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ORIGINAL RESEARCH—CLINICAL

Clinical and Imaging Predictors of Pancreatic Cancer in Patients Hospitalized for Acute Pancreatitis

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BACKGROUND AND AIMS: Identifying factors associated with increased short-term risk of pancreatic cancer in the setting of acute pancreatitis (AP) can inform clinical care decisions and expedite cancer diagnosis. **METHODS:** A retrospective cohort study of patients hospitalized for AP between 2007 and 2017 in an integrated health-care system in Southern California. AP cases were identified by diagnosis code with laboratory confirmation. Multivariable Cox proportional hazards regression model was used to assess risk of pancreatic cancer within 3 years of AP, adjusting for patient demographics, clinical parameters (body mass index, AP etiology, chronic pancreatitis, diabetes) and radiographic imaging features. **RESULTS:** Among 9,490 patients hospitalized with AP, the mean (standard deviation) age was 55.8 (17.8) years, 55% were women, and 42% were Hispanic. Majority of AP cases were biliary (64%), 12% were alcohol-related, 5% were hypertriglyceridemia-induced, and 19% were other/unknown etiology. Ninety-five (1%) patients were diagnosed with pancreatic cancer within 3 years of AP (4.2 cases/1000 person-years). Risk factors for pancreatic cancer were age ≥65 years (hazard risk [HR]: 2.5, 95% confidence interval [CI]: 1.2–5.3), male sex (HR: 1.9, 95% CI: 1.2–2.8), Asian/Pacific Islander race (HR: 2.0, 95% CI: 1.1–3.6), and underweight body mass index (HR: 2.6, 95% CI: 1.1–6.5). In addition, other/unknown AP etiology (HR: 2.0, 95% CI: 1.3–3.1) and dilatation of the main pancreatic duct (HR: 6.6, 95% CI: 4.2–10.5) were independently associated with increased risk of pancreatic cancer. **CONCLUSION:** In addition to older age, the lack of well-established etiology, underweight body habitus, and main pancreatic duct dilatation were independently associated with increased short-term risk of pancreatic cancer among patients hospitalized for AP.

Keywords: Acute Pancreatitis; Pancreatic Cancer; Pancreatic Duct Dilatation; Risk Factors

See editorial on page 1124.

Introduction

Pancreatic cancer is a devastating disease with a 5-year survival rate of 10%.[1] Pancreatic cancer is also a relatively uncommon cancer with an incidence rate of 13.2 per 100,000 in the United States.[2] Meanwhile, acute pancreatitis (AP) is one of the leading causes for hospitalization related to a gastrointestinal illness accounting for over 200,000 hospitalizations annually.[3] The relationship between AP and pancreatic cancer is complex. While repeated episodes of inflammation and injury may lead to fibrosis and ultimately cancer, there are instances where AP can be an initial manifestation of an occult pancreatic cancer. The ability to distinguish cancer-related episodes of pancreatitis from other etiologies represents an important opportunity for early diagnosis and treatment for pancreatic cancer.

Among individuals with AP, the risk of developing pancreatic cancer within 5 years is 0.87%–1.1%,[4–7] representing more than a 6-fold risk compared to an age- and sex-matched population. Based on several population-based studies, the risk appears to be greatest within the initial 2 years after an episode of AP with subsequent decline in risk to background population levels after 10 or more years.[4,5] Given the natural history of pancreatic cancer, which typically involves more than a decade for tumor development,[8] it has been suggested that the excess risk observed in the immediate period following AP likely represents underlying (prevalent) malignancy. However, a significant clinical challenge in identifying cancer in patients that present with AP is the obscured appearance of the pancreas in the acute setting as a result of interstitial edema, fat stranding, acute fluid collection(s) as well as necrosis that may occur as a result of local tissue injury.

The objective of the present study was to characterize specific demographic, clinical, and imaging characteristics associated with increased risk of pancreatic cancer among patients hospitalized for AP. Specifically, we sought to evaluate the relationship of age, sex, race/ethnicity, pancreatitis etiology, as well as ductal dilatation or parenchymal atrophy on the 3-year risk of pancreatic cancer.

Abbreviations used in this paper: **AP, acute pancreatitis; CI, confidence interval; HR, hazard ratio; ICD, International Classification of Diseases; KPSC, Kaiser Permanente Southern California.**

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Methods

Study Design, Setting, and Population

We conducted a retrospective cohort study of the Kaiser Permanente Southern California (KPSC) membership between 2007 and 2017. This study was approved by the KPSC Institutional Review Board, and a waiver of informed consent was obtained. KPSC is an integrated health-care system serving a diverse membership of over 4.7 million patients and reflective of the socioeconomic and racial diversity of Southern California.[9] Patients were eligible if they were hospitalized with a principal discharge diagnosis of AP between 2007 and 2017 with an elevated serum amylase or serum lipase levels of $\geq$3 times the upper limit of normal during their hospitalization. We previously applied this approach to case identification for AP with >95% positive predictive value compared to manual chart validation.[10] For patients with more than 1 AP hospitalization during the study period, only the first hospitalization was included. Patients were required to be at least 18 years of age at the time of hospitalization for AP and had at least 1 year of membership prior to hospitalization to facilitate acquisition of study covariates. Patients were excluded if they had a diagnosis of pancreatic cancer prior to the date of discharge from their hospitalization for AP or if they did not survive beyond 30 days from hospital discharge.

Identification of Pancreatic Cancer (Outcome)

Patients were defined as having pancreatic cancer if they had a diagnosis code for pancreatic cancer by the International Classification of Disease (ICD-9 157.xx or ICD-10 C25.xx) as well as by cross-referencing the internal KPSC Cancer Registry (patients automatically entered prospectively if diagnosed or treated for cancer for reporting purposes). Pancreatic cancer listed as a cause of death from the California Death Master File was also used as a source of outcome if pancreatic cancer was not reported in the Cancer Registry. For purposes of the present study, all histological subtypes, for example, ductal adenocarcinoma, adenocarcinoma not otherwise specified, neuroendocrine carcinoma, etc., were included.

Variable Definitions

Demographic and clinical information was abstracted from KPSC's electronic health record, whereas tumor characteristics of stage, grade, and histology were obtained from the KPSC Cancer Registry. Patients missing information on etiology and/or tumor stage were reviewed by clinicians (T.M.T., B.U.W.), with additional information manually abstracted if available.

Patient Demographics and Clinical Characteristics. Age was examined as a continuous variable and in categories of 18–45, 45–64, and 65 years or older. Sex was identified based on patient self-reporting at the time of health plan enrollment. Baseline weight was that from within 6 months prior to and closest to the date of discharge (index). Baseline variables, except weight and lab parameters, were identified based on proximity to index date. Change in weight was calculated as the difference between weight at the admission date and weight within 9–15 months and closest to that at 12 months prior to baseline (admission). For diabetes, patients were classified as having a diagnosis of diabetes within 6 months prior to the index date, more than 6 months prior to

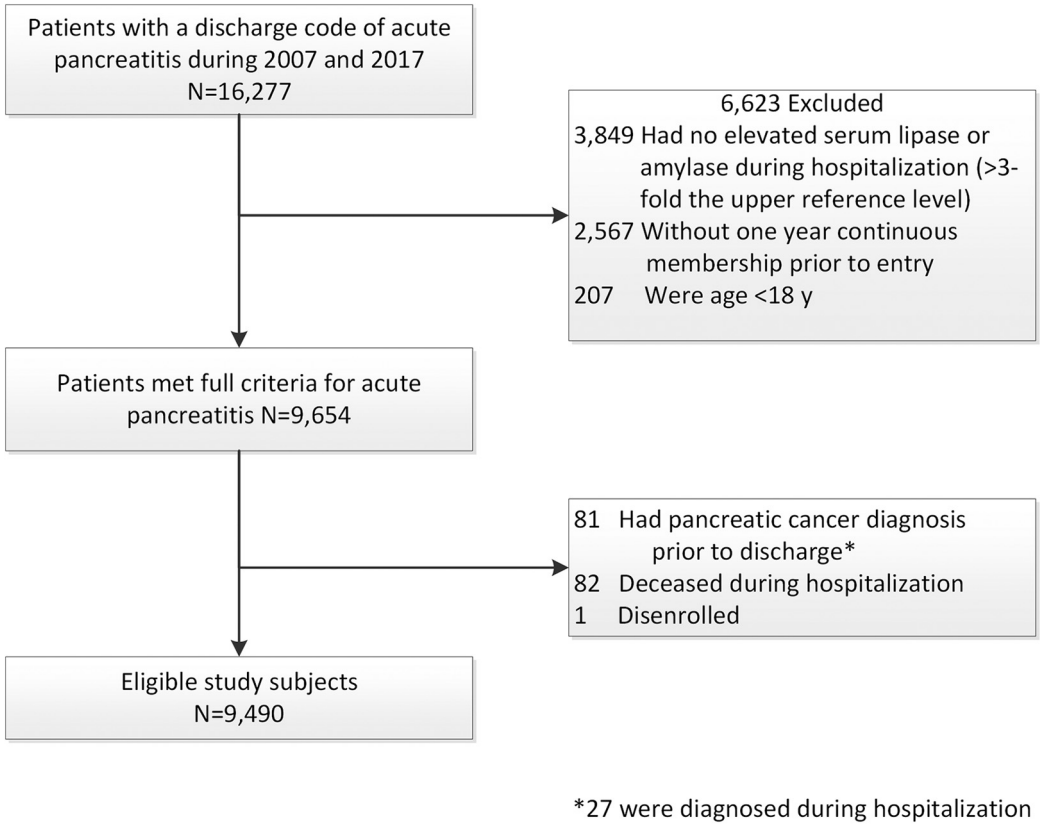

Figure 1. Flow diagram of patient eligibility.

Table 1. Characteristics at Baseline Among Patients With Acute Pancreatitis

Patient characteristics	Patients with AP (N = 9490)
Demographics	
Age in y	
Mean (SD)	55.8 (17.8)
Median (IQR)	56 (43, 69)
Age in y, N (%)	
18–45	2760 (29.1)
46–64	3576 (37.7)
65+	3154 (33.2)
Sex, N (%)	
Female	5254 (55.4)
Male	4236 (44.6)
Race/ethnicity, N (%)	
Non-Hispanic white	3816 (40.2)
Non-Hispanic black	938 (9.9)
Hispanic	3935 (41.5)
Asian/Pacific Islander	724 (7.6)
Other/unknown/multiple	77 (0.8)
BMI in kg/m^2	
N	9348
Mean (SD)	29.8 (6.9)
Median (IQR)	28.8 (25.1, 33.4)
BMI category, N (%)	
Underweight	148 (1.6)
Normal	2129 (22.4)
Overweight	3102 (32.7)
Obese	3969 (41.8)
Unknown	142 (1.5)
Weight change in lbs. within 1 y prior to admission	
N	6764
Mean (SD)	−5.0 (16.2)
Median (IQR)	−3.0 (−10.5, 3.0)
Charlson Comorbidity index	
Mean (SD)	1.9 (2.2)
Median (IQR)	1.0 (0, 3)
Charlson Comorbidity index, N (%)	
0	3292 (34.7)
1	2261 (23.8)
2	1308 (13.8)
3+	2629 (27.7)
Level of education, geocoded, N (%)	
≤ High school	4584 (48.3)
Some college or associate's degree	2209 (23.3)
Bachelor's degree or graduate school	2697 (28.4)
Smoking, N (%)	
Ever	4010 (42.3)
Never	5398 (56.9)
Unknown	82 (0.9)
Had abdominal cross-sectional image (during hospitalization), N (%)	4963 (52.3)
Image features (within 3 y prior to AP discharge)	
Atrophy and/or duct dilatation, N (%)[a]	914 (9.6)
Duct dilatation, N (%)[a]	808 (8.5)
Atrophy, N (%)[a]	161 (1.7)
Missing images, N	440 (-)
Acute pancreatitis etiology, N (%)	
Alcoholic	1105 (11.6)
Biliary	6075 (64.0)
Hypertriglyceridemia	516 (5.4)
Other/unknown	1794 (18.9)
Other conditions	
Chronic obstructive pulmonary disease, N (%)	946 (10.0)
Chronic pancreatitis, N (%)	462 (4.9)
Pancreatic cyst/pseudocyst, N (%)	374 (3.9)
Diabetes, N (%)	
Diabetes within 6 mo prior to index date	368 (3.9)
Diabetes greater than 6 mo prior to index date	2688 (28.3)
No diabetes	6434 (67.8)
Lifetime history of cancer, N (%)	2264 (23.9)
Labs[b]	
A1c	
N	4798
Mean (SD)	6.8 (1.7)
Median (IQR)	6.2 (5.7, 7.2)
A1c, N (%)	
Abnormal	1960 (20.7)
Normal	2838 (29.9)
Not tested	4692 (49.4)
Albumin	
N	5433
Mean (SD)	3.2 (0.6)
Median (IQR)	3.2 (2.8, 3.5)
Albumin, N (%)	
Abnormal	3083 (32.5)
Normal	2350 (24.8)
Not tested	4057 (42.8)

IQR, interquartile range; SD, standard deviation.
[a]Numbers are not mutually exclusive. Fifty-five patients have both atrophy and duct dilatation.
[b]Laboratory results were obtained within 1 year prior and closest to the date of admission for acute pancreatitis.

the index date, or no previous diagnosis of diabetes based on diagnosis codes.

Etiology of AP. Etiology of AP was classified under 1 of the following 4 categories: alcoholic, biliary, hypertriglyceridemia-induced, and other/unknown. AP was classified as alcoholic if the patient was diagnosed with an alcohol-related disease prior to or on the same date as their discharge diagnosis of AP. The pancreatitis was assigned as biliary if the patient had a simultaneous diagnosis of gallstones, cholecystitis, cholangitis, cholelithiasis, choledocholithiasis, or gallstone pancreatitis during hospitalization with AP. The pancreatitis was also defined as biliary if the patient had

an endoscopic retrograde cholangiopancreatography or cholecystectomy procedure within 5 days prior to their hospital admission or up until the date of discharge. Hypertriglyceridemia-induced pancreatitis was defined in the setting where the patient had a measured triglyceride level of ≥1000 mg/dL at any time prior to or on the date of hospital discharge. All other causes of pancreatitis, including idiopathic, were classified as other/unknown.

Imaging Parameters. We identified all reports from abdominal cross-sectional images (computed tomography or magnetic resonance imaging) obtained up to 3 years prior to hospitalization through the date of hospital discharge among patients included in the study cohort. We then applied a previously developed natural language processing algorithm for identification of pancreatic parenchymal atrophy as well as main duct dilatation given the previous association of these features with development of pancreatic cancer.[11–14] Briefly, the algorithm identified duct dilatation from the imaging reports based on the presence of terms such as "dilated", "dilation", and "dilatation", while excluding phrases such as "bile duct", "common duct", and "nondilated".[13] Patients who were identified with pancreatic cancer based on imaging reports were also excluded from the study.

Censoring and Outcome Assessment

Patient outcomes were assessed from the date of discharge for AP through December 31, 2018, death, disenrollment from the health plan, or if the patient had a >45-day gap in membership.

Data Analysis

We first plotted the cumulative 3-year incidence of pancreatic cancer among patients included in the study cohort. The 3-year time frame was chosen to limit the analysis to cancers likely to be detectable during the initial follow-up of pancreatitis. We then calculated overall and age-, gender-, race/ethnicity-, and etiology-specific incidence per 1000 person-years. We then applied Cox proportional hazards regression to assess the risk of pancreatic cancer within 3 years of discharge with AP and also conducted a sensitivity analysis excluding patients diagnosed with pancreatic cancer within 6 months of AP or with less than 6 months of follow-up. The proportional hazards assumption was checked by assessment of Schoenfeld residuals. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC) with 2-sided alpha of 0.05 threshold for significance.

Results

A total of 16,277 unique patients had a discharge diagnosis of AP between 2007 and 2017 (Figure 1). After applying inclusion-exclusion criteria, 9,490 patients were included for analyses.

The mean (standard deviation) age at the time of hospitalization was 55.8 (17.8) years (Table 1). More than two-thirds of patients in the study cohort presented with AP when they were at least 46 years of age. Among the cohort, 55% were women, 42% were Hispanic, 40% were non-Hispanic white, 10% were non-Hispanic black, and 8% were Asian or of Pacific Islander ancestry. The mean (standard deviation) body mass index (BMI) at baseline was 29.8 (6.9) kg/m^2, and 75% of the cohort were overweight or obese. The most common etiology of AP was biliary (64%), followed by alcohol (12%), then hypertriglyceridemia (5%), and 19% of cases having other or unknown etiology. A total of 9,050 patients (95%) from the study cohort had at least 1 cross-sectional image including the pancreas within the predetermined time frame (up to 3 years prior to hospitalization through the date of discharge). A total of 885 (8.5%) patients had evidence of main duct dilatation, while 161 (1.7%) had pancreatic atrophy.

Incidence and Stage of Pancreatic Cancer

A total of 95 (1.0%) cases were diagnosed within 3 years of AP discharge. Table 2 presents the tumor characteristics including stage, histology, and tumor location. Stage 4 (metastatic) disease was the most common stage at the time of cancer diagnosis (43.2%).

Incidence of pancreatic cancer in the study cohort is presented in Table 3. The overall incidence of pancreatic cancer was 2.7 cases per 1000 person-years (95% CI: 2.2,

Table 2. Tumor Characteristics Among Patients Diagnosed With Pancreatic Cancer Within 3 Years of Presenting With Acute Pancreatitis

Characteristic, N (%)	Patients with pancreatic cancer (N = 95)
AJCC stage	
0	1 (1.1)
1	13 (13.7)
2	25 (26.3)
3	13 (13.7)
4	41 (43.2)
Unknown	2 (2.1)
SEER stage	
Distant	34 (35.8)
In situ	1 (1.1)
Localized	16 (16.8)
Regional	32 (33.7)
Unknown	12 (12.6)
Histology	
Ductal adenocarcinoma	76 (80)
Mucinous cystadenocarcinoma	2 (2.1)
Acinar cell carcinoma	2 (2.1)
Cholangiocarcinoma	1 (1.1)
Intraductal papillary-mucinous carcinoma	2 (2.2)
Neuroendocrine carcinoma	1 (1.1)
Unknown	10 (10.5)
Site	
Body of pancreas	3 (3.2)
Head of pancreas	61 (64.2)
Overlapping/unassigned lesion of pancreas	26 (27.4)
Tail of pancreas	5 (5.3)

AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results program.

Table 3. Incidence Rate of Pancreatic Cancer and Follow-up Time

Variable	Incidence	Total person-years	Incidence rate [95% CI] (per 1000 person-years)
Overall	116	43,684	2.7 [2.2, 3.2]
1 y	74	8845	8.4 [6.7, 10.5]
2 y	82	16,482	5.0 [4.0, 6.2]
3 y	95	22,827	4.2 [3.4, 5.1]
3-Y incidence by age group in years (quartile)			
18–43	7	5622	1.2 [0.6, 2.6]
44–56	18	5614	3.2 [2.0, 5.1]
57–69	35	6071	5.8 [4.1, 8.0]
≥70	35	5520	6.3 [4.5, 8.8]
3-Y incidence by sex			
Female	43	12,736	3.4 [2.5, 4.6]
Male	52	10,092	5.2 [3.9, 6.8]
3-Y incidence by race/ethnicity			
Non-Hispanic white	44	9422	4.7 [3.5, 6.3]
Non-Hispanic black	15	2229	6.7 [4.0, 11.2]
Hispanic	21	9404	2.2 [1.5, 3.4]
Asian/Pacific Islander	15	1771	8.5 [5.1, 14.1]
3-Y incidence by pancreatitis etiology			
Alcoholic pancreatitis	7	2519	2.8 [1.3, 5.8]
Biliary pancreatitis	52	14,759	3.5 [2.7, 4.6]
Hypertriglyceridemia-induced pancreatitis	3	1251	2.4 [0.8, 7.5]
Other/unknown	33	4298	7.7 [5.5, 10.8]
3-Y incidence by presence of atrophy on image			
Negative	85	21,425	4.0 [3.2, 4.9]
Positive	6	344	17.4 [7.7, 39.4]
Unknown	4	1058	3.8 [1.4, 10.1]
3-Y incidence by presence of duct dilatation on image			
Negative	51	19,923	2.6 [1.9, 3.3]
Positive	40	1846	21.7 [15.8, 29.7]
Unknown	4	1058	3.8 [1.4, 10.1]

3.2) while the 3-year incidence was 4.2 cases per 1000 person-years (95% CI: 3.4, 5.1). Incidence of pancreatic cancer was the highest in the first year following presentation with AP (Figure 2). The incidence rate was higher among older age populations where the 3-year incidence rate for patients aged ≥65 years was 6.3 cases/1000 person-years (95% CI: 4.5, 8.8). Asians/Pacific Islanders had the highest incidence among race/ethnicities (8.5 cases/1000 person-years [95% CI: 5.1, 14.1]), followed by non-Hispanic black (6.7 cases/1000 person-years [95% CI: 4.0, 11.2]). Hispanic patients had the lowest incidence rate of 2.2 cases/1000 person-years. Patients with other/unknown etiology had the highest incidence among all etiologies with 7.7 cases per 1000 person years (95% CI: 5.5, 10.8). Presence of atrophy or duct dilatation on imaging corresponded to an incidence rate of 17.4 (95% CI: 7.7, 39.4) and 21.7 (95% CI: 15.8, 29.7) per 1000 person-years, respectively.

Risk Factors for Pancreatic Cancer

Table 4 presents the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for 3-year risk of pancreatic cancer determined by Cox regression analysis. The risk of pancreatic cancer was significantly higher among men (HR: 1.9, 95% CI: 1.2, 2.8). Asian/Pacific Islanders had increased risk of developing pancreatic cancer compared to white patients (HR: 2.0, 95% CI: 1.1, 3.6). An underweight BMI (<18.5 kg/m^2) was also associated with an increased risk (HR: 2.6, 95% CI: 1.1, 6.5) compared to normal BMI.

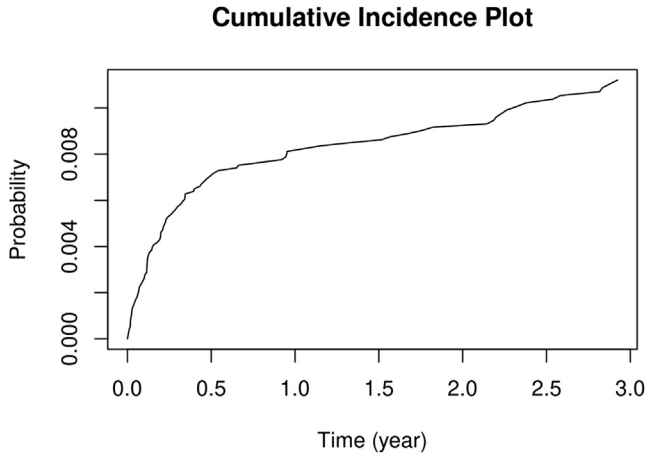

Figure 2. Cumulative incidence curve of pancreatic cancer adjusted for age, sex race/ethnicity, body mass index, smoking, etiology of acute pancreatitis, chronic pancreatitis history, and imaging findings.

Table 4. Adjusted Hazard Ratios and 95% Confidence Intervals for Pancreatic Cancer Within 3 Years After Presentation With Acute Pancreatitis

Variable	Adjusted hazard ratio	95% Confidence interval	
Age in years			
18–45	Referent	-	-
46–64	2.0	0.9	4.2
65+	2.5	1.2	5.3
Sex			
Female	Referent	-	-
Male	1.9	1.2	2.8
Race/ethnicity			
Non-Hispanic white	Referent	-	-
Non-Hispanic black	1.3	0.7	2.4
Hispanic	0.7	0.4	1.1
Asian/Pacific Islander	2.0	1.1	3.6
BMI			
Underweight	2.6	1.1	6.5
Normal weight	Referent	-	-
Overweight	0.7	0.4	1.3
Obesity	1.4	0.8	2.4
Unknown	0.8	0.1	6.1
Smoking	1.1	0.7	1.6
Acute pancreatitis etiology			
Biliary	Referent	-	-
Alcoholic	0.7	0.3	1.7
Hypertriglyceridemia-induced pancreatitis	0.7	0.2	2.4
Other/unknown	2.0	1.3	3.1
Diabetes			
No diabetes	Referent	-	-
Diabetes within 6 mo prior to index date	0.6	0.1	2.4
Diabetes greater than 6 mo prior to index date	1.6	1.0	2.4
Chronic pancreatitis	0.9	0.4	2.0
Pancreatic cyst/pseudocyst	1.9	1.0	3.6
Presence of imaging features (vs no feature)			
Atrophy	1.4	0.6	3.4
Duct dilatation	6.6	4.2	10.5
No imaging available	1.8	0.6	4.9

Patients who were overweight or obese were not at an increased risk of pancreatic cancer. In terms of etiology, other/unknown etiology carried a significant independent risk of pancreatic cancer (HR: 2.0, 95% CI: 1.3, 3.1) and had the highest risk estimate compared to other etiologies. With respect to imaging findings, presence of a cyst/pseudocyst was marginally associated with increased risk of pancreatic cancer (HR: 1.9, 95% CI: 1.0, 3.6), whereas main duct dilation was associated with substantially increased risk (HR: 6.6, 95% CI: 4.2, 10.5). Smoking, history of chronic pancreatitis, and presence of atrophy on imaging were not associated with 3-year risk of pancreatic cancer. Table 5 presents adjusted HRs and 95% CIs for pancreatic cancer within 3 years after presentation with AP, after excluding patients who had less than 6 months of follow-up (including those who developed pancreatic cancer within 6 months). Older age, lack of clear etiology for AP, and presence of main-duct dilatation on cross-sectional imaging remained significant predictors of pancreatic cancer. Figure 3 is a heatmap depicting the 3-year risk of pancreatic cancer cases based on age, sex, and etiology. The risk of pancreatic cancer was highest among other/unknown etiology and predominantly among older age groups for alcohol as well as biliary etiologies.

Discussion

In this retrospective cohort study, we identified clinical as well as imaging parameters associated with increased 3-year risk of pancreatic cancer among patients hospitalized for AP in a diverse regional integrated health-care setting. A total of 1% of the study cohort developed pancreatic cancer within 3 years of AP with a 3-year incidence rate of 4.2 cases per 1000 person-years. The highest incidence rate was observed among patients with ductal dilatation as well as for patients without clearly established etiology of AP. Forty-three percent of cancers were of advanced stage at the time of diagnosis. In multivariable analysis, specific risk factors for pancreatic cancer included age >65 years, male sex, Asian/Pacific Islander race, lack of a clear etiology for AP, underweight

Table 5. Adjusted Hazard Ratios and 95% Confidence Intervals for Pancreatic Cancer Within 3 years After Presentation With Acute Pancreatitis, After Excluding Patients Who Developed Pancreatic Cancer Within 6 months of Their Discharge From Hospitalization for Acute Pancreatitis or Who Had Less Than 6 months of Follow-up

Variable	Adjusted hazard ratio	95% Confidence interval	
Age in years			
18–45	Referent	-	-
46–64	1.7	0.5	6.5
65+	4.2	1.2	14.9
Sex			
Female	Referent	-	-
Male	2.2	1.0	4.8
Race/ethnicity			
Non-Hispanic white	Referent	-	-
Non-Hispanic black	0.7	0.2	2.3
Hispanic	0.5	0.2	1.3
Asian/Pacific Islander	1.4	0.5	4.4
BMI			
Underweight	3.7	0.8	18.0
Normal weight	Referent	-	-
Overweight	0.7	0.3	2.0
Obesity/unknown	1.7	0.7	4.3
Smoking	0.8	0.4	1.8
Acute pancreatitis etiology			
Biliary/hypertriglyceridemia pancreatitis	Referent	-	-
Alcoholic	1.9	0.6	6.4
Other/unknown	3.8	1.8	8.1
Diabetes	1.1	0.5	2.3
Chronic pancreatitis	2.2	0.7	6.3
Pancreatic cyst/pseudocyst	1.7	0.5	5.3
Presence of duct dilatation			
Yes	3.1	1.3	7.5
Unknown	1.1	0.1	8.2

BMI, as well as presence of main-duct dilatation on cross-sectional imaging.

Although recurrent AP and chronic pancreatitis are associated with increased long-term risk of pancreatic cancer, there are circumstances where AP may be the initial manifestation of an underlying cancer. A previous Danish population-based study with 13 years of median follow-up estimated the risk of pancreatic cancer to be highest within the first 2 years following an episode of AP (HR: 19.28) with lower long-term residual risk after 5 years (HR: 2.02).[4] This exaggerated short-term risk of pancreatic cancer is highly suggestive of an underlying neoplasm at the time of AP with up to 5.9%–14.8%[6,15] of patients with pancreatic cancer having prior history of AP, the vast majority of which occurred within 3 years prior to cancer diagnosis.[15]

Determining the conditions in which AP may be an initial presentation of pancreatic cancer is an important opportunity for early detection and intervention. A previous analysis using the Surveillance, Epidemiology, and End Results Program data linked with Medicare claims indicated that patients with pancreatic cancer with prior AP within 90 days of diagnosis had earlier stage of disease as well as improved survival compared to those without such history.[6] The frequency of AP-related cancer cases with a metastatic disease in the present study (43.2%) was higher than previous national estimates from this Surveillance, Epidemiology, and End Results-Medicare analysis (34.4%). While there were differences in the populations being studied, this also suggests there may be opportunities to identify a greater proportion of a localized disease through more timely and vigilant testing in the appropriate clinical setting.

Inflammatory changes that occur in the context of AP can obscure visualization of an underlying tumor, limiting the ability to accurately diagnose cancer in this setting. Therefore, recognition of additional factors that are associated with increased risk of an underlying neoplasm can be helpful in directing additional evaluation. One of the primary factors identified in the present study was dilatation of the main pancreatic duct, which was associated with a 10-fold increase in the short-term risk of pancreatic cancer. This is consistent with previous studies that have noted abnormalities including ductal dilatation in up to 50% of prediagnostic CT scans obtained from patients diagnosed with pancreatic cancer up to 18 months prior to their cancer diagnosis.[16] Conversely, previous work by our group has estimated the 3-year cumulative incidence of pancreatic cancer among a cohort of patients with main duct dilatation to be as high as 10% with a 3-year incidence rate of 4.7 per 100 person-years.[11] In the present study, the 3-year

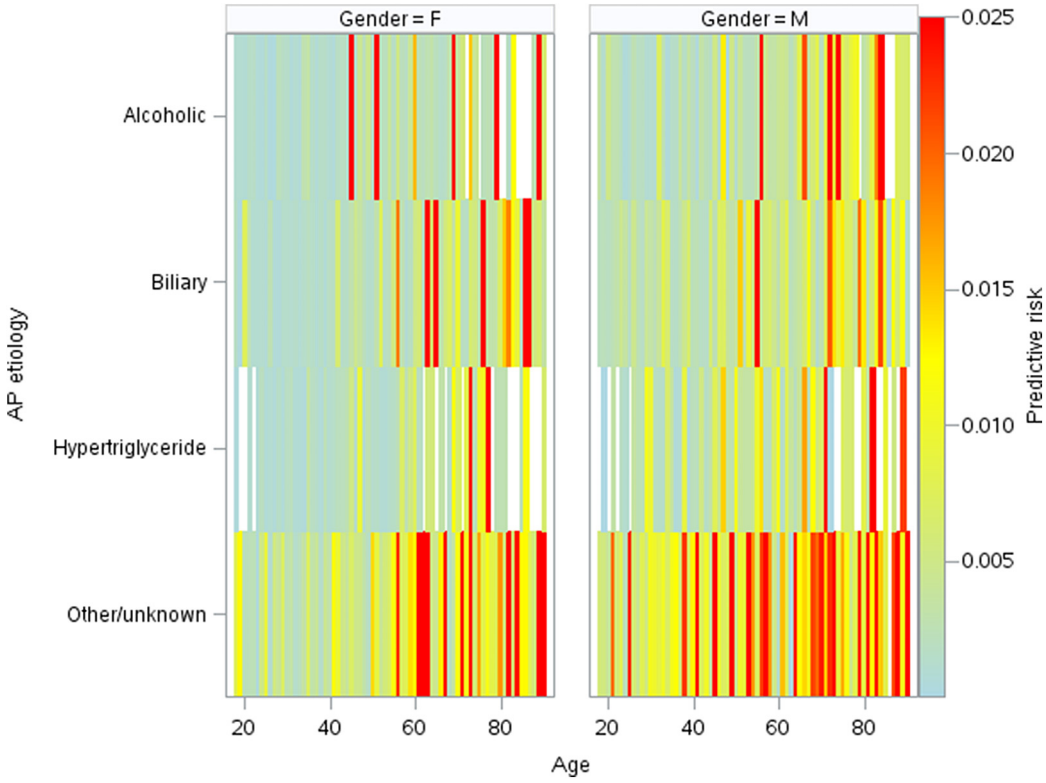

Figure 3. Heatmap of pancreatic cancer risk by age and pancreatitis etiology, stratified by patient sex. This image illustrates the predicted risk of pancreatic cancer by age and pancreatitis etiology, stratified by gender. The predicted risk ranges between 0% and 2.5%, with warmer colors indicating higher risk and cooler colors representing lower risk. For female patients with other/unknown etiology, the predicted risk appears to be higher around 60 years of age, whereas for male patients, the risk is higher among those at least 40 years of age.

incidence rate among patients with ductal dilatation was 21.7 per 1000-years compared to that in a broader population of patients with ductal dilatation. Although main-duct IPMN is a potentially malignant condition that also presents as dilatation of the main pancreatic duct, most cancers (80%) diagnosed in the present AP study cohort were ductal adenocarcinoma.

Consistent with previous studies,[17] older age and lack of established etiology were identified as risk factors associated with increased short-term risk of pancreatic cancer. In addition, we determined that underweight BMI was also an independent risk factor for pancreatic cancer. This likely reflects cancer-related weight loss that can often precede diagnosis with up to 75% of cancer patients experiencing $\geq$5% weight loss in the year prior to diagnosis.[18] Although weight loss coupled with new-onset diabetes in patients older than 50 years has been linked to increased short-term risk of pancreatic cancer in previous studies,[19,20] we did not identify such an association with recent-onset diabetes among patients with AP. This may be due to the small sample of patients with new-onset diabetes (3.9%) in the present study. In contrast, long-standing diabetes (>6 months duration) was present among 28% of the study cohort and associated with increased risk of pancreatic cancer consistent with previous literature examining the overall association between type 2 diabetes mellitus and pancreatic cancer.[21]

Strengths of the present study included the relatively large study population of patients with AP with laboratory-confirmed diagnosis. Previous studies have reported poor performance in terms of accuracy when diagnosis codes are used exclusively for case identification with a positive predictive value of 79% compared to clinical criteria,[22] whereas the approach used in the present study has been reported to have a >95% positive predictive value.[10] In addition, outcome ascertainment was performed by multiple methods including diagnosis codes as well as cross-referencing an internal cancer registry as well as the California state death index. Finally, through the use of natural language processing, we were able to adapt a previously established method for automated analysis of free-text radiology reports to systematically characterize specific imaging features associated with short-term risk of pancreatic cancer in patients with AP. Limitations of the present study included reliance upon radiology reports for determination of imaging findings. It is conceivable that additional more subtle features may be present but potentially underreported. Another limitation is the lack of information on the severity of pancreatitis at the time of hospitalization. However, when we examined the length of hospital stay as a proxy for the

severity of the pancreatitis episode, we did not find a significant association with pancreatic cancer. In addition, we did not assess factors that may be present following an episode of AP such as protracted recovery or persistent weight loss that may be informative regarding a diagnosis of underlying malignancy but would have introduced significant bias in the study design.

In summary, approximately 1% of patients with AP developed pancreatic cancer within 3 years of hospitalization at a rate of 4.2 per 1000 person-years. Age >65 years, idiopathic etiology, as well as main-duct dilatation were independently associated with increased short-term risk of pancreatic cancer as was male sex, Asian/Pacific Islander race/ethnicity, as well as underweight body habitus. Attention to these parameters in patients hospitalized for AP may help direct further investigation for an underlying pancreatic cancer with the potential for earlier diagnosis.

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Data Transparency Statement:
Anonymized data that support the findings of this study may be made available from the investigative team with the following conditions: (1) agreement to collaborate with the study team on all publications, (2) provision of external funding for administrative and investigator time necessary for this collaboration, (3) demonstration that the external investigative team is qualified and has documented evidence of training for human subjects protections, and (4) agreement to abide by the terms outlined in data use agreements between institutions.