



A Study in Clinicopathological Characteristics of Pancreatic Cancer Related Diabetes in Iraqi Patients

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ABSTRACT:

BACKGROUND:

Globally, pancreatic cancer is the 11th most common cancer in women and the 12th most common in men. Many studies have been done to reveal the relationship and the mechanism between diabetes and pancreatic cancer. Some revealed the relationship between diabetes and increased risks of pancreatic cancer in both males and females. Another revealed that new onset diabetes could potentially indicate early stage pancreatic cancer.

OBJECTIVE:

To determine the association between diabetes and clinic-pathological features of pancreatic carcinoma.

PATIENTS AND METHODS:

A case control study conducted in Baghdad Oncology Teaching Hospital and in Al-Amal National Hospital for the treatment of cancerous tumors during a period of nine months from April till the end of December 2020. It included 66 patients referred from GIT centers or any other surgical departments and newly diagnosed as pancreatic cancer and divided into two groups: Case group included 29 patients who were a known case of type 2 diabetes for at least one year and newly diagnosed with pancreatic cancer and control group included 37 patients newly diagnosed with pancreatic cancer but had no diabetes.

RESULTS:

In this study, no significant difference between the study groups in regards to the mean of Ca19.9 level. Diabetes was significantly associated with increase rate of Hypertension among pancreatic cancer patients. Diabetic patients were with shorter PFS and higher incidence of progression than non-diabetic patients were.

CONCLUSION:

Diabetes is not only one of the causes of pancreatic cancer but also as a complication of pancreatic cancer. Diabetic patients are associated with hypertension, worse survival and diabetes can be a predictive factor in pancreatic cancer survival.

KEYWORDS: Pancreatic cancer, diabetes, clinic pathological, Iraq

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INTRODUCTION:

Globally, pancreatic cancer is the 11th most common cancer in women and the 12th most common in men.⁽¹⁾ It is the fourth leading cause of cancer deaths in USA. The 5-year survival rate ranges from 5% to 15%. The overall survival rate of this condition is only 6%.⁽²⁾ Many studies have been done to reveal the relationship and the mechanism between diabetes and pancreatic cancer. Some revealed the relationship between diabetes and increased risks of pancreatic cancer in both males and females.

Another revealed that new onset diabetes could potentially indicate early stage pancreatic cancer.⁽³⁾ At diagnosis, approximately 80% of PanCA patients present with impaired glucose tolerance or recent onset of type II diabetes mellitus (T2DM). By accounting for the duration of T2DM before the PanCA diagnosis, patients with T2DM for more than two years are at higher risk. It has been found that increased duration of DM (more than 5 and 10 years) negatively correlated with risk of PanCA.⁽⁴⁾

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Thus suggesting that patients with DM have a higher risk of developing PanCA within the first 10 years after initial diagnosis, but not for those who have had diabetes for more than 10 years. Mechanistically, IGF-1 and insulin resistance along with hyperglycemia and hyperinsulinemia may be participate in the diabetes-associated risk for PanCA.⁽⁵⁾

AIM OF STUDY:

To determine the association between DM and clinic-pathological features of pancreatic carcinoma.

PATIENTS AND METHODS:

This was a case control study conducted in Baghdad Oncology Teaching Hospital and in Al-Amal National Hospital for the treatment of cancerous tumors during a period of nine months from April till the end of December 2020.

The study included 66 patients referred from GIT centers or any other surgical departments and newly diagnosed as pancreatic cancer and divided into two groups:

- Case group: Included 29 patients who were a known case of type 2 diabetes (type 2 DM) for at least one year and newly diagnosed with pancreatic cancer.
- Control group: Included 37 patients newly diagnosed with pancreatic cancer but had no diabetes.

Exclusion criteria

- Patients with pancreatic neuroendocrine tumor.
- Patients with periampullary tumor.
- Type 1 insulin dependent DM
- Secondary causes of DM (Cushing syndrome, acromegaly, drugs: glucocorticoids, thiazides)

Ethical considerations and official approvals

Verbal permission was obtained from each patient prior to collecting data. Names were removed and replaced by identification codes. All information kept confidential in a password secured laptop and data used exclusively for the research purposes.

RESULTS:

Sixty six pancreatic cancer patients were involved. 29 (43.9%) of them had confirmed DM, and the other 37 (56.1%) did not.

Patients' age ranged from 44 to 82 years with a mean of 60.1 years and standard deviation (SD) of ± 8.89 years. The highest proportion of patients 41 (62.1%) were found in the age group of (50 – 60) years (Figure 1). Regarding gender, 42 (63.6%) of the patients were males and 24 (36.4%) were females, with male to female ratio of 1.75:1. The calculated BMI had a mean of 23.98 ± 4.15 kg/m², and more than half of cases 34 (51.5%) had normal BMI level. In this study, 31 (47%) of the enrolled patients were hypertensive, 13 (19.7%) had family history of malignancy, 40 (60.6%) and nine (13.6%) were smokers and alcoholic, respectively (Table 1)

Table 1: Distribution of the study patients by demographic and clinical characteristics.

Variable	No. (n= 66)	Percentage (%)
Gender		
Male	42	63.6
Female	24	36.4
BMI Level		
Underweight	12	18.2
Normal	34	51.5
Overweight	15	22.7
Obese	5	7.6
Hypertension		
Yes	31	47.0
No	35	53.0
Family History		
Yes	13	19.7
No	53	80.3
Smoking		
Yes	40	60.6
No	26	39.4
Alcohol		
Yes	9	13.6
No	57	86.4

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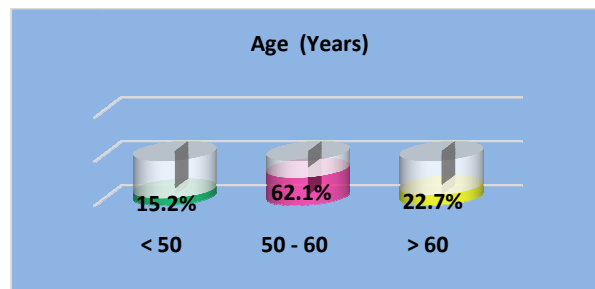


Figure 1: Distribution of the study patients by age.

Concerning site of pancreatic cancer, head of pancreas was the most common site in 46 (69.7%) of cases. The highest proportion of patients was with stage IV and grade III (66.7% and 59.1%, respectively. Lymph node involvement was recorded among 46 (69.7%) of cases, while liver was the most common site of metastasis in 36 (54.6%) of cases (Table 2).

Table 2: Distribution of the study patients by details of pancreatic cancer.

Variable	No. (n= 66)	Percentage (%)
Site		
Head	46	69.7
Body Tail	18	27.3
Neck	2	3.0
Stage		
IA	1	1.5
IIA	4	6.1
IB	3	4.5
IIB	6	9.1
III	8	12.1
IV	44	66.7
Grade		
I	4	6.1
II	23	34.8
III	39	59.1
LN Involvement		
Yes	46	69.7
No	20	30.3
Metastasis		
No	22	33.3
Liver	36	54.6
Lung	4	6.1
Peritoneum	3	4.5
Bone	1	1.5

Association between DM and Ca pancreas

In the current study, we found that DM was significantly associated with increase rate of Hypertension among pancreatic cancer patients.

The proportion of Hypertension was significantly higher in patients who had Ca pancreas and DM (61.3%, $P= 0.008$). No significant association was found between DM and non-DM pancreatic cancer

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patients in terms of patients' age (P= 0.142), (P= 0.154), smoking (P= 0.191), and alcohol (P= gender (P= 0.453), BMI (P= 0.341), family history 0.947) (Table 3).

Table 3: Distribution of the study group by certain demographic and clinical characteristics.

Clinical Characteristics	Study Group		Total (%) n= 66	P- Value
	Ca Pancreas & DM (%) n= 29	Ca Pancreas (%) n= 37		
Age Group (Years)				
< 50	2 (20.0)	8 (80.0)	10 (15.2)	0.142
50 - 60	18 (43.9)	23 (56.1)	41 (62.1)	
> 60	9 (60.0)	6 (40.0)	15 (22.7)	
Gender				
Male	17 (40.5)	25 (59.5)	42 (63.6)	0.453
Female	12 (50.0)	12 (50.0)	24 (36.4)	
BMI Level				
Underweight	3 (25.0)	9 (75.0)	12 (18.2)	0.341
Normal	15 (44.1)	19 (55.9)	34 (51.5)	
Overweight	9 (60.0)	6 (40.0)	15 (22.7)	
Obese	2 (40.0)	3 (60.0)	5 (7.6)	
Hypertension				
Yes	19 (61.3)	12 (38.7)	31 (47.0)	0.008
No	10 (28.6)	25 (71.4)	35 (53.0)	
Family History				
Yes	8 (61.5)	5 (38.5)	13 (19.7)	0.154
No	21 (39.6)	32 (60.4)	53 (80.3)	
Smoking				
Yes	15 (37.5)	25 (62.5)	40 (60.6)	0.191
No	14 (53.8)	12 (46.2)	26 (39.4)	
Alcohol				
Yes	4 (44.4)	5 (55.6)	9 (13.6)	0.974
No	25 (43.9)	32 (56.1)	57 (86.4)	

It was clear that there was no significant relation (P > 0.05) between DM and non DM pancreatic cancer patients in regards to site (P= 0.567), stage (P= 0.787), grade (P= 0.067), LN involvement (P= 0.335), resectability (P= 0.49), and metastasis of tumor (P= 0.535) (Table 4).

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Table 4: Distribution of the study group by certain details of pancreatic cancer.

Clinical Characteristics	Study Group		Total (%) n= 66	P- Value
	Ca Pancreas & DM (%) n= 29	Ca Pancreas (%) n= 37		
Site				
Head	22 (47.8)	24 (52.2)	46 (69.7)	0.567
Body Tail	6 (33.3)	12 (66.7)	18 (27.3)	
Neck	1 (50.0)	1 (50.0)	2 (3.0)	
Stage				
I	2 (50.0)	2 (50.0)	4 (6.1)	0.787
II	3 (30.0)	7 (70.0)	10 (15.1)	
III	4 (50.0)	4 (50.0)	8 (12.1)	
IV	20 (45.5)	24 (54.5)	44 (66.7)	
Grade				
I	3 (75.0)	1 (25.0)	4 (6.1)	0.067
II	6 (26.1)	17 (73.9)	23 (34.8)	
III	20 (51.3)	19 (48.7)	39 (59.1)	
LN Involvement				
Yes	22 (47.8)	24 (52.2)	46 (69.7)	0.335
No	7 (35)	13 (65)	20 (30.3)	
Metastasis				
Yes	20 (45.5)	24 (54.5)	44 (66.7)	0.535
No	9 (40.9)	13 (59.1)	22 (33.3)	
Resectability				
Resectable	2 (25.0)	6 (75.0)	8 (12.1)	0.49
Locally advanced	7 (50.0)	7 (50.0)	14 (21.2)	
Metastasis	20 (45.5)	24 (54.5)	44 (66.7)	

Progression free survival (PFS)

Relation of PFS with presence of diabetes is shown in figure (2). Diabetic patients were with shorter

PFS and higher incidence of progression than non-diabetic patients, and this difference in PFS was statistically significant (P= 0.032).

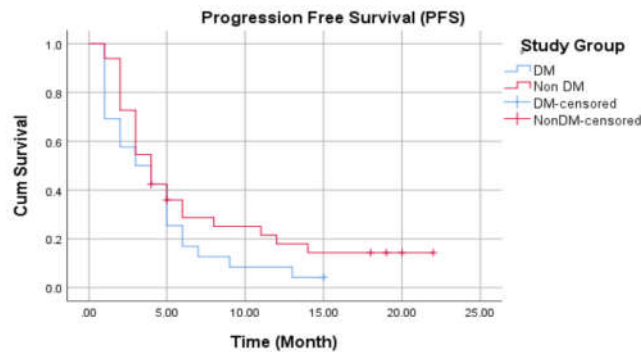


Figure 2: DM related Progression free survival

DISCUSSION:

The relationship between DM and PanCA has been known for more than a century. However, this relationship is complicated with existence of bidirectional link between the two conditions. Long-standing DM has been well established as a risk factor for development of PanCA, but growing epidemiologic, clinical and experimental evidence suggest that new-onset DM is a paraneoplastic phenomenon in a subset of patients that precedes PanCA diagnosis.⁶ In the current study, 66 pancreatic cancer patients were enrolled in this study. 29 of them (43.9%) had confirmed DM, and the other 37 (56.1%) did not.

Concerning site of pancreatic cancer in this study, head of pancreas was the most common site in 69.7% of cases. The highest proportion of patients was with stage IV and grade III (66.7% and 59.1%, respectively). Lymph node involvement was recorded among 69.7% of cases, while liver was the most common site of metastasis in 54.6% of cases, finally, only 12.1% of patients were resectable, 21.2% of patients were locally advanced and 66.7% were metastatic patients.

Lee et al study in 2013 observed a different finding, they found that 22.5% of patients were classified with resectable pancreatic cancer, 38% of patients with locally advanced pancreatic cancer and 39.6% of patients had advanced pancreatic cancer. Tumors were primarily located at the pancreas head in more than half of them (53.5%), also 4.8% of the participants underwent operation, while 41.2% received chemotherapy and 54% were treated with chemo radiotherapy.⁷ A close result by comparison to Eissa et al study in 2014 observed, in which most common site of tumor was the head of pancreas in 63.7%, followed by body (24.2%). Furthermore, Choledochoduodenostomy gastro-jejunoscopy biopsy is the most common palliative bypass procedure (55.6%), followed by biopsy (in case of metastasis) by either excisional or fine needle aspiration cytology in (23.2%). Tumor excision (curative for peri-ampullary and distal pancreatectomy for distal one) in (8.9%) & choledochoduodenostomy for biliary obstruction in (2.9%). Moderately differentiated adenocarcinoma was the most common type in 46.8% of patients, followed by poorly differentiated cancer in 24.6 % of the participants.⁸

In the current study, DM was significantly associated with increase rate of HT among pancreatic cancer patients. The proportion of HT was significantly higher in patients who had

Ca pancreas and DM ($P= 0.008$). No significant association found between DM and patients' age, gender, BMI, family history, smoking, and alcohol ($P>0.05$).

In the same accordance, Li and colleagues in 2011, did not observe significant interaction between DM and sex, race, education, smoking, alcohol, or body mass index (BMI) in diabetic patients diagnosed with pancreatic cancer ($P = 0.28, 0.52, 0.22, 0.95, 0.36, \text{ and } 0.35$, respectively).⁹ In contrary, Antwi et al study in 2016, investigated independent association between inflammatory potential of diet, cigarette smoking, and long-standing T2DM (≥ 5 years) in relation to risk of PanCA. They revealed a 3.09-fold increase ($OR=3.09, 95\% \text{ CI}=2.02-4.72$) in risk of PanCA associated with long-standing T2DM compared to non-diabetics, and a 2.54-fold increase with a more pro-inflammatory diet ($OR=2.54, 95\% \text{ CI}=1.87-3.46$) and a 3.40-fold increase with current smokers ($OR=3.40, 95\% \text{ CI}=2.28-5.07$). Besides, they conclude that long-standing T2DM and cigarette were risk factors of PanCA, while a pro-inflammatory diet might act as cofactor with smoking and DM.¹⁰ Another different finding was observed in Ben et al study in 2012, in which by comparison with T2DM alone, PanCA patients with new-onset DM had an association between DM and age and BMI, as found patients with new-onset DM had an older onset age of DM and lower body mass index (BMI).¹¹

This study revealed no significant relation between DM and non-DM pancreatic cancer patients in regards to site, stage, grade, LN involvement, resectability, and metastasis of tumor ($P > 0.05$).

A similarity to the present work have been observed in Mizuno et al study in 2013, as reported that prevalence of DM in PanCA patients was 45%, also found that no significant relation existed between prevalence of DM different PanCA disease stages ($P>0.05$).¹²

In their research, some authors concluded that hyperglycemia could cause an oxidative stress, which is caused by an imbalance in reactive oxygen species (ROS) antioxidants. Most patients with PanCA suffer from diabetes or hyperglycemia, and high glucose can cause ROS production, which can in turn increase the invasiveness of cancer cells.¹³

As mentioned previously, many recent studies have observed that the relationship between PanCA and T2DM is complex and bidirectional.

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DA Pancreatic ductal adenocarcinoma (PC), the most common form of PanCA, has been found to be more related to T2DM.¹⁴ As American Cancer Society's Cancer Facts & Figures 2013 stated, about 25% of the patients had T2DM at the time of diagnosis of PanCA, and another 40% had pre-diabetes.¹⁵ Besides, 50%-increased risk was noticed in PanCA patients with long-term (≥ 5 years) T2DM, consequently, PanCA can result in T2DM. Moreover, it also found that T2DM was an early sign of the tumor. Therefore, the relationships between PanCA and T2DM are both cause and consequence.¹⁶

Regarding progression free survival (PFS)

In the current study, diabetic patients were with shorter PFS and higher incidence of progression than non-diabetic patients, and this difference was significant ($P=0.032$).

Similarly to the current findings, Mao and co-authors reported in their study in 2015 in the overall comparison of patients with pancreatic cancer and diabetes with their nondiabetic counterparts, the former had significantly higher mortality, concluded that effect of DM on survival was related to stages of tumor and duration of DM ($P<0.05$).¹⁷

Differently, Pusceddu and colleague's in their study in 2018, found that PFS was significantly longer in patients with DM (median, 32.0 months) than without it (median, 15.1 months) ($HR=0.63$; 95% $CI=0.50-0.80$; $P=0.0002$). PFS of patients treated with metformin was significantly longer (median PFS, 44.2 months) than for patients without DM ($HR=0.45$; 95% $CI=0.32-0.62$; $P<0.00001$).¹⁸ Differently, Dong and co-authors in 2017 in a meta-analysis of two randomized controlled trials including 181 pancreatic patients, revealed that T2DM patients on metformin use was not associated with an improved overall survival at six months ($RR=0.90$, 95% $CI=0.67-1.21$), overall survival ($HR=1.19$, 95% $CI=0.86-1.63$) and PFS ($HR=1.39$, 95% $CI=0.97-1.99$).¹⁹

The discrepancies observed can attributed to different factors, as variations in their inclusion criteria, study population, and adjustment for confounding variables, which may have led to both overestimations and underestimations of risks, the status and duration of DM and types of anticancer and antidiabetic therapies and their effects on outcomes. This is important since some therapies (e.g., surgery, adjuvant chemotherapy, and antidiabetic, as metformin) have a more positive effect than others on cancer outcome (like,

Metformin which seems to have anticancer effects, as it inhibited DNA synthesis and proliferation of pancreatic cancer cells close to the desmoplastic reaction by down-regulating receptor-PI3K-mTOR signaling pathway).^{20,21}

There are many explanations for the relation between low survival time and DM in PanCA patients. DM may enhance tumor progression through mechanisms of IR and inflammation. Also, hormonal or metabolic disturbance, as hyperinsulinemia or hyperglycemia, may affect tumor biology at certain stages, as transformation, growth, and metastasis.²² Additionally, high mortality rate among patients with DM may partially be due to noncancerous factors, such as complications of long-term DM.²³

CONCLUSION:

Diabetes is not only one of the causes of pancreatic cancer but also as a complication of pancreatic cancer. Diabetic patients are associated with hypertension, worse survival and diabetes can be a predictive factor in pancreatic cancer survival.

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