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Original Article

CEA and CA 19-9 combined tumor marker index as a prognostic tool for metastatic pancreatic cancer: is two better than one?

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Abstract: Metastatic pancreatic cancer (PC) is one of the cancers with the worst prognosis, and prognostic tests are lacking in this population. If an effective prognostic indicator can be identified, the patient population can be monitored more closely. This retrospective study aimed to investigate the prognostic impact of tumor marker index (TMI) in patients with metastatic PC. Patients diagnosed with metastatic PC at Aydın Adnan Menderes University between 2019 and 2024 were included in the study. Demographic data, tumor marker levels, and treatment received were recorded. The prognostic value of TMI was determined as 3.15 using the receiver operating characteristic (ROC) method. Progression-free survival (PFS) and overall survival (OS) were recorded. 218 metastatic PC patients with a median follow-up duration of 10.81 months were included in the study. The median PFS was 7.26 months for the High TMI group, while it was 10.76 months for the Low TMI group (P=0.003). The median OS of patients with high TMI was 9.3 months, which was significantly lower than the 17.9 months observed in the low TMI group (P<0.001). TMI is a simple and, cost-effective prognostic tool for metastatic PC, and a higher TMI is associated with poorer survival outcomes.

Keywords: Carcinoembryonic antigen, carbohydrate antigen 19-9, tumor marker index, metastatic pancreatic cancer

Introduction

Pancreatic cancer (PC) is one of the most common cancers of the digestive system and is an extremely aggressive malignant tumor [1]. Early diagnosis of PC is difficult, and it is mostly discovered at a metastatic stage that cannot be resected [2]. It is relatively rare compared to other solid organ cancers, but ranks 6th in the cumulative mortality rate [1]. It is estimated that by 2030, PC will be the second leading cause of cancer-related deaths in the United States of America [3]. Pancreatic ductal adenocarcinoma is the most common subtype of PC, and the five-year overall survival (OS) rate of <8% [4]. Median OS for metastatic PC is only 3 months [1]. Currently, despite the identification of proto-oncogenes such as BRCA and PALB2, there is a lack of a promising prognostic marker regarding prognosis.

In recent years, it has been suggested that chronic inflammatory and immune responses play significant roles in the progression and development of PC. Routine indicators of the systemic inflammatory response are circulating leukocyte and acute phase proteins. It has been reported that measurements of leukocytes, including neutrophil, lymphocyte, and monocyte counts, as well as levels of acute phase proteins such as C-reactive protein, have prognostic value in many types of cancer, including PC [5]. Because of this relationship, several inflammation-based scores such as the neutrophil-to-albumin ratio and the hemoglobin, albumin, lymphocyte, and platelet combined index (HALP) have emerged as prognostic tools for PC and various other malignancies [6-8]. In addition, tumor-associated proteins secreted into the peripheral circulation by cancerous tumors also being studied as non-inva-

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sive biomarkers in clinical practice to diagnose cancer, assess tumor progression, and predict prognosis [9]. The commonly used carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) have been reported to be useful PC tumor markers [10]. In a study conducted on patients with metastatic colorectal cancer (CRC), high CA 19-9 levels were associated with a more aggressive disease course, weaker response to treatment, and decreased OS in cancer patients [11]. However, the predictive value of these biomarkers in metastatic PC remains unclear. Therefore, the development of easily accessible, cost-effective, and reliable prognostic markers may help personalize treatments and potentially extend lifespan.

The prognostic significance of CA 19-9 and CEA, which are routinely accessible and frequently used tumor markers in clinical practice, is well known. Numerous studies have demonstrated the potential prognostic value of combining these two tumor markers [12, 13]. In recent years, interest in this field has increased, and significant studies emphasizing the role of combined tumor marker indices have been conducted. For example, a tumor marker index (TMI) derived from cytokeratin 19 fragment (CYFRA21-1) and CEA have been found to be poor prognostic indicators in non-small cell lung cancer (NSCLC) [14]. In a retrospective study, Kamada et al. evaluated the prognostic significance of a newly developed TMI combining CEA and CA 19-9 in 306 patients with stage 1-3 CRC who underwent surgery [13]. Similarly, İlhan et al. evaluated the effectiveness of an innovative TMI consisting of CEA and CA 19-9 in predicting treatment response and long-term disease prognosis in metastatic CRC. These findings indicate that TMI is a simple, accessible, cost-effective, and valuable index with poor prognostic significance for metastatic CRC [15]. However, the sensitivity and specificity of combined tumor marker use remains limited and requires further research.

This study aims to evaluate the effectiveness of an innovative TMI consisting of CEA and CA 19-9 in predicting disease prognosis in metastatic PC, by comparing it with other established prognostic factors. To the best of our knowledge, this is the first study of this subject in metastatic PC.

Materials and methods

Study population and data collection

Our study was designed as a retrospective study and included 218 patients diagnosed with metastatic PC at our hospital (Aydın Adnan Menderes University Medical Oncology Clinic) between January 2019 and August 2024. Patients aged >18 years with histopathologically confirmed metastatic PC were included. Both de novo and recurrent metastatic cases were deemed eligible for inclusion. Patients under 18 years of age, those without a pathological diagnosis, those who had not received any treatment at the metastatic stage, or those whose data could not be reliably obtained retrospectively were excluded from the study. In addition to basic demographic information such as age and gender, clinically significant details such as disease pattern, tumor location, treatments received, and sites of metastasis were meticulously recorded. CEA, CA 19-9 obtained immediately before initiating first-line treatment at the time of metastatic diagnosis, the date of disease diagnosis, treatments received by the patients, date of progression, and final outcomes were comprehensively recorded through review of hospital databases and patient files.

Creation of indexes in the study

The primary objective of this study is to assess the prognostic impact of TMI on progression-free survival (PFS) and OS. PFS is defined as the time from the date of diagnosis of metastatic disease to the date of progression, death without progression, or last follow-up. OS is defined as the time from the date of diagnosis to the date of death or the date of last follow-up for patients who are still alive.

The cutoff values for CEA and CA 19-9 were 5.0 ng/mL and 37.0 U/mL, respectively. TMI is defined as the geometric mean of the normalized CEA and CA 19-9. Normalization was performed by dividing the individual tumor marker values by their respective laboratory cutoff values. In summary, TMI was calculated using the following formula, as described the previous literature.

$$TMI = \sqrt{\frac{CEA\,(ng/mL)}{5.0} \times \frac{CA19\text{-}9\,(U/mL)}{37.0}}$$

In our study, the TMI cut-off value was determined using receiver operating characteristic (ROC) analysis at optimal specificity and sensitivity. A cutoff value of ≥3.15 has been determined for TMI [area under the curve (AUC): 0.668; 95% confidence interval (CI): 0.559-0.778, P=0.022, sensitivity: 63.3%, specificity: 64.7%]. Based on this cutoff value, patients were divided into two main groups: high TMI (TMI ≥3.15) and low TMI (TMI <3.15), and analyses were conducted accordingly.

Statistical analysis

Statistical analyses were performed using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables, and as mean ± SD and Median (min-max) for continuous variables. An independent t-test was used for comparisons between paired groups. ROC Curve analysis was used to assess the predictive ability of various indices for mortality. Pearson's chi-squared test and Fisher's exact test were used to compare categorical variables. The Kaplan-Meier method was used to compare survival and PFS among the clinical groups. Finally, the results of the multivariate Cox regression for the impact of various clinical variables on mortality and progression risk are presented. Statistical significance was set at *p*-value of <0.05.

This study was planned and conducted in accordance with Good Clinical Practices and the Declaration of Helsinki and was approved by the ethics committee of Aydın Adnan Menderes University Hospital (approval date and no: 20.12.2024/E-53043469-050.04-658383).

Results

Population characteristics

In total, 218 patients were included in this study. However, because the tumor markers of 194 patients were accessible, the TMI index was calculated for these 194 patients. The mean age of the entire population was 69.85±10.97. Of the patients whose TMI was calculated, 122 (62.8%) were male and 72 (37.2%) were female. 133 (61%) of the patients had an ECOG score of 0 or 1. 148 (67.9%) of the patients had de novo metastatic disease. The mean CEA level was 81.98±359.22 ng/mL, with a median of 6.64 ng/mL (range: 1.08-4111.13). The mean CA 19-9 level was 2916.22±6944.63 U/mL, with a median of 501.34 U/mL (range: 2.31-65915.70).

Optimal cutoff values

ROC analysis was performed to determine mortality in the most appropriate manner. The cut-off value for TMI was found to be 3.15 for TMI (AUC=0.668; 95% CI 0.559-0.778, 0.022; sensitivity 63.3%; specificity, 64.7%). A TMI <3.15, it was classified as low-TMI, and a TMI ≥3.15, as high-TMI.

Survival analyzes

In our study, patients were divided into two main groups according to TMI categories. While there were 118 patients in the high-TMI group, there were 76 patients in the low-TMI group. The proportion of de novo metastatic patients was 86 (72.9%) in the TMI-high group, while it was 41 (53.9%) in the TMI-low group, and it was significantly higher in the TMI-high group compared to the TMI-low group (P=0.007). The proportion of patients receiving adjuvant chemotherapy was 93 (78.8%) in the high TMI group, while it was 49 (64.5%) in the low TMI group, and it was significantly higher in the high TMI group compared to the low TMI group (P=0.007). The median follow-up period in the high-BMI group was 12.03±12.86, whereas in the low-BMI group, the median follow-up period was 21.82±19.19. The median follow-up in the TMI-low group is significantly higher than in the TMI-high group (P<0.001). The two groups were homogeneously distributed, and the general characteristics and demographic information of the patients are shown in detail in **Table 1**.

Progression-free survival

The median follow-up period of the patients in this study was 10.81 (0.17-96.23) months, and the median PFS was 8.76 (7.23-10.29) months. The 5-year PFS rate was 5.7%. The median of the TMI-high group was 7.26 (5.60-8.92) months, while the median PFS of the TMI-low group was 10.76 (7.00-14.52) months. The median PFS of the TMI-high group was significantly lower than that of the TMI-low group (P=0.003) (**Figure 1**).

Table 1. Comparison of sociodemographic and clinical characteristic data according to TMI groups

Variables	TMI			p
	Total N=218	Low N=76	High N=118	
Age				
Mean ±	69.85±10.97	69.88±10.70	70.07±10.71	0.902
≤65	78 (35.8)	30 (39.5)	38 (32.2)	0.300
>65	140 (64.2)	46 (60.5)	80 (67.8)	
Gender				
Female	72 (37.2)	28 (36.8)	44 (37.3)	0.950
Male	122 (62.8)	48 (63.2)	74 (62.7)	
ECOG				
0	46 (21.1)	15 (19.7)	26 (22)	0.900
1	87 (39.9)	32 (42.1)	49 (41.5)	
2	54 (24.8)	21 (27.6)	28 (23.7)	
3	31 (14.2)	8 (10.5)	15 (12.7)	
Cigarette				
No	102 (46.8)	32 (42.1)	61 (51.7)	0.192
Yes	116 (53.2)	44 (57.9)	57 (48.3)	
Alcohol				
No	167 (76.6)	59 (77.6)	92 (78)	0.956
Yes	51 (23.4)	17 (22.4)	26 (22)	
DM				
No	126 (57.8)	39 (51.3)	70 (59.3)	0.273
Yes	92 (42.2)	37 (48.7)	48 (40.7)	
HT				
No	114 (52.3)	41 (53.9)	58 (49.2)	0.514
Yes	104 (47.7)	35 (46.1)	60 (50.8)	
CAD				
No	180 (82.6)	61 (80.3)	98 (83.1)	0.622
Yes	38 (17.4)	15 (19.7)	20 (16.9)	
COPD				
No	206 (94.5)	71 (93.4)	112 (94.9)	0.754
Yes	12 (5.5)	5 (6.6)	6 (5.1)	
CKD				
No	211 (96.8)	72 (94.7)	115 (97.5)	0.436
Yes	7 (3.2)	4 (5.3)	3 (2.5)	
Metastatis Type				
Denova	148 (67.9)	41 (53.9)	86 (72.9)	0.007
Recurrent	70 (32.1)	35 (46.1)	32 (27.1)	
Adjuvant CT				
No	164 (75.2)	49 (64.5)	93 (78.8)	0.028
Yes	54 (24.8)	27 (35.5)	25 (21.2)	
Stage in Diagnosis				
Stage-1	7 (3.2)	3 (3.9)	4 (3.4)	0.067
Stage-2	41 (18.8)	20 (26.3)	19 (16.1)	
Stage-3	23 (10.6)	12 (15.8)	10 (8.5)	
Stage-4	147 (67.4)	41 (53.9)	85 (72)	

While the PFS of patients with ECOG 0 was 10.60 (7.75-13.44) months, it was found to be 9.33 (8.23-10.43) months for patients with ECOG 1, and 6.00 (4.97-7.02) months for patients with ECOG 2. The PFS of patients with ECOG 0 or 1 was longer and statistically significant compared to the PFS of patients with ECOG 2. The median PFS of relapsed metastatic patients was 16.13 (11.73-20.53) months, while the median PFS of de novo metastatic patients was 3.36 (4.73-8.00) months. The PFS of relapsed metastatic patients was higher than the median PFS of de novo metastatic patients and this difference was statistically significant (P<0.001). The median PFS of the group receiving adjuvant chemotherapy was 19.00 (14.28-23.71) months, which was 6.00 (4.95-7.04) months longer than the median PFS of the group not receiving adjuvant chemotherapy, and this difference was statistically significant (P<0.001). The median PFS of the group without liver metastasis was 10.60 (5.01-16.18) months, while the median PFS of the group with liver metastasis was 7.50 (5.50-9.49) months. The median PFS of the group with liver metastasis was lower compared to those without liver metastasis and this was statistically significant (P= 0.037). According to the univariate analysis, PFS is shown in **Table 2**.

Liver Metastasis				
No	54 (24.8)	23 (30.3)	29 (24.6)	0.383
Yes	164 (75.2)	53 (69.7)	89 (75.4)	
Lung Metastasis				
No	146 (67.0)	50 (65.8)	76 (64.4)	0.844
Yes	72 (33.0)	26 (34.2)	42 (35.6)	
Brain Metastasis				
No	216 (99.1)	75 (98.7)	117 (99.2)	0.631
Yes	2 (0.9)	1 (1.3)	1 (0.8)	
Bone Metastasis				
No	170 (78.0)	57 (75)	92 (78)	0.633
Yes	48 (22.0)	19 (25)	26 (22)	
Peritoneum Metastasis				
No	137 (62.8)	50 (65.8)	70 (59.3)	0.365
Yes	81 (37.2)	26 (34.2)	48 (40.7)	
Other Metastasis				
No	151 (69.3)	51 (67.1)	81 (68.6)	0.822
Yes	67 (30.7)	25 (32.9)	37 (31.4)	
Tumor Location				
Head	143 (65.6)	51 (67.1)	76 (64.4)	0.368
Tail	49 (22.5)	19 (25)	25 (21.2)	
Others	26 (11.9)	6 (7.9)	17 (14.4)	
CT Line				
1.Line	100 (52.6)	32 (47.8)	61 (57)	0.586
2.Line	53 (27.9)	20 (29.9)	29 (27.1)	
3.Line	24 (12.6)	10 (14.9)	10 (9.3)	
4.Line	13 (6.9)	5 (7.5)	7 (6.5)	
First Line Response				
CR	38 (21.5)	18 (27.7)	17 (17.9)	0.096
PR	51 (28.8)	22 (33.8)	24 (25.3)	
SD	6 (3.4)	2 (3.1)	2 (2.1)	
PD	82 (46.3)	23 (35.4)	52 (54.7)	

CAD: Coronary artery disease, CKD: Chronic kidney disease, COPD: Chronic obstructive polmoary disease, CR: Complete response, CT: Chemotherapy, DM: Diabetis mellitus, HT: Hypertension, PD: Progression Disease, PR: Partial response, SD: stabil Disease, TMI: Tumor marker index.

According to the results of the univariate analysis, we found that BMI, ECOG performance status, disease status at diagnosis, and the presence of liver metastasis had an impact on survival. Therefore, multivariate Cox regression analysis was performed. The PFS was found to be lower in the BMI-Low group compared to the BMI-High group [HR (95% CI) =1.69 (1.16-2.46) (P=0.005)].

According to the PFS of patients with ECOG 0, the PFS of patients with ECOG 1 [HR (95% CI) =1.81 (1.08-3.02) (P=0.022)] and the PFS of those with ECOG 2 [HR (95% CI) =3.04 (1.69-5.45) (P<0.001)] were lower. According to the PFS of de novo metastatic patients, the PFS of relapsed metastatic patients was higher, but this was not statistically significant [HR (95% CI) =0.32 (0.04-2.55) (P=0.286)]. Compared to the PFS of patients who did not receive adjuvant chemotherapy, the PFS of patients who received adjuvant chemotherapy was better, but this difference was not statistically significant [HR (95% CI) =0.53 (0.24-1.14) (P=0.108)]. No difference was observed between the group with liver metastasis and the group without [HR (95% CI) =0.70 (0.45-1.07) (P=0.1)]. According to the multivariate analysis, PFS is shown in **Table 3**.

Overall survival

The median OS of all patients in the population was 11.46 (9.58-13.34) months. While the 2-year OS was 21.9%, the 5-year OS was found to be 3.5. The median OS of the TMI-High group was 9.30 (6.05-12.54) months, while the median OS of the TMI-Low group was 17.90 (11.26-24.53) months. The median OS of the TMI-High group was significantly lower than that of the TMI-Low group (P<0.001) (**Figure 2**).

The OS of patients with ECOG 0 was found to be 15.23 (11.00-19.46) months, while it was 13.13 (10.92-15.34) months for patients with ECOG 1, and 10.96 (7.87-14.05) months for patients with ECOG 2. The OS of patients with and ECOG 0 or 1 was significantly longer than that of patients with ECOG 2 (P<0.001). The median OS of recurrent metastatic patients was 22.10 (17.03-27.16) months, while the median OS of de novo metastatic patients was

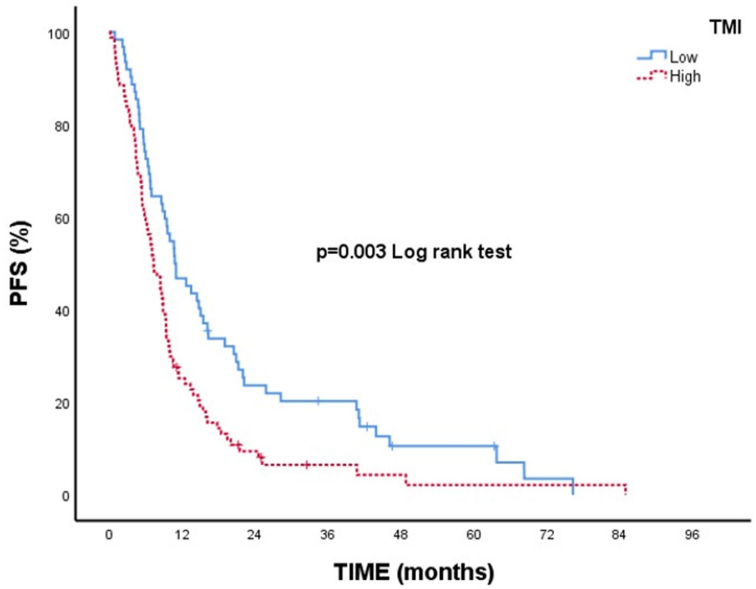

Figure 1. PFS according to TMI.

Table 2. Comparisons of patient PFS

PFS (months)	2 years %	5 years %	Median (95% CI)	p
Total	15.1	5.7	8.76 (7.23-10.29)	
Age				
≤65	19.0	11.0	9.10 (8.12-10.08)	0.189
>65	12.2	3.4	8.40 (6.34-10.45)	
Gender				
Female	15.2	9.1	9.33 (7.41-11.24)	0.162
Male	15.1	4.3	8.43 (6.26-10.60)	
ECOG				
0	30.6	17.5	10.60 (7.75-13.44)	0.002
1	12.5	2.1	9.33 (8.23-10.43)	
2	7.7	5.1	6.00 (4.97-7.02)	
3	9.1	-	3.50 (0.62-6.37)	
Cigarette				
No	12.6	4.7	7.83 (6.12-9.54)	0.712
Yes	17.3	6.9	9.13 (8.07-10.19)	
Alcohol				
No	15.5	5.8	8.56 (6.82-10.30)	0.935
Yes	13.9	-	9.10 (8.00-10.19)	
DM				
No	13.3	7.1	7.50 (5.75-9.24)	0.328
Yes	17.0	4.3	9.23 (7.85-10.61)	
HT				
No	16.4	4.9	8.80 (7.00-10.59)	0.948
Yes	13.4	6.0	8.40 (6.14-10.65)	
CAD				
No	16.0	5.3	8.63 (7.11-10.15)	0.684
Yes	9.5	9.5	8.83 (4.04-13.61)	

5.63 (4.84-6.42) months. The OS of recurrent metastasis was significantly higher than the median OS of de novo metastatic patients (P<0.001). The median OS of the group receiving adjuvant chemotherapy was 23.26 (17.93-28.59) months, which was 7.36 (5.32-9.40) months longer than the median OS of the group not receiving adjuvant chemotherapy, and this difference was statistically significant (P<0.001). The median OS for the group without liver metastasis was 19.50 (12.50-26.49) months, while the median OS for the group with liver metastasis was 9.93 (7.37-12.48) months. The median OS of the group with liver metastasis was significantly lower than that of the group without liver metastasis (P=0.004). The OS according to the univariate analysis, is shown in **Table 4**.

In the multivariate analysis, OS was lower in the TMI-High group than in TMI-Low group [HR (95% CI) =2.17 (1.46-3.2) (P<0.001)].

When we performed multivariate analysis for OS, the OS of relapsed metastatic patients was higher than that of de novo metastatic patients; however, this difference was not statistically significant [HR (95% CI) =0.18 (0.02-1.49) (P= 0.113)]. Compared with the OS of patients who did not receive adjuvant chemotherapy, the OS of patients who received adjuvant chemotherapy was significantly better [HR (95% CI) =0.44 (0.20-0.96) (P=0.041)]. Compared to the group without lung metastasis, the group with lung metastasis had better survival [HR (95% CI) =0.63 (0.41-0.97) (P=0.038)]. Overall survival ac-

COPD				
No	15.9	6.0	8.83 (7.43-10.23)	0.054
Yes	-	-	6.20 (4.99-7.40)	
CKD				
No	14.9	6.0	8.76 (7.23-10.30)	0.938
Yes	25.0	-	5.80 (1.68-9.91)	
Metastatis Type				
Denova	5.0	-	3.36 (4.73-8.00)	<0.001
Recurrent	33.7	10.9	16.13 (11.73-20.53)	
Adjuvant CT				
No	6.7	4.5	6.00 (4.95-7.04)	<0.001
Yes	36.6	11.0	19.00 (14.28-23.71)	
Liver Metastasis				
No	29.8	7.4	10.60 (5.01-16.18)	0.037
Yes	11.1	5.1	7.50 (5.50-9.49)	
Lung Metastasis				
No	16.1	6.8	8.56 (6.68-10.45)	0.597
Yes	13.3	3.8	8.83 (5.47-12.19)	
Bone Metastasis				
No	15.8	5.6	8.83 (7.15-10.51)	0.524
Yes	12.8	5.1	8.40 (5.91-10.88)	
Peritoneum Metastasis				
No	16.2	5.8	7.33 (5.23-9.43)	0.420
Yes	13.6	6.1	9.33 (8.07-10.58)	
Other Metastasis				
No	15.1	7.1	8.56 (6.64-10.48)	0.797
Yes	15.6	3.1	8.83 (7.69-9.97)	
Tumor Location				
Head	15.5	4.3	8.83 (7.49-10.16)	0.714
Tail	13.2	10.5	8.43 (3.44-13.41)	
Others	16.7	8.3	5.33 (4.84-5.81)	
CT Line				
1.Line	19.7	11.5	5.80 (2.57-9.02)	0.685
2.Line	9.4	-	9.96 (8.37-11.56)	
3.Line	12.5	4.2	7.26 (4.30-10.22)	
4.Line	23.1	15.4	9.36 (8.42-10.30)	
First Line Response				
CR	23.5	9.4	10.76 (7.71-13.81)	<0.001
PR	25.6	9.9	11.40 (6.35-16.44)	
SD	-	-	8.63 (6.20-11.06)	
PD	6.2	1.2	4.86 (4.06-5.66)	
TMI				
<3,15	23.7	10.5	10.76 (7.00-14.52)	0.003
≥3,15	9.4	2.2	7.26 (5.60-8.92)	

CAD: Coronary artery disease, CI: Confidence interval, CKD: Chronic kidney disease, COPD: Chronic obstructive polmoary disease, CR: Complete response, CT: Chemotherapy, DM: Diabetis mellitus, HT: Hypertension, PD: Progression Disease, PFS: Progression free survival, PR: Partial response, SD: stabil Disease, TMI: Tumor marker index.

cording to the multivariate analysis is shown in **Table 5**.

Discussion

In this study, we aimed to evaluate the prognostic significance of TMI, an innovative and simple-to-apply index, in patients diagnosed with metastatic PC. We demonstrated that TMI, which is created by combining the tumor markers CA 19-9 and CEA, has a significant prognostic value in patients with metastatic PC. The prognosis of patients with TMI-high metastatic PC is poor.

In our study, the most common site of metastasis was the liver region, and as expected in the general population, it appeared more frequently in men. Demographic data were similar among the groups, and our study is consistent with the literatüre [16, 17].

CEA is a tumor marker indicator composed of a glycoprotein in the endodermal epithelium that was first identified in CRC in the 1960s [18]. Historical studies, have shown that CEA can also be found in inflamed and normal tissues, which reduces its sensitivity [19]. Using biological techniques on resected pancreatic cancer tissues, it is possible to characterize of pancreatic cancer cells as well as the excessive expression of growth factors and adhesion molecules [20]. CEA has been found to have low sensitivity and specificity in identifying early-stage pancreatic cancer. At the same time, it has also been observed to be elevated in all gastrointestinal cancers, particularly those with liver metastases [21]. CA

Table 3. Multivariate cox regression results for the risk of progression of various clinical variables

PFS (months)	HR (95% CI)	p
ECOG		0.002
0	ref	
1	1.81 (1.08-3.02)	0.022
2	3.04 (1.69-5.45)	<0.001
3	2.68 (1.12-6.38)	0.026
Metastatis Type		
Denova	ref	
Recurrent	0.32 (0.04-2.55)	0.286
Adjuvant CT		
No	ref	
Yes	0.53 (0.24-1.14)	0.108
Liver Metastasis		
No	ref	
Yes	0.70 (0.45-1.07)	0.100
TMI		
<3.15	ref	
≥3.15	1.69 (1.16-2.46)	0.005

CI: Confidence interval, CT: Chemotherapy, HR: Hazard ratio, TMI: Tumor marker index, PFS: Progression free survival.

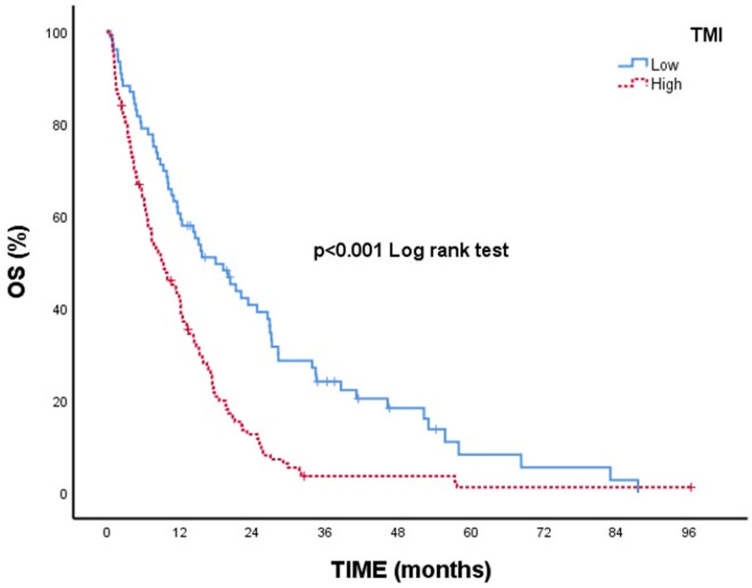

Figure 2. OS according to TMI.

Table 4. Comparisons of patients' OS

OS (months)	2 years %	5 years %	Median (95% CI)	p
Total	21.9	3.5	11.46 (9.58-13.34)	
Age				
≤65	26.9	7.0	13.26 (8.54-17.98)	0.392
>65	19.2	2.2	10.66 (8.39-12.94)	

19-9 was first detected in the blood of a patient with pancreatic cancer in 1982 [22]. CA 19-9 is a Lewis A blood group antigen and may also increase in healthy individuals without pancreatic cancer or in conditions with elevated inflammation [23].

If we look at studies conducted with tumor markers in PC; in a study of pancreatic cancer patients who received chemoradiotherapy, a high level of CA19-9 was found to be a poor prognostic indicator [24]. Correlation between CEA levels and tumor stage has been observed, with high levels indicating unfavorable prognosis in early and metastatic PC [25]. Lower post-treatment CA 19-9 levels predict a greater likelihood of surgical candidacy in non-metastatic pancreatic cancer patients treated with neoadjuvant therapy [26]. Lower CA 19-9 levels (<150) after neoadjuvant therapy are indicative of a more favorable prognosis [27]. Elevated peritoneal CA 19-9 levels are associated with reduced survival in patients with surgically treated pancreatic cancer patients [28]. High CA 19-9 levels in early stage pancreatic cancer are associated with more severe symptoms, increased tumor burden, and worse clinical outcomes than in CA 19-9-negative cases [29]. Among patients with resected pancreatic cancer, elevated CA 19-9 levels were more prominent in younger individuals with poor prognosis, whereas higher CEA levels were observed in older patients with similarly poor outcomes [30]. Although CEA and CA 19-9 show potential as early diagnostic and prognostic biomarkers in early-stage pancreatic cancer, the study's

Gender				
Female	28.4	4.9	15.10 (11.39-18.80)	0.147
Male	18.5	3.5	10.10 (7.26-12.57)	
ECOG				
0	32.0	11.4	15.23 (11.00-19.46)	<0.001
1	23.3	2.3	13.13 (10.92-15.34)	
2	18.1	-	10.96 (7.87-14.05)	
3	9.7	-	2.06 (1.40-2.73)	
Cigarette				
No	22.8	3.0	11.46 (8.72-14.20)	0.799
Yes	21.3	3.8	11.36 (8.81-13.91)	
Alcohol				
No	22.8	4.2	10.96 (8.89-13.04)	0.598
Yes	19.4	-	12.43 (9.26-15.59)	
DM				
No	19.2	2.4	9.83 (6.46-13.20)	0.069
Yes	25.6	4.9	12.16 (9.72-14.61)	
HT				
No	24.0	2.0	12.13 (8.36-15.90)	0.913
Yes	19.6	4.9	10.26 (7.71-12.82)	
CAD				
No	21.0	3.2	10.96 (8.74-13.19)	0.661
Yes	26.1	4.8	11.63 (4.88-18.37)	
COPD				
No	22.8	3.7	11.46 (9.75-13.18)	0.340
Yes	8.3	-	5.76 (0.00-21.04)	
CKD				
No	21.7	3.9	11.46 (9.59-13.33)	0.724
Yes	28.6	-	10.66 (4.08-17.25)	
Metastatis Type				
Denova	10.8	-	5.63 (4.84-6.42)	<0.001
Recurrent	45.0	10.3	22.10 (17.03-27.16)	
Adjuvant CT				
No	12.7	0.9	7.36 (5.32-9.40)	<0.001
Yes	49.0	10.9	23.26 (17.93-28.59)	
Liver Metastasis				
No	37.6	6.2	19.50 (12.50-26.49)	0.004
Yes	16.9	2.6	9.93 (7.37-12.48)	
Lung Metastasis				
No	18.1	3.1	9.53 (6.94-12.12)	0.021
Yes	29.5	4.8	15.10 (12.45-17.74)	
Bone Metastasis				
No	19.9	2.8	10.26 (8.06-12.46)	0.245
Yes	29.2	5.4	14.26 (9.01-19.51)	
Peritoneum Metastasis				
No	21.1	3.6	9.53 (6.69-12.37)	0.528
Yes	23.4	2.7	14.23 (10.64-17.82)	
Other Metastasis				
No	19.0	3.9	9.33 (6.89-11.77)	0.076
Yes	28.5	2.6	15.13 (9.56-20.69)	

limited sample size (n=50) must be considered when interpreting the results [31]. Patients with periampullary carcinoma and a high CA 19-9/CEA ratio exhibited a median OS of 28 months, in contrast to 93 months in those with a low ratio [32]. Higher CA 19-9 levels correlate with poorer overall survival in patients with metastatic pancreatic cancer [33]. In the context of second-line gemcitabine plus nab-paclitaxel treatment for metastatic pancreatic cancer, elevated CEA levels predict worse PFS [34].

The concept of TMI was first introduced by Muley et al. as a marker, calculated using the geometric mean of CYFRA 21-1 and CEA. Looking at the literature; in this study involving patients with early-stage NSCLC, shorter OS was observed in the group with high TMI and it was interpreted as a negative prognostic factor [35]. In studies involving early-stage adenosquamous NSCLC [35], and NSCLC [36], patients, where TMI was calculated and evaluated using Muley's method, TMI was found to be associated with poor PFS and OS. Lower TMI levels are associated with improved survival in patients with metastatic gastric cancer [36]. In two other studies conducted on patients with operable esophageal squamous cell carcinoma (SCC), TMI was calculated by taking the geometric mean of CYFRA 21-1 and squamous cell carcinoma antigen (SCC-Ag), and the 5-year survival was found to be better in the TMI-Low group than in TMI-High group. At the same time, it was shown that TMI is more predictive than CYFRA 21-1 and SCC-Ag. In another study involving pa-

Tumor Location				
Head	23.0	4.0	12.36 (10.24-14.48)	0.137
Tail	20.9	5.6	10.46 (5.47-15.45)	
Others	17.6	-	6.76 (1.81-11.72)	
CT Line				
1.Line	15.1	3.0	6.16 (4.25-8.01)	<0.001
2.Line	23.5	-	15.86 (12.44-19.28)	
3.Line	37.5	7.8	16.16 (11.76-20.56)	
4.Line	61.5	15.4	25.70 (18.22-33.17)	
First Line Response				
CR	45.3	11.1	20.30 (12.21-28.38)	<0.001
PR	32.6	3.3	16.46 (12.90-20.02)	
SD	66.7	-	26.83 (0.00-54.33)	
PD	7.3	1.2	6.56 (4.73-8.40)	
TMI				
<3.15	40.7	8.3	17.90 (11.26-24.53)	<0.001
≥3.15	12.7	1.2	9.30 (6.05-12.54)	

CAD: Coronary artery disease, CI: Confidence interval, CKD: Chronic kidney disease, COPD: Chronic obstructive polmoary disease, CR: Complete response, CT: Chemotherapy, DM: Diabetis mellitus, HT: Hypertension, OS: Overall survival, PD: Progression Disease, PR: Partial response, SD: stabil Disease, TMI: Tumor marker index.

Table 5. Multivariate cox regression results for the mortality risk of various clinical variables

OS (months)	HR (95% CI)	p
ECOG		0.082
0	ref	
1	1.33 (0.82-2.17)	0.239
2	1.89 (1.10-3.26)	0.021
3	2.19 (0.92-5.19)	0.073
Metastatis Type		
Denova	ref	
Recurrent	0.18 (0.02-1.49)	0.113
Adjuvant CT		
No	ref	
Yes	0.44 (0.20-0.96)	0.041
Liver Metastasis		
No	ref	
Yes	0.85 (0.55-1.32)	0.490
Lung Metastasis		
No	ref	
Yes	0.63 (0.41-0.97)	0.038
TMI		
<3.15	ref	
≥3.15	2.17 (1.46-3.20)	<0.001

CI: Confidence interval, CT: Chemotherapy, HR: Hazard ratio, OS: Overall survival, TMI: Tumor marker index.

tients with early-stage NSCLC, the TMI was calculated by taking the geometric mean of CEA and Krebs von den Lungen-6 levels. The 5-year disease-free survival rate was found to be 82.9% for the TMI-low group, while it was 47.5% for the TMI-high group [37]. In metastatic colorectal cancer, higher TMI levels were associated with poorer overall survival [15]. In operated colorectal cancer patients, higher TMI levels were associated with shorter PFS and were more predictive of 5-year mortality than CEA and CA 19-9 [13]. In this study, PFS was found to be lower in the TMI-High group (7.26 months) than in the TMI-Low group (10.76 months) [HR (95% CI) =1.69 (1.16-2.46) (P=0.005)]. OS was found to be lower in the TMI-High group (9.3 months) than in TMI-Low group (17.9 months) [HR (95% CI) =2.17 (1.46-3.2) (P<0.001)]. In conclusion, TMI was associated with poor survival and demonstrated prognostic value as a simple, inexpensive, and practical index for use in patients with metastatic PC.

To our knowledge, this study is the first to demonstrate the prognostic impact of TMI in patients with metastatic pancreatic cancer.

Limitations

First, our study is retrospective, and this is the most important limitation of our study. The fact that recurrent metastatic patients received different treatments during the adjuvant period and that de novo metastatic patients were significantly more prevalent has made our population heterogeneous.

At the same time, since there is no standard cut-off value, a ROC analysis was performed, and with a sensitivity and specificity of approximately 60%, the reliability of the results was reduced.

Conclusion

We found a negative relationship between the TMI obtained using CEA and CA 19-9 and both PFS and OS. If a prospective study is designed with a larger number of patients, this index could be used for prognosis determination owing to its simplicity, practicality, and low cost.

Disclosure of conflict of interest

None.

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