1226]				
No	974 (79)	577 (80)	397 (79)	0.625[b]
Yes	252 (21)	145 (20)	107 (21)	
Alcohol intake history [n = 1224]				
No	999 (82)	589 (82)	410 (82)	0.967[b]
Yes	225 (18)	133 (18)	92 (18)	
Diabetes [n = 1226]				
No	935 (76)	515 (71)	420 (83)	<0.0001*[b]
Yes	291 (24)	207 (29)	84 (17)	

[a]Mann Whitney U test was used; [b]Chi square test was used; [c]Fisher's Exact test was used

PanIN: Pancreatic Intraepithelial Neoplasia; IQR: Interquartile Range; IPMN: Intraductal Papillary Mucinous Neoplasm; MCN: Mucinous Cystic Neoplasm

diagnosis. In terms of the clinical history, patients with diabetes mellitus had 2 times higher odds of PanIN than those without.

Based on the multivariable analysis (i.e., adjusted OR), age and histopathologic diagnosis are the only variables which are significantly associated with PanIN. Gender, history of smoking, alcohol intake and diabetes mellitus are not significantly associated with PanIN. Table 2 shows the association between patient characteristics and presence of PanIN.

Comparison of patient's characteristics based on presence of low-grade versus high-grade PanIN: A total of 72 (9.8%) patients had high-grade PanIN and a total of 657 (90.2%) patients had low-grade PanIN. The patients with low-grade PanIN have median age of 64-years-old while those with high-grade PanIN have median age of 65-years-old. More than half of those with low-grade or high-grade PanIN are males. There is no significant difference between age and gender. In comparison to those with low-grade PanIN, a higher proportion of patients with high-grade PanIN has pancreatic ductal adenocarcinoma. There is no significant difference between the two groups in terms of smoking history, alcohol intake and history of diabetes mellitus. Table 3 shows the comparison of the patient's characteristics based on the presence of either low-grade or high-grade PanIN.

A comparison of median age by diagnosis is done among the 729 patients found to have PanIN. It is noted that median age significantly differs by diagnosis (p = 0.0001). Further pair wise analysis shows the following:

- Median age of pancreatic ductal cancer patients is significantly higher than patients with MCN (p < 0.00001), neuroendocrine neoplasm (p = 0.0495), non-ductal cancer (p = 0.0003), and non-tumoral (p < 0.00001). However, it is not significantly different with IPMN (p = 0.4341) and non-pancreatic cancer (p = 0.3212).
- Median age of IPMN patients is significantly higher than patients with MCN (p < 0.00001),

Table 2: Association between patient characteristics and presence of PanIN (n = 1224).

	Crude OR	P value	Adjusted OR	P value
Age (in years)	1.04 (1.03-1.05)	< 0.0001*	1.03 (1.02-1.04)	< 0.0001*
Gender				
Female	*Ref*	*Ref*	-	-
Male	0.87 (0.69-1.10)	0.246	-	-
Diagnosis				
Pancreatic ductal cancer	*Ref*	*Ref*	*Ref*	*Ref*
IPMN	0.37 (0.20-0.72)	0.003*	0.39 (0.20-0.76)	0.006*
MCN	0.20 (0.09-0.43)	< 0.0001*	0.37 (0.16-0.86)	0.020*
Neuroendocrine Neoplasm	0.08 (0.05-0.15)	< 0.0001*	0.12 (0.06-0.22)	< 0.0001*
Non-ductal cancer	0.02 (0.01-0.05)	< 0.0001*	0.04 (0.02-0.12)	< 0.0001*
Non-pancreatic cancer	0.08 (0.05-0.12)	< 0.0001*	0.08 (0.05-0.12)	< 0.0001*
Non-tumoral	0.08 (0.05-0.12)	< 0.0001*	0.11 (0.07-0.18)	< 0.0001*
Smoking history				
No	*Ref*	*Ref*	-	-
Yes	0.93 (0.70-1.23)	0.600	-	-
Alcohol intake history				
No	*Ref*	*Ref*	-	-
Yes	1.01 (0.75-1.35)	0.967	-	-
Diabetes				
No	*Ref*	*Ref*	-	-
Yes	2.00 (1.50-2.66)	<0.0001*	-	-

Ref: Reference category; PanIN: Pancreatic Intraepithelial Neoplasia; OR; Odds Ratio; IPMN: Intraductal Papillary Mucinous Neoplasm; MCN: Mucinous Cystic Neoplasm

Table 3: Comparison of patient's characteristics: low-grade versus high-grade PanIN (n = 729).

Characteristics	All patients (n = 729)	PanIN		
		Low grade PanIN (n = 657)	High-grade PanIN (n = 72)	P value
Age (in years), median	64 [IQR: 56-72]	64 [IQR: 56-72]	65 [IQR: 56-75]	0.4363[a]
Gender				
Female	349 (48)	316 (48)	33 (46)	0.715[b]
Male	380 (52)	341 (52)	39 (54)	
Diagnosis				
Pancreatic ductal adenocarcinoma	312 (43)	242 (37)	70 (97)	< 0.0001*[c]
IPMN	62 (8)	60 (9)	2 (3)	
Others (MCN, Neuroendocrine, non-ductal, non-pancreatic, non-tumoral)	355 (49)	355 (54)	0	
Smoking history [n = 722]				
No	577 (80)	519 (80)	58 (83)	0.518[b]
Yes	145 (20)	133 (20)	12 (17)	
Alcohol intake history [n = 722]				
No	589 (82)	531 (81)	58 (83)	0.772[b]
Yes	133 (18)	121 (19)	12 (17)	
Diabetes [n = 722]				
No	515 (71)	467 (72)	48 (69)	0.591[b]
Yes	207 (29)	185 (28)	22 (31)	

[a]Mann Whitney U test was used; [b]Chi square test was used; [c]Fisher's Exact test was used

PanIN: Pancreatic Intraepithelial Neoplasia; IQR: Interquartile Range; IPMN: Intraductal Papillary Mucinous Neoplasm; MCN: Mucinous Cystic Neoplasm

non-ductal cancer (p = 0.0007) and non-tumoral (p = 0.0001) but it is not significantly different with neuroendocrine neoplasm (p = 0.0977) and non-pancreatic cancer (p = 0.3260).

- Median age of MCN patients is significantly lower than patients with neuroendocrine neoplasm (p = 0.0011), non-pancreatic cancer (p < 0.00001) and non-tumoral (p = 0.0130) but it is not significantly different with non-ductal cancer (p = 0.2843).
- Median age of neuroendocrine neoplasm patients is significantly higher than patients with non-ductal cancer (p = 0.0068) and non-pancreatic cancer (p = 0.0339) but not with non-tumoral lesions (p = 0.0520).
- Median age of non-ductal cancer patients is significantly lower than patients with non-pancreatic cancer (p = 0.0003) and non-tumoral lesions (p = 0.0327).
- Median age of non-pancreatic cancer patients is significantly higher than those with non-tumoral lesions (p < 0.0000).

Further analysis shows that history of diabetes mellitus also significantly differs by diagnosis. A higher proportion of patients with pancreatic ductal adenocarcinoma has diabetes mellitus than those with IPMN and other diagnosis. There is no significant difference between gender, smoking history and alcohol intake by diagnosis. Table 4 shows the comparison of patient's characteristics by diagnosis among patients with PanIN.

Incidence of PanIN among resected pancreatic specimens

During the 15-year study period (2007 to 2022), a total of 1242 pancreatic resection specimens are identified from the digital pathology archives of Chang Gung Memorial Hospital, Linkou branch. In this institution, the overall prevalence of pancreatic intraepithelial neoplasia is 58.7%.

Demographic and clinical characteristics of study cohort

The study cohort is comprised mostly of male patients (53.0%) with a median age of 62-years-old. Of these pancreatic resection cases, majority are composed of non-pancreatic carcinoma (34.0%) followed by pancreatic ductal adenocarcinoma (28.0%). Among the patients with PanIN, a higher frequency is observed among male patients (52.0%) with median age of 64-years-old and a diagnosis of pancreatic ductal adenocarcinoma (90.7%).

Demographic and clinical characteristics of patients with PanIN lesions

The overall prevalence of PanIN in this study (58.7%) is comparable to the results of three other studies (86.4%, 80% and 68.2%) [6,12,13]. Excluding the non-ductal carcinoma cases, our study has shown an increasing frequency of PanIN among non-tumoral cases to tumoral cases (non-pancreatic carcinoma, neuroendocrine neoplasm, mucinous cystic neoplasm, intraductal papillary mucinous neoplasm and pancreatic ductal adenocarcinoma). This is similar to the finding of Andea, et al. [14] which has shown that the frequency and grade of PanIN lesions increase from normal pancreas to non-tumoral lesion (i.e. pancreatitis) and eventually pancreatic ductal adenocarcinoma. This is however in contrast to the findings of Zinczuk, et al. [15] wherein no statistical difference in pancreatic

Table 4: Comparison of characteristics by diagnosis among patients with PanIN (n = 729).

	Pancreatic ductal cancer (n = 312)	IPMN (n = 62)	Others (n = 355)	P value
Age (in years), median	66 [IQR: 57-73]	67 [IQR: 56-73]	62 [IQR: 54-71]	0.0005*[a]
Sex				
Female	154 (49)	24 (39)	171 (48)	0.305[b]
Male	158 (51)	38 (61)	184 (52)	
Smoking history [n = 722]				
No	253 (82)	46 (74)	278 (79)	0.300[b]
Yes	55 (18)	16 (26)	74 (21)	
Alcohol intake [n = 722]				
No	253 (82)	49 (79)	287 (82)	0.847[b]
Yes	55 (18)	13 (21)	65 (18)	
Diabetes [n = 722]				
No	203 (66)	46 (74)	266 (76)	0.021*[b]
Yes	105 (34)	16 (26)	86 (24)	

[a]Kruskall Wallis test was used, posthhoc analysis using Dunn's test; [b]Chi square test was used

PanIN: Pancreatic Intraepithelial Neoplasia; IQR: Interquartile Range; IPMN: Intraductal Papillary Mucinous Neoplasm; MCN: Mucinous Cystic Neoplasm

intraepithelial frequency is noted among patients with pancreatic ductal adenocarcinoma, neuroendocrine tumors, chronic pancreatitis and pancreatic cyst ($p = 0.592$). The high frequency of PanIN among pancreatic ductal adenocarcinoma cases in our study (90.7%) can demonstrate that it is an established precursor lesion.

Notably, the median age of individuals with PanIN is significantly higher than those without (64-years-old versus 58-years-old, $p < 0.00001$). This is concordant with the findings of four other independent studies [13,14,16,17].

There are varying results in terms of gender predilection across different literature sources, with one reporting more females (63%) [11] and other more males (62.5%) [18]. In this study, the majority of PanIN cases are found among male patients (52%), which is potentially related to the higher frequency of pancreatic ductal adenocarcinoma among this gender group. This observation is consistent with a recent research suggesting that lifestyle differences, particularly a higher rate of smoking among males, is a contributing factor [19]. Some studies have also implicated estrogen as a factor since the hormone has been found to decrease the growth of pancreatic carcinoma [20-22]. While a higher frequency of PanIN is noted among males in this study, there is no significant difference between the presence or absence of PanIN and gender ($p = 0.315$).

In terms of clinical data, diabetes mellitus, smoking and alcohol intake are established risk factors for pancreatic ductal adenocarcinoma. This study found a significant association between PanIN and diabetes mellitus ($p < 0.0001$) but not with smoking ($p = 0.625$) or alcohol intake ($p = 0.967$). These findings are concordant with previous research, which has shown a higher prevalence of low-grade PanIN among patients with type 2 diabetes mellitus [23]. Likewise, an autopsy study has noted that high-grade PanIN lesion is more frequently found in patients with type 2 diabetes mellitus [24]. The link between hyperglycemia and PanIN progression has also been documented at the molecular level. A study has shown that the numbers of low-grade and high-grade as well as the total PanINs increased in the animal models with induced hyperglycemia [25]. In terms of smoking and alcohol intake, the lack of statistically significant association is similar to the findings of Recavarren, et al. [16] and the authors attributed this to the low number of cases with available data. Findings from prospective cohort and case-control studies linking hyperglycemia to increased free radical formation. Elevated blood sugar levels may contribute to the development of advanced glycosylation end products (AGEs), potentially triggering inflammation. Furthermore, in mice susceptible to pancreatic cancer (PC), the introduction of exogenous AGEs has been observed to up regulate the expression of the AGE receptor (RAGE) in pancreatic intraepithelial neoplasia. This, in turn, significantly promotes the development of invasive pancreatic cancer [26].

Histopathologic and clinical implications

The follow-up of the patients under the 'others' category reveals that no patient developed pancreatic ductal adenocarcinoma or had a subsequent resection for carcinoma. The youngest patient under this category is a 29-year-old female who underwent resection last 2017 with a final histopathological diagnosis of mucinous cystic neoplasm. Given that the aforementioned patient did not undergo subsequent resection, she has been asymptomatic for almost 6 years as of the writing.

Next to pancreatic ductal adenocarcinoma, the intraductal papillary mucinous neoplasm has a high frequency of PanIN (78.5%). The former is also a distinct precursor lesion of pancreatic ductal adenocarcinoma which is defined as a grossly visible intraductal epithelial neoplasm of mucin-producing cells arising in the main pancreatic duct and/or its branches [9]. A relationship between gastric-type intraductal papillary mucinous neoplasm and low-grade pancreatic intraepithelial neoplasia can be elucidated by the reported frequent occurrence of low-grade PanIN next to a gastric-type intraductal papillary mucinous neoplasm [27,28]. Likewise, both lesions usually co-exist among patients with family history of pancreatic ductal adenocarcinoma [29-31]. A study in 2013 [31,32] identified the presence of pancreatic intraepithelial neoplasia among 40 patients (52.5% with low-grade and high-grade dysplasia and 47.5% with associated invasive carcinoma) who underwent resection for intraductal papillary mucinous neoplasm. The said study has noted the frequent presence of PanIN in 78% of the cases. Both the gastric-type intraductal papillary mucinous neoplasm and pancreatic intraepithelial neoplasia exhibit positivity with MUC5 AC and absence of MUC1 and MUC2 positivity [28]. The shared histomorphology, mucin immunoprofile, location within branch ducts and frequent co-existence may suggest that the lesions are spectrum of the same disease such that low-grade pancreatic intraepithelial neoplasia may actually represent small sized gastric-type intraductal papillary mucinous neoplasm [28,33].

Majority of the PanIN cases in the study cohort are found to have low-grade PanIN (90.2%). Morphologically, the low-grade PanIN cases are characterized by flat architecture with bland, basally located nuclei and abundant apical mucin. In a study in 2008 [34] on the spontaneous induction of murine pancreatic intraepithelial neoplasia (mPanIN), it was shown that acinar cell targetic of oncogenic KRAS results in the spontaneous development of the mPanIN. Notably, the histology of the lesions resembles that of the low-grade PanINs usually described in human pancreatic lesions and in our study. Since KRAS is the most common oncogene identified in pancreatic ductal adenocarcinoma, the finding of the aforementioned study further highlights the role of PanIN as an important precursor lesion of

pancreatic ductal adenocarcinoma. For the non-tumoral pancreatic lesions with PanIN, most of the cases show low-grade PanIN which interestingly is similar to the histomorphology of the slide study decks uploaded in the Mouse Model of Pancreas Cancer Atlas (MMPCA).

In our study, it is also noted that all the low-grade PanIN lesions have gastric-type morphology and immunophenotype showing positivity with MUC5AC. On the other hand, the high-grade PanIN lesions have pancreaticobiliary-type morphology and immunophenotype characterized by positivity with MUC1 and MUC5AC. No cases showed an intestinal-type morphology. Notably, the results of the study are concordant to the findings that the immunohistochemical profile of PanINs vary with the grade of dysplasia. MUC1 is almost exclusively expressed in high-grade PanIN and this is often associated with an invasive pancreatic ductal adenocarcinoma [35]. On the other hand, MUC5AC is expressed in low-grade PanIN lesions while the intestinal marker MUC2 is negative in PanINs [36]. The association of MUC1 positivity with high-grade PanIN is also correlated with the findings in mouse model wherein MUC1-mediated mechanism enhanced the development and progression of PanIN to pancreatic ductal adenocarcinoma [37]. Another study has shown that MUC1 is over expressed during the progression of pancreatic ductal adenocarcinoma and it has role in invasion and metastatic capability of the carcinoma [38]. A related study using real time-PCR analysis exhibited that MUC1 expression increases with the age (10 weeks to 50 weeks) of the $KRAS^{G12D}$ mouse model [39]. In the same study, it was noted that MUC5AC is absent in normal pancreas but it is detected in early lesions. This is correlated to our study as the low-grade PanINs exhibited MUC5AC immunoprofile. Two other studies noted that MUC1 expression is correlated with higher stage of PanIN lesions [40,41]. Similar to our study, Lo, et al. [41] also observed that no positive expression of MUC1 is noted in low-grade PanINs and that it was expressed only in high-grade PanINs. The author attributed this to the possible loss of ductal tissue architecture and low differentiation of carcinoma and thus the MUC1 expression in the early stages of carcinoma can be considered as a potential biomarker. Congruent to our study, a gastric phenotype with MUC5AC expression is more often observed in low-grade PanIN lesion and that this may imply that MUC5AC expression is found early in the progression of carcinoma [42,43].

Conclusion

Pancreatic intraepithelial neoplasia is identified in 58.7% of pancreatic resection specimen cases. This study suggests that institution-wise, PanIN lesions are commonly seen among male patients with median age of 64-years-old. The median age of patients found to have PanIN is significantly higher than those without PanIN. The median age of pancreatic ductal adenocarcinoma is significantly higher than those with other diagnosis ($p = 0.0001$) but not with IPMN ($p = 0.4341$). The median age of IPMN patients is also significantly higher than those with other diagnosis ($p = 0.0249$). The association between gender and PanIN development is inconclusive. On the other hand, pancreatic intraepithelial neoplasia is significantly associated with diabetes mellitus. Hyperglycemia, a characteristic of diabetes, may contribute to PanIN progression. In this study, lifestyle factors like smoking and alcohol intake are found not to be significantly associated with PanIN. This study further highlights the role of PanIN progression in the development of pancreatic ductal adenocarcinoma and establishing the relationship can benefit in the prevention and management of pancreatic ductal adenocarcinoma. In terms of morphology, the low-grade PanINs have gastric phenotype with MUC5AC expression while high-grade PanINs exhibit pancreaticobiliary phenotype with both MUC1 and MUC5AC expression. Additional research especially on the ancillary screening tests is of utmost importance in order to detect the PanIN precursor lesion.

Data Availability Statement

All the data are collected from the Chang Gung Memorial Hospital, Linkou Branch.

Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

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