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Original Article

Impacts of new-onset and long-term diabetes on clinical outcome of pancreatic cancer

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Abstract: Patients with pancreatic cancer have a high frequency of concurrent diabetes. This study is aimed to demonstrate the impact of diabetes on clinical outcome of pancreatic cancer. Clinical and epidemiological information was collected from medical records or by personal interview in 1328 patients with pancreatic ductal adenocarcinoma. Diabetes was defined by a known medical history, or abnormal fasting blood glucose (FBG) and HbA1c levels within three months of the cancer diagnosis. Duration of ≤3 years was used as the cutoff to arbitrarily define the new-onset and long-term diabetes. Logistic regression, Kaplan-Meier plot, log-rank test and Cox regression models were employed in the data analysis. Elevated level of FBG or HbA1c was observed in 24.7% and 11.5% of the patients without a known diabetes history, respectively. The prevalence of DM was 44.4% and was comparable by strata of tumor stage. New-onset diabetes was a significant independent predictor for risk of death in metastatic patients (HR=1.35, 95% CI=1.11-1.63, *P*=0.002) and in all patients (HR=1.23, 95% CI=1.09-1.40, *P*=0.001). Both new-onset and long term diabetes were significantly associated with older age, obesity, hypertension and coronary artery disease as well as weight loss. New-onset diabetes was also significantly related to larger tumors and elevated level of CA19-9 but not to tumor site and presence of biliary obstruction. Diabetes in general and new-onset diabetes in particular, is associated with poor outcome of pancreatic cancer. New-onset and long-term diabetes share common risk factors for type 2 diabetes.

Keywords: Diabetes, pancreatic cancer, HbA1c, glucose, obesity, survival

Introduction

Patients with pancreatic cancer (PanCa) often have a high prevalence (50-80%) of concurrent diabetes mellitus (DM) or impaired glucose tolerance (IGT) [1, 2] and the majority of DM occurred shortly before the cancer diagnosis. Although previous epidemiologic studies have found consistent associations between type 2 DM or IGT and a higher mortality rate from PanCa [3, 4], the association of DM and clinical outcomes, particularly overall survival (OS), of PanCa remains controversial. DM was related to a significantly shorter OS in several studies [5-9] mostly in patients with resected tumors. On the other hand, DM was not related to OS in some studies including patients with advanced PanCa [10-15]. Two studies actually reported a better OS among diabetic patients [16, 17]. When DM was stratified by duration of diabetes to PanCa diagnosis, on study demonstrated that both new-onset (<2 years) and longstanding DM (≥2 years) were associated with shorter survival by log-rank test [6]. Five studies did not find a correlation between new-onset DM and OS [18-21]. New-onset DM, but not longstanding DM was associated with reduced OS in two studies [22, 23]. These inconsistent findings might be partially explained by the different patient populations studied [24], difference in DM definition, and the small sample size in some of these studies.

Because DM has been shown to influence the development, treatment and outcomes of several common human malignancies [25], it is necessary to clarify the impact of diabetes on PanCa outcome, so that clinical management of the disease can be improved. For this purpose, we conducted a single institution retrospective study on the association of DM and clinical outcome in a relatively large population of patients with all stages of PanCa. In particular, we demonstrated the differences between new-onset and long-term DM in clinical characteristics and impact on survival.

Table 1. Clinical characteristics of the patients

Characteristics	N (%)	MST (months)*	$P_{log\text{-}rank}$
Age (years)			
£50	176 (13.3)	12.8	
51-60	389 (29.3)	13.6	0.217
61-70	477 (35.9)	13.6	0.598
>70	286 (21.5)	14.1	0.255
Sex			
Men	787 (59.3)	13.4	
Women	541 (40.7)	13.7	0.717
Race			
White (non-Hispanic)	1162 (87.5)	13.7	
Hispanic	70 (5.3)	12.4	0.569
African American	76 (5.7)	13.4	0.190
Other	20 (1.5)	14.7	0.597
Body Mass Index (kg/m^2)			
<25	352 (26.5)	14.8	
25-30	487 (36.7)	13.7	0.623
>30	483 (36.4)	12.4	0.012
History of DM			
No	991 (74.6)	13.9	
Yes	337 (25.4)	12.7	0.041
≤3 years	200 (15.8)	12.5	0.081
>3 years	128 (9.6)	14.4	0.418
Stage at diagnosis			
Resected	399 (30.0)	30.7	
Locally advanced	373 (28.1)	13.3	<0.001
Metastatic	556 (41.9)	8.2	<0.001
Tumor size (cm)			
<2.0	126 (9.5)	15.8	
≥2.0	339 (25.5)	18.0	0.409
≥3.0	388 (29.2)	13.3	<0.001
^{3}4.0	464 (34.9)	10.8	<0.001
Tumor site			
Head	861 (64.8)	14.8	
Other sites	467 (35.2)	10.8	<0.001
CA19-9 (units/mL)			
≤37	234 (17.6)	19.9	
38-500	527 (39.8)	15.8	0.003
>500	554 (41.8)	10.1	<0.001
Weight loss (lbs)			
0	391 (29.4)	15.9	
1-12	297 (22.4)	13.9	0.041
13-25	326 (24.5)	13.4	0.007
>25	314 (23.6)	11.5	<0.001
Hypertension			
No	731 (55.0)	14.6	
Yes	597 (45.0)	12.6	0.001

Patients and methods

Patient population and data collection

A total of 1328 patients with pathologically confirmed pancreatic ductal adenocarcinoma of all stages seen at MD Anderson Cancer Center were drawn from a case-control study conducted between March 1998 and April 2009 [26, 27]. An informed consent was obtained from each study participant for an interview, a blood sample collection and for reviewing the medical record. The study was approved by the institutional review board of MD Anderson.

Clinical information was collected from the patients' medical records by trained personnel using a structured medical record abstraction form. Baseline tumor stage was assessed by physicians on the basis of initial computed tomography (CT) images and defined according to the American Joint Committee on Cancer (AJCC) cancer staging using the tumor-node-metastasis system. The CT findings defining a potentially resectable PanCa (AJCC stages I and II) are (i) the absence of extra-pancreatic disease, (ii) a patent superior mesenteric-portal vein confluence, and (iii) no direct tumor extension to the celiac axis or superior mesenteric artery. A patient was deemed to have locally advanced, unresectable cancer (AJCC stage III) when the CT scans did not show clear evidence of encasement of the superior mesenteric artery or celiac axis or occlusion of the superior mesenteric-portal vein confluence. Tumor size was estimated either through endoscopic ultrasonography or radiologic measurement at the time of cancer diagnosis in 80% of the patients. For the remaining 20% of the patients, information on tumor size was obtained from pathological evaluation of the resected tumor at the time of cancer diagnosis. Serum carbohydrate antigen 19-9 (CA19-9) levels were measured at the time of cancer diagnosis. Tumor differentiation was evaluated in most surgically resected tumors and a few biopsy samples. Chemotherapy and radiotherapy received by each patient was not considered in this study. Information on comorbidities such

Biliary obstruction			
No	729 (54.9)	12.4	
Yes	599 (45.1)	14.7	0.002

*MST: median survival time. Missing information on BMI in 6 cases, CA19-9 in 6, tumor size in 11, and tumor site in 9 cases.

as hypertension, cerebrovascular disease, coronary artery disease, peripheral vascular disease, biliary obstruction, or weight loss prior to or around the time of cancer diagnosis was collected.

The demographic factors and information on history of diabetes, body weight and height, were collected by personal interview and verified from medical records. Body mass index (BMI) was calculated using the height and usual adult body weight.

Definition of DM

A history of DM was defined if the DM diagnosis was listed on the medical history or if a patient was on an antidiabetic regimen at the time of their PanCa diagnosis. Of all the patients with a known DM history, only one was reported to have type 1 DM (juvenile). Patients who had been diagnosed with DM three years or more before their PanCa diagnosis were assigned to the long-standing type 2 DM group; otherwise they were assigned to the new-onset DM group. The fasting blood glucose (FBG) level at cancer diagnosis or recruitment to the study was recorded. In a subset of 774/1328 (58%) patients who were recruited after 2004, a blood sample was collected at recruitment and glycosylated hemoglobin (HbA1c) level was measured using potable DCA 2000 systems (Bayer HealthCare, Tarrytown, New York). According to the American Diabetes Association (ADA) criteria, patients with a FBG ≥126 mg/dL or HbA1c ≥6.5% without a known history of diabetes was included in the new-onset DM group in the analyses unless otherwise indicated.

Survival measurements

Date of death was obtained and verified using at least one of the following sources: inpatient medical records, the MD Anderson tumor registry, and the Social Security Death Index. For all patients, survival time was calculated from the date of pathological diagnosis of the cancer to the date of death or last follow-up. The data from patients who were alive on the last day of follow-up were censored.

Statistical methods

The distribution of demographic and clinical characteristics between groups were compared and the difference was tested using Pearson Chi Square test and Fisher's exact test when the sample size is less than five in any group. The prevalence of diabetes and patients with abnormal levels of FBG and HbA1c were presented as percentage. The median overall survival time of patients with or without diabetes was assessed using the Kaplan-Meier plot and the log-rank test was performed to compare the survival distributions between subgroups. The impact of diabetes on the risk of death was evaluated using the multivariable Cox proportional-hazard models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. All clinical factors with a log-rank test P value <0.05 were included in the multivariate model. All statistical testing was conducted using SPSS software, version 22.0 (SPSS, Chicago, IL), and values of P<0.05 were considered statistically significant.

Results

Patient characteristics

The demographic and clinical characteristics of the study population and their association with overall survival (OS) are summarized in **Table 1**. Kaplan Meier plot and log rank tests showed that age, sex, and race were not related to OS. A significantly reduced OS was associated with obesity (BMI >30 kg/m^2), a known history of DM, hypertension, advanced disease stage, larger tumor size, tumor of the pancreas body and tail, elevated level of CA19-9, and weight loss.

Prevalence of DM

Known history of DM was reported in 25.4% (337/1328) PanCa patients at their cancer diagnosis, including 15.8% new-onset (≤3 years) and 9.6% long-term cases (>3 years). The frequency of a known DM history was 24.6%, 26.0%, and 25.5% in patients with localized, locally advanced and metastatic tumors, respectively.

Within three months of the cancer diagnosis, 70% of the patients had a blood sample collected and 90% of the patients had a blood glucose reading in their medical records. Based on

Table 2. Frequency of patients with abnormal level of FBG or HbA1c by stage and DM history (n, %)

	No history of DM				With history of DM			
Glucose (mg/dL)	Localized	Locally Advanced	Metastatic	Total	Localized	Locally Advanced	Metastatic	Total
<126	238 (79.3)	209 (76.0)	306 (74.3)	743 (75.3)	35 (35.7)	30 (30.9)	42 (29.6)	107 (31.8)
126-200	52 (17.3)	60 (21.8)	93 (22.6)	215 (21.8)	46 (46.9)	37 (38.1)	52 (36.6)	135 (40.1)
>200	10 (3.3)	6 (2.2)	13 (3.2)	29 (2.9)	17 (17.3)	30 (30.9)	48 (33.8)	95 (28.2)
Total	300	275	412	987	98	97	142	337
HbA1c (%)								
<5.7	99 (61.9)	84 (54.9)	125 (49.6)	308 (54.5)	14 (23.7)	8 (14.5)	13 (13.7)	35 (16.7)
5.8-6.4	47 (29.4)	53 (34.6)	105 (41.7)	192 (34.0)	14 (23.7)	11 (20.0)	28 (29.5)	53 (25.4)
≥6.5	14 (8.8)	16 (10.5)	22 (8.7)	52 (11.5)	31 (52.5)	36 (65.5)	54 (56.8)	121 (57.9)
Total	160	153	252	565	59	55	95	209

Table 3. Impact of new-onset and long-term DM on overall survival in all patients and in patients by disease stage

Group	Patients n (%)	MST* (month)	*P* (Log-rank)	HR (95% CI)†	*P*
All					
Non-DM	738 (55.6)	14.2		1.0	
DM	590 (44.4)	12.6	0.001	1.22 (1.07-1.39)	0.002
New-onset	462 (34.8)	12.4	0.001	1.23 (1.09-1.40)	0.001
Long-term	128 (9.6)	14.4	0.19	1.14 (0.93-1.39)	0.21
Resected					
Non-DM	232 (58.1)	33.3		1.0	
DM	167 (41.9)	27.4	0.06	1.13 (0.87-1.47)	0.38
New-onset	133 (33.3)	28.8	0.18	1.08 (0.82-1.43)	0.60
Long-term	34 (8.5)	25.4	0.05	1.35 (0.87-2.10)	0.18
Locally Advanced					
Non-DM	206 (55.2)	13.1		1.0	
DM	167 (44.8)	13.9	0.40	1.08 (0.87-1.35)	0.50
New-onset	124 (33.2)	14.2	0.27	1.13 (0.89-1.43)	0.33
Long-term	43 (11.5)	12.6	0.92	0.95 (0.65-1.37)	0.79
Metastatic					
Non-DM	300 (54.1)	8.6		1.0	
DM	256 (45.9)	7.5	0.009	1.24 (1.04-1.48)	0.018
New-onset	205 (36.9)	7.3	0.001	1.35 (1.11-1.63)	0.002
Long-term	51 (9.2)	8.2	0.70	0.92 (0.68-1.29)	0.63

*MST, median survival time. †HR adjusted for BMI, tumor size, tumor site, CA19-9, and weight loss.

the medical records and the HbA1c measurement, 4.7% and 11.5% of the patients without a known history of DM had a level of FBG ≥126 mg/dL or a HbA1C ³6.5%, both being diagnostic criteria for DM according to American Diabetes Association (ADA). An even greater number (41.7%) of patients had a pre-diabetic HbA1c level (5.8-6.4%) (**Table 2**). There was a slightly increasing trend in the number of patients with abnormal glucose metabolism by tumor stage among patients without a prior history of DM. On the other hand, patients with a history of DM showed a higher frequency of normal levels of blood glucose and HbA1c in those with localized disease than those with advanced disease (**Table 2**).

Following the ADA criteria, we included the patients with HbA1c level ≥6.5% (n=52) or fasting blood glucose level ≥126 mg/dL (n=244) in the new-onset DM group. After correcting 43 patients with both elevated FBG and HbA1c, the total number of patients with diabetes was added to 590 including 337 patients with a known history of DM and 253 cases with abnormal FBG or HbA1c (**Table 3**). Seven patients that did not have a known history of diabetes but with elevated levels of glucose or HbA1c more than three months of the cancer diagnosis were considered as non-diabetic.

The prevalence of DM was 44.4% in all patients and 41.9%, 44.8% and 45.9% in patients with localized, locally advanced and metastatic tumors, respectively. New-onset DM contributed to 78% of the total DM cases. Because HbA1c was not measured in all patients, we compared the prevalence of DM between

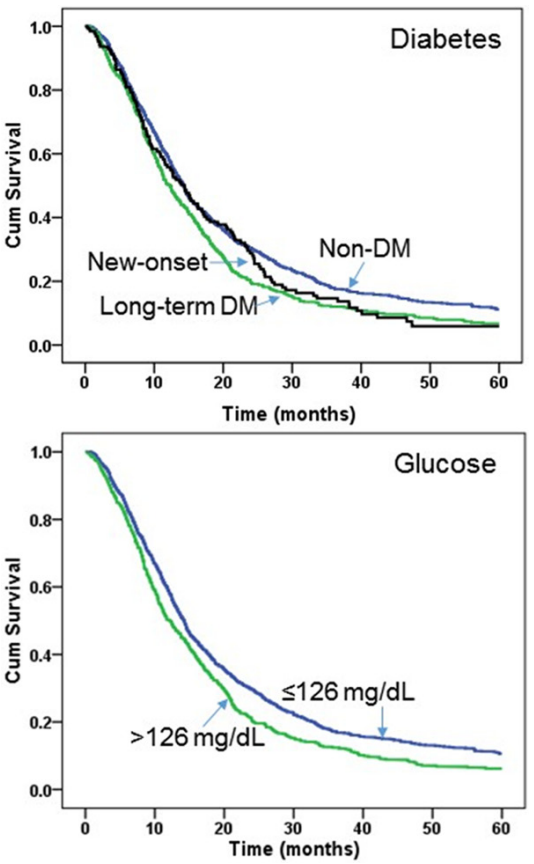

Figure 1. Kaplan Meier plot of overall survival time in patients with all stage pancreatic cancer by diabetes status (upper panel) or fasting blood glucose level (lower panel). Non-DM, no diabetes; new-onset DM, diabetes duration ≤3 years; long-term DM, diabetes duration >3 years. The median survival time and *P* values from log rank test for diabetes are presented in **Table 3**. The median survival time was 11.7 months versus 14.2 months for patients with FBG <126 versus ≥126 mg/dL, respectively (*P*=0.002, log rank test). The HR (95% CI) was 1.14 (1.01-1.30) after adjusting for other clinical predictors (*P*=0.04). The HR (95% CI) was 1.14 (1.01-1.30) after adjusting for stage, tumor site, tumor size, BMI and CA19-9 (*P*=0.04).

patients with or without this measurement. The prevalence of DM was 44.4% versus 44.4% in all patients and 42.2% versus 40.2%, 47.1% versus 41.5% and 44.1% versus 49.2% in patients with localized, locally advanced and metastatic tumors, respectively.

Impact of DM on survival

A history of DM before cancer diagnosis was associated with 1.2 months shorter OS time in all patients (*P*=0.041, log rank test) and 11 months shorter OS in patients with resected tumors (*P*=0.025, log rank test). However, Cox regression analysis found that a history of DM was not a significant predictor for risk of death in all patients or in strata of tumor stage after adjusting for other clinical predictors, such as BMI, tumor size, tumor site, CA19-9 level and weight loss (All *P* values >0.05) (data not shown).

When patients with abnormal FBG and HbA1c levels were included in the DM group, DM was significantly associated with reduced OS (median survival time 12.6 months versus 14.2 months in non-DM patients; *P*=0.001, log rank test) (**Figure 1**) and increased risk of death (hazard ratio [HR]=1.22, 95% confidence interval [95% CI]=1.07-1.32, *P*=0.002) (**Table 3**). New-onset DM was a significant predictor for death in metastatic patients and in all patients after adjusting for other clinical predictors, such as BMI, tumor size, tumor site, CA19-9 level and weight loss; the HR (95% CI) was 1.35 (1.11-1.63) and 1.23 (1.09-1.40), respectively (**Table 3**). Long-term DM (>3 years of duration) was associated with reduced OS time by log rank test among patients with localized disease (*P*=0.05) but was not a significant independent predictor for risk of death (HR=1.35, 95% CI=0.87-2.10, *P*=0.18). Because anti-diabetic therapy information is not available for most patients with new-onset diabetes (those defined by FBG or HbA1c), this factor was considered in the current analysis.

We noticed that patients with elevated FBG (>126 mg/dL) in general had a reduced median survival time compared to those with normal glucose level (11.7 versus 14.2 months, *P*=0.002, log rank test) (**Figure 1**). The HR (95% CI) was 1.14 (1.01-1.30) after adjusting for other clinical predictors (*P*=0.04). On the other hand, HbA1c was not significantly associated with survival (data not shown).

DM and post-surgical complications

Among patients who underwent tumor resection at MD Anderson, we compared the post-surgical recovery and complication events between patients with or without DM. The average length of hospital stay was 10.9 ± 4.2 days for 167 patients without DM, 11.4 ± 5.7 days for 93 patients with new-onset DM, and 11.6 ± 6.4 days for 27 patients with long-term DM (*P*=0.691, t test). Seventy two percent of non-DM versus 68.3 of DM patients had uneventful recovery. There are no statistical differences in

Table 4. Comparison of DM versus non-DM and new-onset versus long-term DM patients

Variable	Non-DM	DM	P (χ^2)*	≤3 yr	P (χ^2)*	>3 yr	P (χ^2)*	P (χ^2)†
Age (years)								
<50	130 (17.6)	46 (7.8)		39 (8.4)		7 (5.5)		
51-60	233 (31.6)	156 (26.4)		119 (25.8)		37 (28.9)		
61-70	239 (32.4)	238 (40.3)		180 (39.0)		58 (45.3)		
>70	136 (18.4)	150 (25.4)	<0.001	124 (26.8)	<0.001	26 (20.3)	0.001	0.379
Race								
White	666 (90.2)	496 (84.1)		400 (86.6)		96 (75.0)		
Hispanics	29 (3.9)	41 (6.9)		24 (5.2)		17 (13.3)		
Black	33 (4.5)	43 (7.3)		30 (6.5)		13 (10.2)		
Other	10 (1.4)	10 (1.7)	<0.001	8 (1.7)	0.268	2 (1.5)	<0.001	0.250
Body Mass Index (kg/m^2)								
<25	237 (32.2)	115 (19.6)		106 (23.1)		9 (7.0)		
25-30	281 (38.2)	206 (35.1)		163 (35.5)		43 (33.6)		
>30	217 (29.5)	266 (45.3)	<0.001	190 (41.4)	<0.001	76 (59.4)	<0.001	0.009
Weight loss (lbs)								
0	243 (32.9)	148 (25.1)		116 (25.1)		32 (25.0)		
1-12	182 (24.7)	115 (19.5)		99 (21.4)		16 (12.5)		
13-25	172 (23.3)	154 (26.1)		127 (27.5)		27 (21.1)		
>25	141 (19.1)	173 (29.3)	<0.001	120 (26.0)	0.002	53 (41.4)	<0.001	0.010
Hypertension								
No	456 (61.8)	275 (46.6)		235 (50.9)		40 (31.3)		
Yes	282 (38.2)	315 (53.4)	<0.001	227 (49.1)	<0.001	88 (68.7)	<0.001	0.163
Coronary artery disease								
No	661 (89.6)	500 (84.7)		398 (86.1)		102 (79.7)		
Yes	77 (10.4)	90 (15.3)	0.008	64 (13.9)	0.073	26 (20.3)	0.001	0.163
Cerebral vascular disease								
No	693 (93.9)	527 (89.3)		416 (90.0)		111 (86.7)		
Yes	45 (6.1)	63 (10.7)	0.002	46 (10.0)	0.014	17 (13.3)	0.004	0.070
Tumor size (cm)								
≤2	282 (38.5)	183 (31.3)		139 (30.4)		44 (34.6)		
>2	451 (61.5)	401 (68.7)	0.035	318 (69.6)	0.005	83 (65.4)	0.412	0.044
CA19-9 (units/ml)								
≤144	303 (44.5)	300 (37.4)		157 (37.7)		43 (36.1)		
>144	378 (55.5)	335 (62.6)	0.012	259 (62.3)	0.028	76 (63.9)	0.089	0.386
Perineural invasion								
No	35 (17.4)	20 (13.6)		19 (16.5)		1 (3.1)		
Yes	166 (82.6)	127 (86.4)	0.336	96 (83.5)	0.840	31 (96.9)	0.036‡	0.811

*All comparisons were made to the non-DM group. †Comparison between new-onset and long-term DM. ‡Fisher's exact test.

the frequency of infection (12.0% vs. 11.7%), biliary leak (4.2% vs. 6.7%) or other events (12.0% vs. 13.3%) between non-DM and DM patients (P=0.355, Chi-square test).

Characteristics of patients with DM

Compared with non-DM patients, DM patients were significantly older, were more likely to be Hispanic or African American, obese (BMI >30 kg/m^2), and were more likely to have hypertension and coronary artery disease CAD and cerebral vascular disease (CVD) (**Table 4**, Chi square test). Furthermore, DM was associated with a significantly higher frequency of weight loss, larger tumor (>2 cm), and elevated level of CA19-9. Although DM patients tended to have more margin-positive tumor resections than the non-DM patients, the difference was not

statistically significant (22.3% versus 17.3%, *P*=0.216). DM was not associated with tumor site, grade, differentiation, and biliary obstruction (data not shown). Both new-onset or long-term DM showed a significantly higher frequency of old age, obesity, hypertension, cerebral vascular disease, and weight loss than non-DM. New-onset DM also showed a significantly higher frequency of large tumor and elevated serum level of CA19-9. Long-term DM was much more common in ethnic minorities and was associated with a higher frequency of perineural invasion.

Discussion

In this large-scale single hospital study, we have shown that a high proportion of patients without a known history of DM at their cancer diagnosis had elevated level of FBG and HbA1c. When these patients were considered as new onset diabetes, DM in general was significantly associated with poorer survival and increased risk of death among all patients. New-onset DM in patients with metastatic disease and in all patients also showed significantly reduced survival and increased risk of death. These findings confirmed the negative impact of DM, especially new-onset DM, on clinical outcome of PanCa.

Previous studies have shown that new-onset DM could be an early sign of occult PanCa [28, 29]. Clinically, it is difficult to clearly distinguish new-onset type II DM from PanCa-induced type 3c DM at onset. Because 90% of patients with PanCa would die within 2 years of diagnosis, it is unlikely that DM has a prolonged subclinical phase with systemic effects several years prior to cancer diagnosis. Therefore, we used 3 years as an arbitrary cutoff to define patients with long-standing or new-onset DM. Our study showed that the prevalence of a known history of DM was 25.4% (15.8% for long-standing and 9.6% for new-onset DM) and the prevalence was comparable in patients with different disease stage. However, the prevalence of DM rose to 44.4% if patients with unknown DM history but having an abnormal level of FBG or HbA1c at cancer diagnosis were included. This finding was consistent with estimates reported from a previous study that one third of the DM cases in PanCa was undiagnosed [30]. It also supports the notion that some of the inconsistencies in the DM prevalence and impact of DM on survival from previous studies were related to the various ways that DM was defined.

Even though long-term DM conferred a 7.9-month shorter survival than those without DM among patients with resected tumors, it is not a significant independent predictor for risk of death (**Table 3**). Consistent with findings from a previously reported study [31], long-term DM was not related to postsurgical events because patients with or without DM had similar length of hospital stay and comparable frequencies of postsurgical complications. Consistent with known risk factors for type II DM, the long-term DM patients were significantly older in age, more in ethnic minorities, and having a higher frequency of obesity, hypertension and CAD. In this study, obesity was significantly associated with reduced OS and increased risk of death, as previously reported in several individual studies [13, 14, 27, 32]. In fact long-term DM was not an independent predictor for risk of death in the multivariate Cox regression model. The reduced OS associated with DM could be a residual confounding effect of obesity. Although obesity and type II DM and other metabolic syndrome-related conditions could all share the same mechanisms, i.e. insulin resistance and inflammation in contributing to the progression of PanCa [33-37].

New-onset DM accounted for 78% of the total DM cases in this study and the frequency did not significantly vary by strata of tumor stage. However, there seem to be an increasing trend of patients with abnormal glucose metabolism by tumor stage, i.e. the number of patients with normal level of FBG and HbA1c decreased as tumor stage advanced. New-onset DM was also associated with larger tumor and elevated level of CA19-9. These observations support the concept that new-onset DM in PanCa is a consequence of the cancer and the deregulated glucose metabolism may be an indicator of disease occurrence. This is consistent with the observation that new-onset DM was significantly associated with reduced survival and increased risk of death in patients with metastatic disease and in all patients. Although our study did not investigate whether intensive glucose control could improve survival, we did observe that elevated FBG level but not HbA1c was a significant independent predictor for increased risk of death.

Our study has found that both new-onset and long-term DM is more common in individuals at older age, with obesity, hypertension and CAD; and both are associated with more severe weight loss than non-DM patients. These observations suggest that risk factors for type II DM, i.e. obesity or other conditions associated with metabolic syndrome may also predispose patients with PanCa to the development of type 3c DM. It is possible that individuals with existing insulin resistance and inflammatory state associated with obesity are more susceptible to the extra stress of pancreatic tissue damage caused by the tumor. Weight loss, associated with DM and occurring prior to the onset of cachexia, has been suggested as a paraneoplastic phenomenon induced by PanCa [38]. In our study, we did not find a significant difference between new-onset and long-term DM in weight loss, both showed significantly more weight loss that the non-DM patients.

The strengths of our study are the large sample size, the detailed clinical information collected from medical records as well as epidemiological risk factor information collected from patient interviews. The large dataset offered an opportunity for analysis in strata of tumor stage and diabetes duration, which helped to clarify some previous inconsistent findings. The combined dataset of clinical and epidemiological information allowed better characterization of the study population. The limitations of our study include our decision to base DM status on past medical history and the initial FBG and HbA1c level. For example, the sampling of blood glucose level was not standardized; HbA1c was not measured in all patients; and the effect of pre-DM or IGT on survival was not evaluated. Thus, the possibility of misclassification is unavoidable and the risk estimate could be biased towards to either direction.

In conclusion, the current study has demonstrated the high prevalence and significant impact of new-onset DM or elevated glucose level on prognosis of PanCa. Both new-onset and long-term DM in PanCa patients were positively correlated with age and parameters of metabolic syndrome. Further research on the mechanisms underlying the complex associations between DM and PanCa is required to find new strategies in clinical management of patients with DM and PanCa.

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Disclosure of conflict of interest

None.

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