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ORIGINAL ARTICLE

Prognostic factors and prognostic index for patients with advanced pancreatic cancer: Single center experience and review of the literature

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Summary

Purpose: *Despite the developments in diagnostic techniques and therapeutic methods in recent years, the prognosis of advanced pancreatic cancer is still very poor. The purpose of our study was to research the prognostic importance of easily-accessible clinical and laboratory parameters used in clinical practice at the time of diagnosis for patients with advanced pancreatic cancer, to create a prognostic index model via the independent prognostic factors that will be identified and to separate patients into risk groups.*

Methods: *This study included 118 patients with advanced pancreatic cancer the medical records of whose were retrospectively reviewed.*

Results: *The median overall survival of patients was 4.4 months, with 6-month and 12-month overall survival rates 40% and 22%. Weight loss, low albumin level, liver metastasis, presence of ascites and not receiving chemotherapy were statistically significantly associated with shorter survival ($p<0.05$). The regression coefficients obtained for these 5 variables were used to calculate the prognostic index. Patients were divided into two groups as prognostic index value ≤2 (low-risk group) and prognostic index value >2 (high-risk group). The median overall survival in the low-risk group was 8.8 months, while the median overall survival in the high-risk group was 2.6 months (log-rank $p<0.001$).*

Conclusions: *Prognostic index models created with easily accessible clinical and laboratory parameters for advanced pancreatic cancer, as in our study, may aid clinicians in daily clinical practice to divide patients into risk groups, determining survival, and creating the most appropriate treatment protocols.*

Key words: *ascites, chemotherapy, liver metastasis, pancreatic cancer, prognostic index, weight loss*

Introduction

Pancreatic cancer is one of the deadliest cancers and is in the 4th place among cancer-related deaths [1]. Surgical resection is the only curative method; however, surgical resection may only be possible in 20% of patients. Most patients are diagnosed in locally advanced or metastatic stage [2-4]. Until 2011, the standard treatment for advanced pancreatic cancer (APC) was single-agent gemcitabine, while 5- fluorouracil, folinic acid, irinotecan and oxaliplatin combination regimen (FOLFIRINOX)

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became standard with the publication of the PRODIGE 4/ACCORD 11 study in 2011. Compared with single-agent gemcitabine, FOLFIRINOX obtained significant survival advantage (6.8 versus 11.1 months) [5,6]. The MPACT study published in 2013 compared single-agent gemcitabine with gemcitabine and nab-paclitaxel combination regimen. The gemcitabine and nab-paclitaxel combination was identified to have longer median overall survival (OS) compared to gemcitabine monotherapy (8.7 months vs. 6.6 months) [7].

Despite the developments in diagnostic techniques and therapeutic methods in recent years, the prognosis of pancreatic cancer is still very poor. Though palliative chemotherapy is shown to lengthen survival, the median OS for current treatments of metastatic pancreatic cancer is less than 1 year and there is considerable toxicity due to current combination regimens [2-7]. As a result, identification of prognostic factors determining patient survival is very important for separation of patients into risk groups via these prognostic factors, determination of patients who will benefit from chemotherapy and making decisions about optimal treatment strategies. In our study, the purpose was to research the prognostic importance of easily-accessible clinical and laboratory parameters used in clinical practice at time of diagnosis for locally advanced unresectable and/or metastatic patients, to create a prognostic index model via the independent prognostic factors that will be identified and to separate patients into risk groups.

Methods

This study included 118 patients with locally advanced unresectable and/or metastatic pancreatic adenocarcinoma diagnosed and treated at Dokuz Eylul University Faculty of Medicine, Department of Medical Oncology between 1998-2009. The medical records of these patients were retrospectively reviewed. Registered were patient sex, age, Eastern Cooperative Oncology (ECOG) performance status (PS), smoking history, comorbid diseases, thrombosis history, primary tumor localization (pancreas head, body and tail), metastasis localization, diagnostic biopsy site, presence of ascites, presence of symptoms linked to tumor (jaundice, pain in abdomen or low back, more than 10% weight loss), carbohydrate antigen 19-9 (CA 19-9) levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glumatyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin, albumin, hemoglobin, white blood cell (WBC) and platelet levels at the time of diagnosis and chemotherapy regimens administered. OS was defined as the period from the date of initial chemotherapy to the patient's last visit or date of death. This study was approved by the local ethics committee of the Dokuz Eylul University.

Table 1. Characteristics of patients with advanced pancreatic cancer (APC)

Characteristics	*n (%)*
Gender	
Male	73 (62)
Female	45 (38)
Age, years (median, range)	63 (38-84)
Smoking	
Never	50 (42.4)
Ever	68 (57.6)
Co-morbidity	
DM	35 (29.7)
Others	30 (25.4)
Performance status	
0-1	94 (79.7)
2-3	24 (20.3)
Tumor location	
Head	66 (55.9)
Body/Tail	52 (44.1)
Stage	
III	6 (5.1)
IV	112 (94.9)
Diagnostic biopsy site	
Liver	67 (56.8)
Pancreas	26 (22.0)
Peritoneum	10 (8.5)
Ascites	6 (5.1
Lymph node	4 (3.4)
Lung	4 (3.4)
Subcutaneous nodule	1 (0.8)
Metastatic site	
Liver	86 (72.9)
Lymph node	46 (72.9)
Peritoneum	20 (16.9)
Lung	19 (16.1)
Others	7 (5.9)
Tumor-related symptoms	
Jaundice	30 (25.4)
Abdominal/Back Pain	104 (88.1)
Weight loss ≥10%	57 (48.3)
Palliative surgery	
Biliary by-pass surgery	15 (12.7)
Chemotherapy	
None	31 (26.3)
Gemcitabine + 5FU	63 (53.4)
Gemcitabine	15 (12.7)
5-FU + Folinic acid	6 (5.1)
Others	3 (2.5)

DM: diabetes mellitus; FU: fluorouracil

Statistics

All analyses were performed with SPSS 22.0 for Windows statistical program. The patient survival time was evaluated by the Kaplan-Meier method and log-rank test. Univariate and multivariate analyses were performed using Cox regression method. P<0.05 was considered as statistically significant.

Results

The clinical features of 118 cases with locally advanced unresectable and/or metastatic pancreatic cancer diagnosis at the time of diagnosis are shown in Table 1. Of these cases, 62% were male and 38% female. Median age at diagnosis was 63 years. Of the patients, 57.6% had smoking history and 29.7% had diabetes mellitus. Diagnostic biopsy site was the liver for 57% of patients and the pancreas for 22%. Primary tumor localization was head of pancreas for 56%, and body/tail of pancreas for 44%. Of these patients, 6 (5.1%) were locally advanced unresectable and the remaining 112 (94.9%) had metastatic stage. Liver, lymph nodes, peritoneum and lung metastasis were 73%, 39%, 17% and 16% of patients, respectively. ECOG performance status was 0-1 for 94 patients (79.7%) and 2-3 for 24 patients (20.3%). At the time of diagnosis or during follow-up, 29 patients (24.6%) were identified to have thrombosis. Of the 118 patients with advanced stage pancreatic cancer, 31 (26.3%) had no chemotherapy and 87 (73.7%) had first-line chemotherapy administered with a median of 5 cycles (1-30). Of these patients, 53.4% had gemcitabine and 5-fluorouracil combination, 12.7% had gemcitabine monotherapy, 5.1% had 5-fluorouracil plus folinic acid combination and 2.5% had other therapeutic regimes administered. Of the 94 patients with ECOG PS 0-1, 18 (19.2%) did not receive chemotherapy, while 13 (54.2%) of the 24 patients with ECOG PS 2-3 did not receive chemotherapy. When the clinical features of patients with APC were investigated in the two groups (those receiving chemotherapy and those not receiving it), it was noticed that the percentage of those with ECOG PS 2-3 was significantly higher in the group not receiving chemotherapy compared to the group receiving chemotherapy (41.9% vs. 12.6%; p=0.001). There were no significant differences found for other clinical and laboratory parameters.

Table 2. Univariate analysis of prognostic factors in patients with APC

Parameters	*Median overall survival (months)*	*6-month survival (%)*	*1-year survival (%)*	*Log-rank p*
Gender				0.375
Male	4.07	38	23	
Female	4.93	44	22	
Age, years				0.785
<60	4.63	38	24	
≥60	4.07	42	21	
Smoking				0.043
Never	4.93	44	27	
Ever	3.56	37	18	
Co-morbidity				0.817
None	4.43	39	20	
DM	4.43	42	22	
Others	2.73	40	26	
Thrombosis				0.970
Absent	4.23	42	21	
Present	4.70	34	27	
Liver metastasis				0.008
Absent	8.30	65	43	
Present	3.30	31	15	
ECOG PS				0.002
0-1	4.73	46	26	
2-3	1.50	16	8	
Jaundice				0.247
Absent	4.70	43	25	
Present	2.73	33	16	

Continued on the next page

Parameters	*Median overall survival (months)*	*6-month survival (%)*	*1-year survival (%)*	*Log-rank p*
Pain				0.922
Absent	4.67	42	21	
Present	4.23	40	23	
Weight loss ≥10%				0.004
Absent	5.66	49	32	
Present	3.30	31	12	
Ascites				0.036
Absent	4.70	44	25	
Present	2.73	29	15	
CA19-9 (U/mL)				0.019
≤400	4.63	43	36	
>400	3.16	40	20	
Hemoglobin (g/dL)				0.004
<11	2.66	23	12	
≥11	4.93	47	27	
WBC (/μL)				0.007
≤10.000	6.80	52	29	
>10.000	2.46	25	13	
AST (U/L)	6.50	52	27	
≤34	2.70	23	15	
>34				0.005
ALT (U/L)	4.67	45	26	
≤55	2.67	24	8	
>55				0.017
ALP (U/L)	7.10	55	38	
≤150	3.57	34	17	
>150				0.010
GGT (U/L)	6.80	56	37	
≤64	3.53	30	14	
>64				
T.Bilirubin (mg/dl)				0.324
≤1.2	4.43	41	26	
>1.2	3.57	38	16	
Alb (g/dL)				<0.001
≤3.5	2.17	20	10	
>3.5	6.23	52	31	
Chemotherapy				<0.001
Absent	2.27	19	3	
Present	5.63	48	30	

Alb: albumin; ALP: alkaline phosphatase; ALT: serum alanine aminotransferase; AST: serum aspartate aminotransferase; CA 19-9: carbohydrate antigen 19-9; DM: diabetes mellitus; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GGT: gama-glutamyl transpeptidase; T.Bilirubin: total bilirubin; WBC: white blood cell.

Table 3. Multivariate analysis of prognostic factors in patients with APC

Parameters	*Coefficient β*	*SE*	*p value*	*Odds ratio*	*95% CI*
Liver Metastasis	1.090	0.334	0.001	2.975	1.545-5.729
Weight loss (≥%10)	0.552	0.302	0.068	1.737	0.961-3.138
Ascites	1.176	0.335	<0.001	3.242	1.682-6.251
Albumin ≤3.5 (g/dL)	0.637	0.312	0.041	1.890	1.025-3.485
Chemotherapy	2.109	0.440	<0.001	8.237	3.480-19.498

The median OS of patients was 4.4 months, with 6-month and 12-month OS rates 40% and 22%. When the survival was investigated according to treatment subgroups, the median OS of patients receiving chemotherapy was 5.63 months, while the median OS of patients not receiving chemotherapy was 2.27 months. The 6- and 12-month OS rates were 48% and 30% for patients receiving chemotherapy and 19% and 3% for those not receiving chemotherapy, respectively (p<0.001, Table 2).

Univariate analysis

When factors affecting the OS of 118 cases with locally advanced and/or metastatic pancreatic cancer at the time of diagnosis were investigated, smoking history, presence of liver metastasis, low performance status, weight loss, presence of ascites, high CA 19-9, low hemoglobin, high WBC, high AST, ALT, ALP and GGT, low albumin and not receiving chemotherapy were found to be associated with shorter survival (p<0.05, Table 2).

Multivariate analysis

With the aim of determining independent prognostic factors, multivariate Cox regression analysis was performed. Weight loss, low albumin, liver metastasis, presence of ascites and not receiving chemotherapy were statistically significantly associated with shorter survival (p<0.05, Table 3). Using these independent prognostic factors, the regression coefficients obtained for these 5 variables were used to calculate the prognostic index. The prognostic index was calculated as follows; 1.090 x (0 when liver metastasis was absent and 1 when liver metastasis was present) + 0.552 x (0 when weight loss was absent and 1 when weight loss was present) + 1.176 x (0 when ascites was absent and 1 when ascites was present) + 0.637 x (0 when serum albumin level was higher than 3.5 g/dl and 1 when serum albumin level was equal/lower than 3.5 g/dl) + 2.109 x (0 when chemotherapy was present and 1 when chemotherapy was absent). The prognostic index values for 118 patients ranged between 0 and 5.56. Patients were divided into two groups as prognostic index value ≤2 (low-risk group) and prognostic index value >2 (high-risk group). The median OS in the low-risk group was 8.8 months, while the median OS in the high-risk group was 2.6 months. The 1-year survival rates were 43% in the low-risk group and 2% in the high-risk group (log-rank p<0.001, Figure 1).

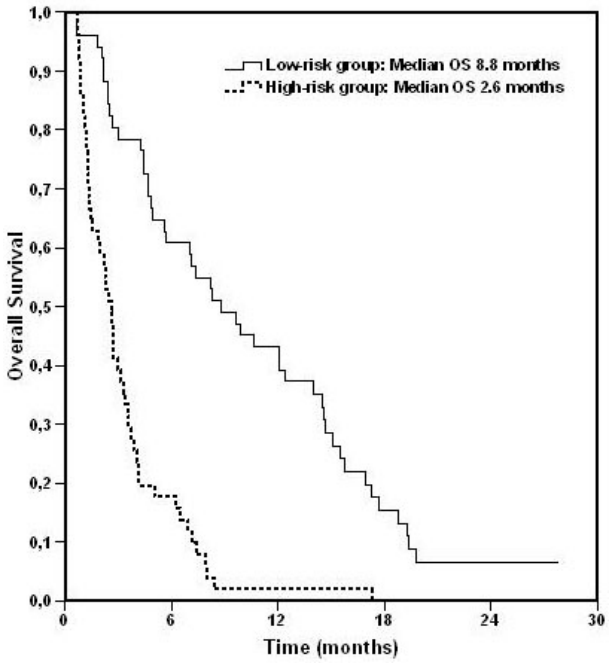

Figure 1. Kaplan-Meier plot of overall survival in patients with APC stratified by prognostic group (log-rank p<0.001).

Discussion

In this study, weight loss, low albumin, liver metastasis, ascites and not receiving chemotherapy were associated with shorter survival for patients with APC (p<0.05, Table 3). Many clinical and laboratory parameters were identified as independent determinants of disease prognosis for patients with APC (Table 4) [8-53]. In the literature, using determined independent prognostic factors, there are prognostic index model studies separating patients with APC into risk groups (Table 5) [54-78]. Among the most frequently used prognostic models are nomograms, models based on regression coefficients of prognostic factors and models based on numbers of prognostic factors [75]. In this study, a prognostic index model was created using regression coefficients. The prognostic index model created using independent prognostic factors determined in our study identified the median OS as 8.8 months in the low-risk group patients and 2.6 months for patients in the high-risk group. The OS for patients according to risk groups in prognostic index models published in the literature are shown in Table 5.

In 80% of pancreatic cancer patients, there is at least 10% weight loss, while 20-25% have cachexia syndrome [79]. The correlation of weight loss with poor prognosis in pancreatic cancer patients has been shown in many studies, as in this one (Tables 4 and 5) [12,13,29,32,51,59]. For unresectable pancreatic cancer patients with weight loss, those with weight stabilization after nutritional supplementation are reported to have longer survival [13]. Among the causes of weight loss in pancreatic cancer patients, reduced oral intake, increased catabo-

Table 4. Published studies reporting independent prognostic factors for overall survival in patients with APC

Authors [Ref.]	*Year*	*Independent Prognostic Factors*
Falconer JS, et al. [8]	1995	Age, stage, alb, CRP
Storniolo AM, et al. [9]	1999	PS, M1 stage, prior ChTx (none vs. ≥1)
Saad ED, et al. [10]	2002	Ca 19-9
Engelken FJF, et al. [11]	2003	WBC, GGT, therapeutic intervention
Van Cutsem E, et al. [12]	2004	Weight loss, alb, tumour localisation, pain
Davidson W, et al. [13]	2004	Weight loss
Louvet C, et al. [14]	2005	Ca 19-9, PS, T4 stage, M1 stage
Maisey NR, et al. [15]	2005	Ca 19-9, PS, sex
Sezgin C, et al. [16]	2005	PS
Krishnan S, et al. [17]	2006	PS, hemoglobin
Heinemann V, et al. [18]	2006	PS, M1 stage
Glen P, et al. [19]	2006	Age, stage, GPS
Siddiqui A, et al. [20]	2007	WBC, alb
Reni M, et al. [21]	2008	Ca 19-9
Hess V, et al. [22]	2008	Ca 19-9
Nakai Y, et al. [23]	2008	Ca 19-9, PS
Tanaka T, et al. [24]	2008	Ca 19-9, PS, M1 stage, CRP, hemoglobin
Ohta H, et al. [25]	2008	PS, liver metastasis, ChTx response
Park JK, et al. [26]	2008	Ca 19-9, M1 stage, treatment (ChTx vs BSC)
Moses AGW, et al. [27]	2009	Stage, body mass index, CRP, IL-6
Pine JK, et al. [28]	2009	Age, CRP
Tsvaris N, et al. [29]	2009	Ca 19-9, CEA, CRP, jaundice, PS, weight loss, treatment (ChTx vs BSC), M1 stage, tumour localisation, palliative surgery
Shimoda M, et al. [30]	2010	Ca 19-9, GPS, alb
Weber A, et al. [31]	2010	M1 stage
Inal A, et al. [32]	2012	M1 stage, weight loss, CEA
Wang DS, et al. [33]	2012	PS, stage, type of surgery, treatment (ChTx vs BSC), NLR
Zhang DX, et al. [34]	2012	Ca 19-9, stage, alb, WBC, platelet, BUN, treatment (ChTx vs BSC)
Tas F, et al. [35]	2013	Ca 19-9, CEA, PS, tumour localisation, jaundice, age, ChTx response, platelet
Bauer TM, et al. [36]	2013	Ca19-9
Kuroda T, et al. [37]	2013	Stage, tumour localisation, treatment (ChTx vs BSC)
Lee SR, et al. [38]	2013	Treatment (ChTx vs BSC)
Xue P, et al. [39]	2014	NLR
Martin HL, et al. [40]	2014	Ca19-9, PS, alb, ANC, NLR, PLR, GPS
Peixoto RD, et al. [41]	2015	Ca 19-9, PS, gender, M1 stage
Lo Re G, et al. [42]	2015	PS, number of ChTx cycle
Tabernero J, et al. [43]	2015	PS, age, liver metastasis, number of metastatic sites
Qi Q, et al. [44]	2015	WBC, neu, monocyte, NLR, PLR, LMR
Luo G, et al. [45]	2015	Age, M1 stage, Ca 19-9, NLR
Takahara N, et al. [46]	2015	PS, CRP, amount of ascites, treatment (ChTx vs BSC)
Kim HW, et al. [47]	2015	PS, alb, CRP, NLR, treatment (ChTx vs BSC), metastatik site (liver metastasis or liver + extrahepatic metastasis)
Xue P, et al. [48]	2017	LMR, M1 stage, Ca 19-9
Xiao Y, et al. [49]	2017	PLR
Hang J, et al. [50]	2017	Ca 19-9, CRP/alb ratio, M1 stage
Duconseil P, et al. [51]	2019	PS, weight loss
Ramsey ML, et al. [52]	2019	IL-6
Zhang K, et al. [53]	2019	SII (Platelet*Neu/Lymph)

ANC: absolute neutrophil count; alb: albumin; BSC: best supportive care; BUN: blood-urea nitrogen; Ca 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; ChTx: chemotherapy; CRP: C-reactive protein; GGT: gamma-glumatyl transpeptidase; GPS: Glasgow prognostic score; IL-6: interleukin-6; LMR: lymphocyte/monocyte ratio; Neu: neutrophil; NLR: neutrophil/lymphocyte ratio; PS: performance status; PLR: platelet/lymphocyte ratio; SII: systemic immune-inflammation index; WBC: white blood cells.

Table 5. Published studies reporting prognostic index models for overall survival in patients with APC

Authors [Ref.]	*Year*	*Independent prognostic factors*	*Median overall survival according to risk groups (mo;months, d; days)*
Ishii H, et al. [54]	1996	PS, CEA, M1 stage	Group A: 7.4 mo Group B: 3.5 mo Group C: 2 mo
Cubiella J, et al. [55]	1999	PS, M1 stage	Group 1: 5.6±0.9 mo Group 2: 2.0±0.6 mo Group 3: 0.7±0.2 mo
Ueno H, et al. [56]	2000	CA 19-9, PS, CRP	Good: 5.2 mo Intermediate: 2.6 mo Poor: 1.4 mo
Ikeda M, et al. [57]	2001	CA 19-9, PS, LN metastasis	Group A: 410 d Group B: 239 d Group C: 143 d
Sawaki A, et al. [58]	2006	PS, tumour localisation, CRP	Good prognostic: 265 d Fair: 155 d Poor: 65 d
Marechal R, et al. [59]	2007	CA 19-9, PS, weight loss, alb, AST	Group A: 356 d Group B: 212 d Group C: 80 d
Zhang Y, et al. [60]	2007	Age, ascites, serum cholinesterase	Group A: 4.9 mo Group B: 3.2 mo Group C: 2.0 mo
Yi JH, et al. [61]	2011	Liver metastasis, ascites/PC, CRP, alb	Low-risk: 10.0 mo Intermediate-risk: 6.7 mo High-risk:4.4 mo
Morizane C, et al. [62]	2011	Pain, PC, liver metastasis, CRP	Low-risk: 11.0 mo Intermediate-risk: 7.3 mo High-risk:3.2 mo
Kim ST, et al. [63]	2012	PS, alb, ChTx response	Good prognostic: 5.5 mo Intermediate: 3.3 mo Poor prognostic: 2.1 mo
Forssell H, et al. [64]	2013	PS/ChTx, tumour size, liver metastasis	Low-risk: 6.7 mo Medium-risk: 4.5 mo High-risk: 1.2 mo
Hamada T, et al. [65]	2014	PS, tumour size, LN metastasis, M1 stage	Very low-risk: 17.5 mo Low-risk: 13.7 mo High-risk: 8.9 mo Very high-risk: 5.5 mo
Xue P, et al. [66]	2015	CA 19-9, PS, CRP	Low-risk: 9.9 mo High-risk: 5.3 mo
Kurihara T, et al. [67]	2015	PS, stage, ANC	NA
Vernerey D, et al. [68]	2016	Age, pain, tumour size, alb, Ca 19-9	Low-risk: 15.3 mo Intermediate: 11.7 mo High-risk: 8.5 mo
Kou T, et al. [69]	2016	CA 19-9, PS, M1 stage, initially unresectable disease, CEA, NLR	Favorable: 16.5 mo Intermediate: 12.3 mo Poor: 6.2 mo
Park I, et al. [70]	2016	CEA, initially metastatic disease, sarcopenia, neutrophilia, LDH	Favorable: 11.04 mo Intermediate: 5.36 mo Poor risk: 2.17 mo

Continued on the next page

Authors [Ref.]	*Year*	*Independent prognostic factors*	*Median overall survival according to risk groups (mo: months, d: days)*
Park HS, et al. [71]	2016	PS, hemoglobin, WBC, NLR, CEA	Low-risk: 11.7 mo Intermediate-risk: 6.2 mo High-risk: 1.3 mo
Deng Q-L, et al. [72]	2017	CA 19-9, age, M1 stage, tumour size, ALT, alb, HBV infection	Group 1: 13.4 mo Group 2: 8.6 mo Group 3: 5.7 mo Group 4: 3.7 mo
Wang YI, et al. [73]	2018	CA 19-9, alb, CRP, LDH	Score 0: 18.5 mo Score 1: 10.5 mo Score 2: 6.0 mo Score 3: 3.0 mo Score 4: 2.0 mo
Ventriglia J, et al. [74]	2018	PS, liver metastasis, NLR	Good-risk: 22 mo Intermediate-risk: 10 mo Poor-risk: 7 mo
Hang J, et al. [75]	2018	CA19-9, PS, alb, liver metastasis, ANC	Low-risk: 11.7 mo Intermediate-risk: 7.0 mo High-risk: 3.7 mo
Kim HJ, et al. [76]	2018	Age, CA 19-9, number of metastatic lesions, NLR, PLR, CRP/alb ratio	NA
Chang CF, et al. [77]	2019	PS, M1 stage, alb, NLR	Good-prognostic: 21.1 mo Intermediate: 9.2 mo Poor-prognostic: 5.8 mo
Gargiulo P, et al. [78]	2019	AST, ALP, PS, NLR, CA 19-9, hemoglobin, pain, M1 stage.	NA
Current study		Weight loss, alb, liver metastasis, ascites, absence of chemotherapy	Low-risk: 8.8 mo High-risk: 2.6 mo

ALP: Alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ANC: absolute neutrophil count; alb: albumin; Ca 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; ChTx: chemotherapy; CRP: C-reactive protein; HBV: hepatitis B virus; LDH: lactic acid dehydrogenase; LN: lymph node; NA: not available; NLR: neutrophil/lymphocyte ratio; PS: performance status; PC: peritoneal carcinomatosis; PLR: platelet/lymphocyte ratio; WBC: white blood cells.

lism related to the tumor, and malabsorption developing due to exocrine and endocrine insufficiencies may be listed [51]. Another reason for weight loss observed in pancreatic cancer and cancer cachexia syndrome is the systemic inflammatory response to the tumor. Activation of the immune and inflammatory system by the tumor leads to the release of many cytokine and acute phase reactants which may cause cancer cachexia and malnutrition, and hence shorter survival [24,52,53,80,81].

Malnutrition suppresses albumin synthesis. Additionally, increased production of acute phase proteins in cancer patients increases amino acid requirements, causes catabolic effects in patients with limited protein intake in diet and causes skeletal muscle destruction. Patients with continuing tumor progression consume proteins and energy in the body and have significant reductions in serum albumin levels as a result of chronic systemic inflammation [20,27,61,82,83]. Low serum albumin level is frequently observed in advanced stage pancreatic cancer patients and the correlation with shorter survival was shown in many studies (Tables 4 and 5) [8,12,20,30,34,40,59,61,68,72,73,75,77]. A review of 36 studies evaluating prognostic factors for APC including a total of 653 patients identified albumin and 6 other prognostic factors (CA 19-9, M1 stage, AST, ALP, lactic acid dehydrogenase, WBC, blood-urea nitrogen) were independent predictors of survival [84]. In accordance with the literature, in this study compared with patients with albumin level >3.5 mg/dL, those with albumin ≤3.5 mg/dL were identified to have significantly shorter survival. Due to the frequent observation of malnutrition in pancreatic cancer patients and it being a poor prognostic factor, all pancreatic cancer patients should have nutritional screening performed. If necessary multimodal methods (diet counseling, oral nutritional supplements, enteral/parenteral nutrition, vitamins and micro/macronutrient replacement therapy, pancreatic enzyme replacement therapy, psychosocial counselling, increased physical activity, appetite

enhancing agents, anti-inflammatory treatment, anemia treatment) to ensure delay of cachexia and/or death should be recommended [79,85,86].

There are studies identifying history of prior chemotherapy, lack of response to chemotherapy, reduced numbers of chemotherapy cycles, and not receiving chemotherapy as an independent poor prognostic factor for advanced stage pancreatic cancer (Table 4) [9,25,26,29,33-35,37,38,42,46,47,63,64]. In accordance with the literature, in our study not receiving chemotherapy was identified as a poor prognostic factor independently determining survival [26,29,33,34,37,38,46,47,64]. Most prognostic index model studies in the literature were performed with patients receiving palliative chemotherapy with very low numbers of prognostic index model studies including patients not receiving chemotherapy [55,64,71]. Park et al retrospectively investigated 403 patients with metastatic pancreatic cancer and identified PS, hemoglobin, WBC, neutrophil/lymphocyte ratio (NLR) and carcinoembryonic antigen (CEA) levels as independent poor prognotic factors. Patients were separated into risk groups using these independent factors. In the low- and moderate-risk groups, receiving chemotherapy was associated with longer survival compared to not receiving chemotherapy, while in the high-risk group the survival of those receiving or not receiving chemotherapy was similar [71]. However, there is no prognostic index study, apart from our study and one by Forsell et al that found not receiving chemotherapy was an independent poor prognostic factor [64].

For patients with APC, there are lower rates of reporting about the correlation of liver metastasis and/or ascites with poor prognosis compared to prognostic factors like CA 19-9, PS, stage and albumin (Tables 4, 5) [25,43,46,47,60-62,64,74,75]. When making treatment decisions and designing clinical studies for patients with APC, the necessity to note the presence of liver metastasis is emphasized [25,43,61,64,74]. Yi et al reported that liver metastasis, presence of ascites/peritoneal carcinomatosis, high C-reactive protein (CRP) and low albumin levels were identified as poor prognostic factors determining OS in patients with APC [61]. Similar to the study by Yi et al, in our study liver metastasis, presence of ascites and low albumin levels were identified as independent prognostic factors. Another study determining presence of ascites as an independent poor prognostic factor for patients with APC was published by Zhang et al [60]. Ascites, intestinal obstruction and abdominal pain were the clinical findings of peritoneal carcinomatosis and frequently caused malnutrition and general worsening. Patients with liver metastasis have a tendency for jaundice and hepatic coma. As the side effects of chemotherapy are more pronounced in patients with peritoneal carcinomatosis or liver metastasis, it may be necessary to reduce or postpone chemotherapy doses [62,87]. Prognosis of patients with pancreatic cancer presenting with peritoneal carcinomatosis is very poor with median OS 7-8 weeks [87,88]. A retrospective study including metastatic pancreatic cancer patients identified that the survival of those with malignant ascites was statistically significantly shorter than those with liver metastasis [88]. The presence of peritoneal metastasis in patients with APC is reported to be a marker of lack of response to chemotherapy [89]. The most accurate diagnosis of peritoneal carcinomatosis in preoperative evaluation is possible with laparoscopy, while for patients treated with palliative aims and without malignant ascites or radiological peritoneal implants, it is difficult to perform such an invasive method for most accurate diagnosis of peritoneal carcinomatosis [46]. In our study, 32% of patients had clinical/radiological ascites, 5.1% had pathological malignant ascites and 8.5% had radiological peritoneal carcinomatosis. Radiologically-identified peritoneal carcinomatosis was not identified to correlate with OS, while the presence of clinical/radiological ascites was identified as an independent poor prognostic factor determining survival.

The clinical and laboratory parameters and their prognostic importance reported in APC studies are very heterogeneous. Recently, an expert consensus statement defined mandatory age, albumin, bilirubin, CA19-9, CRP, disease status, LDH, liver metastasis, NLR, number of metastatic sites, pain at baseline and PS and recommended ALP, sex, primary tumor location, pulmonary metastasis, previous deep venous thrombosis or embolus, quality of life, synchronous or metachronous metastasis as prognostic factors for randomized controlled studies evaluating first-line treatment of APC. In this way, the target was to ensure appropriate comparisons of the results of clinical studies for patients with APC [90].

In conclusion, in our study 5 parameters (weight loss, albumin level, liver metastasis, ascites, chemotherapy) were identified independently predicting prognosis in patients with APC. Based on these prognostic factors a prognostic index was created and patients were divided into two groups as low and high risk. Prognostic index models created with easily accessible clinical and laboratory parameters for APC, as in our study, may aid clinicians in daily clinical practice in dividing patients into risk groups, determining survival, and creating the most appropriate treatment protocols.

Conflict of interests

The authors declare no conflict of interests.

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