Is diabetes onset at advanced age a sign of pancreatic cancer?

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AIM: *Pancreatic cancer is the 11th most common cancer in the world. The importance of early diagnosis and treatment for curative treatment is very high. Many studies have shown a relationship between diabetes mellitus (DM), smoking, genetic factors, obesity, nutritional habits and sedentary life and pancreatic ductal adenocarcinoma (PDAC). In this study, we aimed to investigate the relationship between DM onset age and PDAC.*
MATERIALS AND METHODS: *158 patients with PDAC and DM were compared with 244 patients with DM in the control group. We retrospectively analyzed PDAC risk factors with a focus on DM onset age.*
RESULTS: *It was calculated that the risk of PDAC increased 8.5 times in patients diagnosed with DM after 60 years of age compared to those diagnosed with DM before 60 years of age (HR = 8.54, 95% CI 5.66-12.90, p<0.0001). The interval between the diagnosis of DM and the diagnosis of PDAC peaked at 32 months (95% CI 27.90-35.56). When the age of DM onset was evaluated, it was observed that peaks were around 50 years in the group without PDAC and 60 years in the group with PDAC.*
CONCLUSION: *In patients with DM onset after the age of 60, we recommend keeping in mind the increased risk of PDAC and evaluating these patients for PDAC, even if they are asymptomatic.*

KEY WORDS: Diabetes, Early detection of cancer, New onset diabetes, Pancreatic cancer, Relative risk, Screening

Introduction

Pancreatic cancer is the 11th most common cancer in the world, accounting for 4.5% of cancer-related deaths [1]. The most common type is pancreatic ductal adenocarcinoma (PDAC) with a rate of 85% [3]. While 5-year survival for PDAC is less than 1%, the expected survival in metastatic disease is between 4-6 months [3]. Only 15-20% of the patients are suitable for surgical treatment at the time of diagnosis [4]. The 5-year survival after resection of tumors around 30mm is approximately 10-20% [5,6]. On the other hand, 5-year survival after resection of ≤20 mm tumors can be 30-60% [7-9], whereas it can reach 75% for ≤10 mm tumors [9,0]. The importance of early diagnosis and treatment for curative treatment is very vital. PDAC is often asymptomatic or shows non-specific symptoms in the early stages. In symptomatic cases, it is often at an advanced stage. Therefore, determining risk factors and screening for early diagnosis in patients with risk is very important. Many studies have shown a relationship between PDAC and type II diabetes mellitus (DM), smoking, genetic factors, obesity, nutritional habits and sedentary life [11-14]. It has been reported that long-term DM can cause PDAC [15,16], however it has also been shown that DM may be a consequence of PDAC [17,18]. The findings suggest that there is a two-way causal relationship between DM and PDAC. However, the number of studies investigating the relationship between DM onset age and PDAC is rather limited. In this study, we aimed to investigate the relationship between DM onset age and PDAC.

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Materials and Methods

The patients who were diagnosed as PDAC pathological in biopsy or surgical materials were detected in our hospital between January 2013 and January 2019 by scanning through the automation system of our hospital. Patients with pancreatic adenocarcinoma and type II DM were included in the study group. PDAC diagnostic age, DM diagnosis age, gender, CA 19-9 level were retrospectively reviewed. A control group was created to calculate the DM age of onset of patients who were not diagnosed with PDAC. For the control group, the consecutive patient group who had admitted to the endocrine outpatient clinic with the diagnosis of DM and had CA 19-9 level was screened retrospectively through the automation system of our hospital and the age and diagnosis age of the patients were determined. Patients with any known malignancy, hyperglycemic drug use (organ transplantation, rheumatologic disease, ulcerative colitis, crohn's disease, etc.), patients with chronic renal failure or chronic liver disease were not included in the control group. CA 19-9 levels between 0-37 U / mL were considered normal.

Statistical analyzes were done by using SPSS software (version 21.0; IBM, Armonk, NY) and MedCalc trial version. Statistical analyses were performed using χ^2 tests for comparisons of discrete variables and independent two-tailed t tests for comparisons of continuous variables. Descriptive statistical graphs of age distribution of DM in patients with and without PDAC were plotted. Analyses of pooled data were conducted using univariate logistic regression models to compute the hazard ratio (HR) with 95% confidence intervals (CI) as an estimate of relative risk. The receiver operating characteristic (ROC) curve analysis was used to calculate the cut-off values of age level as a screening test for PDAC. P<0.05 was considered statistically significant.

Ethics committee approval was received for this study from the Local Ethics Committee (Decision date 12.06.2019. Decision number 460).

Results

289 patients with PDAC were detected. Among these, 158 patients were diagnosed with DM at or before PDAC. A total of 402 patients were included in the study, with the addition of 244 patients in the control group. Of 402 patients, 178 (44%) were male and 224 (56%) were female. PDAC was diagnosed in 88 (49%) of 178 male patients and in 70 (31%) of 224 female patients. In our study, a statistically significant relationship was observed between male gender and PDAC (p<0.0001) (Table I).

While evaluating the relationship between age and PDAC; Based on the age at which PDAC patients were diagnosed with PDAC and the real-time age of patients in the control group, it was aimed to calculate the time patients spent until they were diagnosed with cancer in accordance with the purpose of the study. The age of the patients ranged between 29-88 and the mean age was 62.48 ± 10.39. The mean age of the males was 62.51 ± 10.52 and the mean age of the females was 62.45 ± 10.30. While the mean age of the PDAC group was 63.37 ± 10.34, the mean age of the non-PDAC group was 61.88 ± 10.39, and no statistically significant relationship was found between age and PDAC (p = 0.16) (Table I).

TABLE I - *Clinical characteristics of DM patients with and without PDAC*

	DM with PDAC (n=158)	DM w/o PDAC (n=244)	p
Male/Female	88/70	90/154	p<0.0001
Age (Mean ±SD)	63.37±10.34	61.88±10.39	p=0.16
CA 19-9 (Normal/High)	31/127	225/19	p<0.0001

DM: Diabetes Mellitus; PDAC: Pancreatic Ductal Adenocarcinoma; CA 19-9: Carbohydrate Antigen 19-9

TABLE II - *The receiver operating characteristic (ROC) curve variables with optimal cut-off values and test performance using PDAC as a classification variable*

Variable	AUC (95% CI)	Cut-off value (Youden's Index)	Sensitivity (95% CI)	Specificity (95% CI)
Age	0.75 (0.70-0.79)	60 (0.39)	61.39 (53.3-69.0)	78.28 (72.60-83.30)

AUC: Area Under the Curve; ROC: Receiver Operating Characteristic; CI: Confidence Interval

TABLE III - *The relationship between DM onset age and PDAC*

PDAC	DM onset after 60 age (n = 130)	DM onset before 60 age (n = 272)	p
Present	89	69	
Absent	41	203	P<0.0001

DM: Diabetes Mellitus; PDAC: Pancreatic Ductal Adenocarcinoma; CA 19-9: Carbohydrate Antigen 19-9

TABLE IV - *Univariate logistic regression analyses for the risk of PDAC*

Variants	HR	(95 %CI)	p value
DM onset age	8.54	(5.66-12.90)	p<0.0001

DM: Diabetes Mellitus; PDAC: Pancreatic Ductal Adenocarcinoma; HR: Hazard Ratio; CI: Confidence Interval

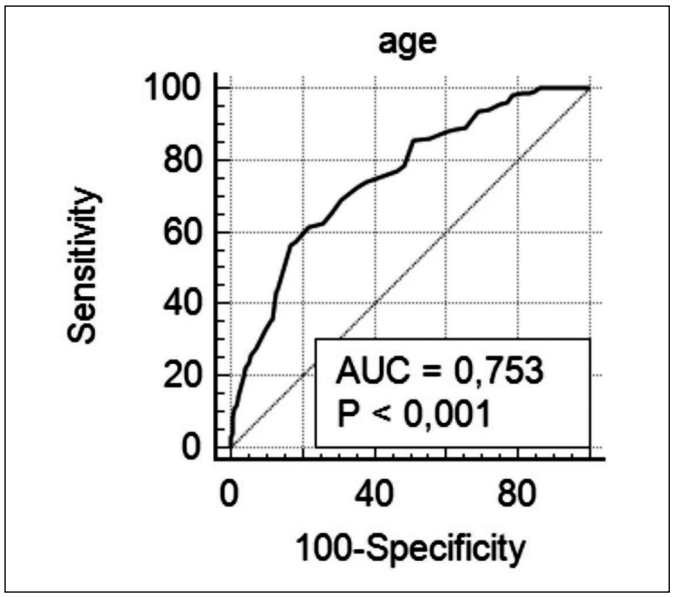

Fig. 1: Determination of the relationship between age of onset of DM and PDAC risk by the receiver operating characteristic (ROC) curve analysis.

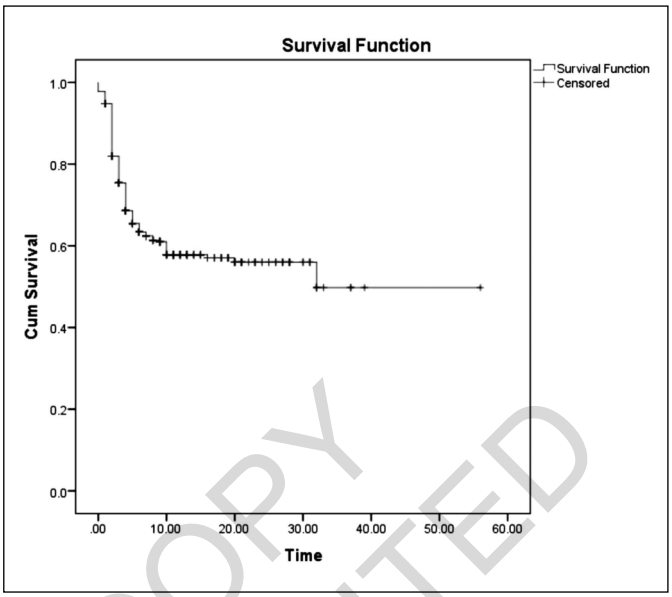

Fig. 2: PDAC curve of patients diagnosed with DM after 60 years of age.

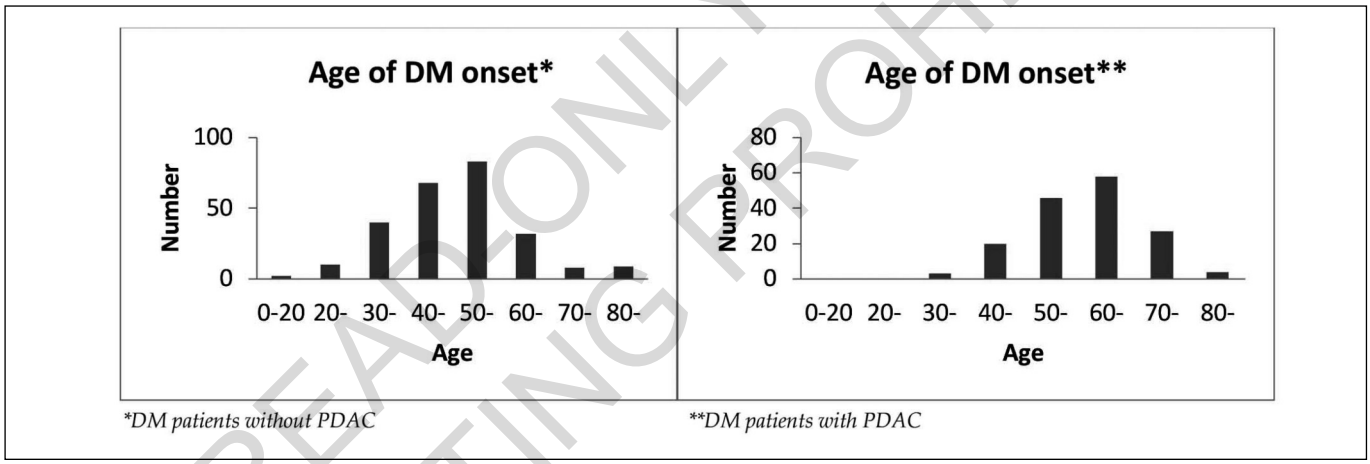

Fig. 3: Age distribution of DM diagnosis in patients with and without PDAC.

While 127 (87%) of 146 patients with high CA 19-9 levels were diagnosed with PDAC, 31 (12%) of 256 patients with normal CA 19-9 levels had PDAC. A statistically significant correlation was found between CA 19-9 level and PDAC (p<0.0001) (Table I).

The cut-off value of age was calculated as 60 according to the ROC curve analysis based on PDAC (Fig. 1). Area under the curve (AUC), and test performance (sensitivity and specificity) for an optimal cut-off value are shown in Table II. The receiver operating characteristic (ROC) curve analysis shows that the cut-off value of age was 60 (AUC:0.753, 95% CI 0.70–0.79, p<0.001) (Table II).

PDAC was detected in 89 (68%) of 130 patients diagnosed as DM after 60 years of age, and in 69 (25%) of 272 patients diagnosed as DM before 60 years of age. A statistically significant relationship was found between the diagnosis of DM after the age of 60 and the incidence of PDAC (p<0.001) (Table III).

In the univariate logistic regression test, the risk of PDAC increased 8.5 times with the onset of DM after the age of 60 (≥60 vs <60 HR = 8.54, 95% CI 5.66-12.90, p <0.001) (Table IV). In patients had DM after the age of 60 and were subsequently diagnosed with PDAC, the time between the diagnosis of DM and the diagnosis of PDAC peaked at 32 months (95% CI 27.90-35.56) (Fig. 2).

DM onset age peaked around 50 years old in the group without PDAC and around 60 years old in the group with PDAC (Fig. 3).

Discussion

The relationship between PDAC and DM is often the subject of research. Long-term DM has been found to be a risk factor for PDAC [15,16]. On the other hand, it has been shown that DM may be a result of PDAC [17,18]. The findings suggest that there is a two-way causal relationship between DM and PDAC. The high mortality of PDAC and the possibility of curative treatment in the early stage increases the importance of markers that can be used in asymptomatic patients. Only 1-2% of new-onset DM patients are expected to develop PDAC within 3 years [19], so screening for PDAC doesn't seem practical and economically viable for all newly diagnosed DM patients. In this case, "Which of the patients with DM should be screened for pancreas?" can be asked.

Despite the classical knowledge that there is a significant relationship between advanced age and PDAC in the literature [1,13,20,21], no relation was found between age and PDAC in our study (Table I). Although all of our patients are diagnosed with DM, there is no such distinction in other studies. We think this may be the reason for the difference in results. Similar to the literature, there was a significant relationship between male gender and PDAC frequency [1] (Table I).

In our study, a significant relationship was found between CA 19-9 height and frequency of PDAC (Table I). However, 95 of 158 patients with PDAC were metastatic or locally advanced and CA 19-9 levels were not measured when DM was diagnosed, limiting our study. Based on the findings in our study, we think that there is not enough evidence to use CA 19-9 as a screening test in the early diagnosis of PDAC. Similarly, although there are many studies investigating the relationship between PDAC and CA 19-9 level, the findings are insufficient to be used as a screening test alone in asymptomatic patients [22-24].

In our study, the relationship between the age of onset of DM and the risk of PDAC was evaluated by ROC curve analysis and the cut-off value was found to be 60 years (Fig. 1). It was calculated that the incidence of PDAC increased and 8.5-fold increased risk compared to patients diagnosed with DM after 60 years of age and before 60 years of age (≥60 vs <60 HR = 8.54, 95% CI 5.66-12.90, p<0.0001) (Table IV). It has been reported that PDAC increases with advanced age and peaks between 60-80 years of age [1,13,20,21]. However, no relationship was found between age and PDAC in our patient group, all diagnosed with DM. On the other hand, it is noteworthy that the age of DM onset is associated with increased risk. The onset of DM peaks around 60 years of age in patients diagnosed with PDAC, while peaks around 50 years in patients without PDAC support that late-onset DM may be a marker for PDAC (Fig. 3). In patients had DM after the age of 60 and were subsequently diagnosed with PDAC, the time between the diagnosis of DM and the diagnosis of PDAC peaked at 32 months (95% CI 27.90-35.56) (Fig. 2). According to the study of Chari et al, the prevalence of DM among patients with PDAC was around 40% and half of the patients had a diagnosis of DM 2 years or less early [17]). In the study of Mizuno et al, no PDAC has been observed in a 2-year period in any patient diagnosed with DM before the age of 55, while 33% of patients diagnosed with DM after the age of 55 have been reported to develop PDAC within 2 years [25]. Early diagnosis is very important in diseases such as PDAC that lose the chance of surgery when it is diagnosed late, has a high mortality, has a long hospital stay and has a high financial burden. Although the relationship between advanced age and PDAC has been frequently investigated, the relationship between DM onset age and PDAC has been subject to much less study. Our study and other similar results showed that DM onset age may be a marker for PDAC. It is very important to evaluate patients with advanced DM in terms of PDAC. Providing early diagnosis in this way may contribute to prolonging survival by detecting patients at an early stage. DM start time is as important as the bidirectional relationship between DM and PDAC. Increased risk should be kept in mind in patients diagnosed with DM over 60 years of age and PDAC should be evaluated.

Conclusion

Our study showed that PDAC risk increased 8.5 times in patients diagnosed with DM after age 60. In PDAC, early diagnosis is very important to prolong survival. In patients with DM onset after the age of 60, we recommend keeping in mind the increased risk of PDAC and evaluating these patients for PDAC, even if they are asymptomatic.

Riassunto

Il cancro al pancreas è l'undicesimo tumore più comune al mondo. L'importanza della diagnosi precoce e del trattamento per il trattamento curativo è molto alta. Molti studi hanno dimostrato una relazione tra diabete mellito (DM), fumo, fattori genetici, obesità, abitudini alimentari e vita sedentaria e adenocarcinoma duttale pancreatico (PDAC).

In questo studio, abbiamo mirato a indagare la relazione tra età di insorgenza del DM e PDAC.

Materiali e Metodi: 158 pazienti con PDAC e DM sono stati confrontati con 244 pazienti con DM nel gruppo di controllo. Abbiamo analizzato retrospettivamente i fattori di rischio PDAC con un focus sull'età di insorgenza del DM.

Risultati: È stato calcolato che il rischio di PDAC è aumentato di 8,5 volte nei pazienti con diagnosi di DM

dopo i 60 anni di età rispetto a quelli con diagnosi di DM prima dei 60 anni di età (HR = 8,54, IC 95% 5,66-12,90, p <0,0001) . L'intervallo tra la diagnosi di DM e la diagnosi di PDAC ha raggiunto il picco a 32 mesi (IC 95% 27,90-35,56). Quando è stata valutata l'età di insorgenza del DM, è stato osservato che i picchi erano di circa 50 anni nel gruppo senza PDAC e di 60 anni nel gruppo con PDAC.

CONCLUSIONE: nei pazienti con insorgenza di DM dopo i 60 anni, si consiglia di tenere presente l'aumento del rischio di PDAC e di valutare questi pazienti per PDAC, anche se sono asintomatici.

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