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Factors independently associated with prognosis in patients operated for pancreatic cancer: Assessing the role of various parameters including red cell distribution width, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio

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ABSTRACT

Objective: We aimed to assess whether, among other parameters, preoperative red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) values were associated with prognosis in patients operated for pancreatic cancer (PC).

Material and Method: This retrospective cohort was conducted from February 1, 2016 to February 1, 2021 at the general surgery department of a university hospital in Turkey. A total of 75 patients histologically diagnosed with PC who had undergone surgery were included in the study.

Results: The PLR values of patients with poorly differentiated and undifferentiated tumors were found to be higher than those with moderately and highly differentiated tumors. Also, there was a significant relationship between PLR values and the length of hospital stay. PLR values increased as the length of hospital stay increased. There was a statistically significant positive correlation between CA 19-9 levels and NLR and PLR. High total bilirubin level was related with increased risk of death, while adjuvant chemotherapy recipients had 4.049-fold lower risk of death than those without adjuvant chemotherapy.

Conclusion: Our results indicate that preoperative NLR, PLR and RDW cannot be used as prognostic indicators of mortality in patients with operated PC, but high PLR appears to be associated with lower level of tumor differentiation and prolonged hospital stay. We also found that high total bilirubin was a poor prognostic factor, while adjuvant chemotherapy was a good prognostic factor. Further multicenter, prospective studies with larger sample sizes will help to verify these results.

Keywords: Pancreatic cancer, NLR, PLR, RDW, CA 19-9, bilirubin

INTRODUCTION

Pancreatic cancer (PC) is one of the malignancies with the highest reported levels of short- and mid-term morbidity and mortality (1). Despite developing medical technologies, adjuvant therapies and surgical techniques, the 1-year and 5-year survival rates of the operated patients are reported to be 21% and 3%, respectively (1-3). Surgical resection and adjuvant chemotherapy remain as the primary management options in PC; however, overall survival (OS) and prognosis are still very poor due to rapid local recurrence and systemic spread of disease (4). Careful preoperative risk assessment of patients with PC can optimize patient selection for radical surgery and improve treatment outcomes and patient outcomes. Therefore, there is a fundamental need for the identification of preoperatively-measurable prognostic markers (5).

Various markers have been associated with poor prognosis in PC, such as carbohydrate antigen 19-9 (CA 19-9) and bilirubin (6,7). In addition, it is well established that inflammatory activation plays a key role in carcinogenesis and the tumor microenvironment (8). Despite the fact that information is limited regarding the mechanisms of these relationships (5), a number of inflammation markers and indices, including neutrophil-to-lymphocyte ratio (NLR),

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platelet-to-lymphocyte ratio (PLR) and lymphocyte-monocyte ratio (LMR), and red cell distribution width (RDW), have been investigated for their potential importance in PC prognosis and diagnosis (9,10). Many authors have identified pretreatment RDW (10), NLR (11) and PLR (12) values as being associated with OS in patients with PC. Meta-analyses have also supported these suggestions by showing that high PLR, NLR, and RDW were suggestive of poor prognosis in PC (1,4,10,13). Since PLR, NLR, and RDW are easily-accessible inflammatory indices, their possible association with postoperative outcomes can be valuable for the assessment of patients with PC and treatment decisions, such as identifying candidates for either surgery or neoadjuvant therapy (5).

We hypothesized that these markers could predict prognosis in patients with operated for PC. In this study, we aimed (i) to reveal whether preoperative levels of RDW, PLR, NLR and other parameters were associated with stage, morbidity and survival of PC, and (ii) to identify significant prognostic factors associated with mortality in patients with operated PC.

MATERIAL AND METHOD

Study Design

This was a retrospective single center study conducted between February 1, 2016 to February 1, 2021 at the General Surgery & Surgical Oncology Department of Osmangazi University Faculty of Medicine, Eskişehir, Turkey. The protocol of this study was approved by the Medical Ethics Committee of Osmangazi University Faculty of Medicine (Date: 15.06.2021, Decision No: 04), and all steps and procedures associated with the research were carried out in accordance with the ethical standards stated in the Declaration of Helsinki and its amendments. As the study has a retrospective nature, Osmangazi University Medical Ethics Committee did not require acquisition of written informed consent from patients. All data were recorded anonymously.

Study Population and Follow-up

A total of 75 patients histologically diagnosed with PC who had undergone surgery were included in the study. Exclusion criteria were presence of synchronous or metachronous cancer, undergoing emergency tumor surgery, having cirrhosis, autoimmune disease or hematological malignancy, and having used corticosteroids within the last 6 months. In addition, recipients of neoadjuvant treatment and subjects with stage 4 disease or incomplete data were also excluded.

The following information of each patient was acquired from hospital records: demographic characteristics, laboratory measurements, pathological outcomes (detailed later), preoperative application of endoscopic retrograde cholangiopancreatography (ERCP) and stenting, time between diagnosis and surgery (days), resectable lesion (according to preoperative computed tomography), whether adjuvant chemotherapy or adjuvant radiotherapy was applied, length of stay in hospital. Recorded surgical characteristics were: operation type, whether the spleen was preserved, pancreaticojejunostomy type, gastrojejunostomy type, whether the pylorus was preserved, and portal vein resection. Finally, all recurrences and outcomes, such as leakage, fistula, postoperative infection, recurrence and mortality data (including survival time) were recorded.

Laboratory Analysis

Blood samples were acquired from the antecubital vein for complete blood count (CBC) and other parameters including albumin, total bilirubin, direct bilirubin, and CA 19-9. Hemoglobin level, RDW value, and counts for neutrophils, lymphocytes and platelets were obtained from CBC. NLR was defined as the total number of neutrophils divided by the total number of lymphocytes. PLR was defined as the total number of platelets divided by the total number of lymphocytes. Laboratory analyses were carried out in all patients within 2 weeks prior to respective surgeries via routine devices in the Clinical Biochemistry Department of Osmangazi University Faculty of Medicine.

Pathological Analysis

All of the specimens obtained from fully resected tumors were sent to the pathology unit of the Pathology Department of Osmangazi University Faculty of Medicine for pathological examinations. Pathological diagnosis, differentiation, tumor primary and localization, tumor size (mm), number of lymph nodes, number of metastatic lymph nodes, extracapsular invasion, perineural invasion, lymphovascular invasion, resection margin, surgical margin, clinical stage (reported according to the pathological classification criteria of the 7th Edition of the American Joint Committee on Cancer guidelines for PC) were determined and reported by qualified pathologists.

Statistical Analysis

The statistical analyses of this study were performed with SPSS ver. 25.0 (SPSS Inc., Chicago, IL, USA). Histogram and Q-Q plots were used to determine whether variables are normally distributed. Data are given as mean±standard deviation or median (1st quartile-3rd quartile; interquartile range; IQR) for continuous variables according to normality of distribution, and as frequency (percentage) for categorical variables. Between-group analyses were performed with the Mann-Whitney U test. Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. Survival times were calculated with the Kaplan Meier method. Between-group comparisons of survival times were performed with the Log rank test. Cox regression analysis (forward conditional method) was performed to determine

significant prognostic factors that were independently associated with mortality. Two-tailed p values of less than 0.05 were considered statistically significant.

RESULTS

Forty-six male and 29 female patients were included in our study, and the median age of the patients was 65 (IQR: 59-70) (range: 40-80) years. Summary of patients and tumor characteristics, laboratory measurements, pathological features, surgical features and all other outcomes are depicted in **Table 1** and **Table 2**.

Table 1. Summary of patients and tumor characteristics

Age	65 (59-70)
Sex	
Female	29 (38.7%)
Male	46 (61.3%)
Preoperative ERCP + Stent	19 (25.3%)
Time between diagnosis and surgery, days	22 (14-36)
Operation	
Whipple procedure	66 (88.0%)
Distal pancreatectomy	5 (6.7%)
Total pancreatectomy	4 (5.3%)
Diagnosis	
Adenocarcinoma	72 (96.0%)
Neuroendocrine tumor	0 (0.0%)
Other	3 (4.0%)
Spleen	
Not-preserving	52 (69.3%)
Preserving	23 (30.7%)
Differentiation	
Undifferentiated	2 (2.7%)
Poorly differentiated	23 (30.7%)
Moderately differentiated	42 (56.0%)
Highly differentiated	8 (10.7%)
Stage	
Stage 1A	4 (5.3%)
Stage 1B	3 (4.0%)
Stage 2A	4 (5.3%)
Stage 2B	38 (50.7%)
Stage 3	26 (34.7%)
Primary tumor	
Pancreas	75 (100.0%)
Ampulla	0 (0.0%)
Distal choledochal	0 (0.0%)
Location	
Head	69 (92.0%)
Neck	0 (0.0%)
Body	2 (2.7%)
Tail	4 (5.3%)
Uncinate process	0 (0.0%)
Tumor size, mm	31.83±13.27
Number of lymph nodes	23.79±12.91
Number of metastatic lymph nodes	2 (1-4)
Extracapsular invasion	14 (18.7%)
Resectability (preoperative CT)	
Resectable	48 (64.0%)
Borderline	27 (36.0%)
Unresectable	0 (0.0%)
Perineural invasion	62 (82.7%)
Lymphovascular invasion	52 (69.3%)

Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

Table 2. Summary of laboratory and surgical outcomes

Resection margin	
R0	59 (78.7%)
R1	16 (21.3%)
R2	0 (0.0%)
Surgical margin	
Negative	59 (78.7%)
Pancreatic parenchyma	3 (4.0%)
Choledochal	1 (1.3%)
Retropancreatic	12 (16.0%)
Choledochal and pancreatic parenchyma	0 (0.0%)
Pancreaticojejunostomy type	
Ducto-jejunostomy	60 (80.0%)
Others	6 (8.0%)
None	9 (12.0%)
Gastrojejunostomy type	
Simple	58 (77.3%)
Roux-en-Y	11 (14.7%)
None	6 (8.0%)
Pylorus	
Preserving	0 (0.0%)
Classic	69 (92.0%)
None	6 (8.0%)
Portal vein resection	12 (16.0%)
Adjuvant chemotherapy	59 (78.7%)
Adjuvant radiotherapy	11 (14.7%)
Length of stay in hospital, days	11 (7-15)
Leakage	
Biochemical	4 (5.3%)
Macroscopic	10 (13.3%)
Fistula	
Grade A	3 (4.0%)
Grade B	3 (4.0%)
Grade C	7 (9.3%)
Postoperative infection	21 (28.0%)
Recurrence	24 (33.8%)
Albumin	4.04±0.52
Hemoglobin	12.78±1.58
Neutrophil ($\times 10^3$)	4.8 (3.8-6.4)
Lymphocyte ($\times 10^3$)	1.7 (1.4-2.11)
Platelet ($\times 10^3$)	276.56±79.43
RDW	14.9 (13.7-16.8)
Total bilirubin	3.69 (1.15-8.18)
Direct bilirubin	2.87 (0.43-6.91)
CA 19-9	122.5 (39.5-476.0)
Neutrophil / lymphocyte ratio	2.92 (1.92-3.79)
Platelet / lymphocyte ratio	157.14 (116.74-203.36)
Status	
Exitus	38 (50.7%)
Alive	37 (49.3%)

Data are given as mean±standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

We examined the association of tumor characteristics and tumor related continuous variables with RDW, NLR, and PLR. It was observed that the PLR value decreased significantly as the degree of differentiation of

the tumor (un-differentiated and poorly differentiated versus moderately and highly differentiated) increased (p=0.030). There was a significant positive correlation between the length of stay in hospital and PLR value (r=0.262, p=0.023). We also found a significant positive correlation between CA 19-9 values and NLR (r=0.277, p=0.016) and PLR (r=0.278, p=0.016). The RDW, PLR and NLR values did not demonstrated any significant relationships with other tumor characteristics or tumor-related continuous variables, including differentiation, clinical stage, extracapsular invasion, perineural invasion, lymphovascular invasion, resection margin, tumor size, number of lymph nodes, number of metastatic lymph nodes, leakage, fistula, postoperative infection, recurrence, death status, resectability, length of stay in hospital and CA 19-9 (**Table 3** and **Table 4**).

Table 4. Relationships between RDW, PLR, NLR and tumor related continuous variables

		RDW	NLR	PLR
Tumor size	r	-0.143	0.155	0.060
	p	0.221	0.185	0.612
Number of lymph nodes	r	0.117	-0.071	-0.039
	p	0.316	0.547	0.740
Number of metastatic lymph nodes	r	0.005	-0.022	0.002
	p	0.968	0.854	0.986
Length of stay in hospital	r	0.068	0.152	0.262
	p	0.561	0.192	0.023
CA 19-9	r	0.093	0.277	0.278
	p	0.427	0.016	0.016

r: Spearman correlation coefficient

Table 3. Summary of RDW, NLR and PLR with regard to tumor characteristics

	RDW	p	NLR	p	PLR	p
Differentiation		0.800		0.067		0.030
Un-differentiated & poorly differentiated	14.5 (13.5-17.2)		3.14 (2.43-5.63)		174.00 (138.57-220.00)	
Moderately & highly differentiated	15.0 (14.1-16.1)		2.75 (1.74-3.70)		147.45 (111.76-181.82)	
Stage		0.978		0.956		0.533
Stage 1 & 2	14.8 (13.7-16.5)		2.92 (1.93-3.79)		156.80 (115.64-188.89)	
Stage 3	15.15 (13.8-17.0)		2.89 (1.92-3.78)		164.67 (126.95-203.77)	
Extracapsular invasion		0.678		0.523		0.138
No	14.9 (13.7-16.7)		2.92 (1.92-3.78)		151.58 (114.55-195.07)	
Yes	14.9 (14.5-17.0)		2.90 (2.43-4.86)		169.17 (137.70-253.57)	
Resectability (preoperative CT)		0.187		0.877		0.453
Resectable	15.2 (13.7-17.6)		2.99 (1.83-3.80)		164.35 (126.34-203.65)	
Borderline	14.5 (13.7-15.9)		2.82 (1.93-3.54)		141.73 (111.76-195.65)	
Perineural invasion		0.700		1.000		0.944
No	15.2 (13.5-15.9)		2.36 (1.95-3.60)		164.36 (114.55-188.89)	
Yes	14.8 (13.8-17.0)		2.94 (1.75-3.79)		154.19 (117.14-203.36)	
Lymphovascular invasion		0.304		0.654		0.679
No	15.7 (13.5-18.4)		3.03 (1.61-4.06)		158.50 (105.88-195.07)	
Yes	14.7 (13.9-16.15)		2.92 (1.95-3.74)		156.97 (122.87-203.57)	
Resection margin		0.591		0.393		0.130
R0	14.7 (13.7-16.8)		2.92 (1.83-3.79)		151.58 (114.55-188.89)	
R1	15.25 (13.8-16.7)		3.09 (2.24-4.66)		176.65 (128.75-230.18)	
Leakage		0.812		0.765		0.978
No	14.9 (13.8-16.7)		3.03 (1.83-3.81)		156.80 (115.64-203.36)	
Yes	14.95 (13.6-17.2)		2.87 (2.22-3.43)		161.42 (125.73-168.10)	
Fistula		0.732		0.425		0.644
No	14.85 (13.8-16.7)		3.04 (1.83-3.96)		156.97 (115.64-203.77)	
Yes	15.2 (13.6-17.2)		2.82 (2.22-3.03)		158.50 (125.73-166.00)	
Postoperative infection		0.781		0.962		0.243
No	14.85 (13.7-16.8)		2.99 (1.83-3.81)		146.32 (110.96-195.65)	
Yes	15.2 (14.0-16.4)		2.92 (2.22-3.60)		164.35 (144.00-203.95)	
Recurrence		0.711		0.488		0.402
No	14.9 (13.5-17.0)		2.82 (1.92-3.78)		161.82 (116.74-206.92)	
Yes	14.55 (13.8-16.3)		3.17 (1.84-4.25)		151.50 (121.29-179.60)	
Status		0.311		0.147		0.275
Exitus	15.2 (14.2-16.8)		3.10 (2.15-4.29)		165.29 (126.95-210.00)	
Alive	14.6 (13.4-16.5)		2.49 (1.83-3.50)		144.00 (116.74-181.82)	

Data are given as median (1st quartile-3rd quartile) according to normality of distribution

In addition, we evaluated patient-related, tumor-related and surgical characteristics, presence/absence of chemotherapy or radiotherapy after surgery, and complications during follow-up with respect to their possible association with survival time, 2-year survival rate and mortality rates using the Kaplan Meier method with Log rank test (**Table 5**). There was a significant positive correlation between receiving adjuvant chemotherapy and survival time and survival percentage ($p < 0.001$). No significant correlation was found between survival and any of the other variables (**Table 5**, **Figure 1**, **Figure 2**).

Table 5. Survival times (months) with Kaplan Meier method and comparisons of groups with Log rank test

	n	Exitus	Mean (95% CI)	Median (95% CI)	2-year survival rate (%)	p
Overall survival	75	38	25.17 (18.51-31.84)	15 (10.36-19.64)	29.6±7.2	N/A
Sex						0.095
Female	29	12	34.05 (22.18-45.93)	23 (7.8-38.2)	42.2±12.2	
Male	46	26	17.89 (12.97-22.81)	15 (10.89-19.11)	21.8±8.6	
Operation						0.216
Whipple procedure	66	35	20.14 (15.44-24.83)	15 (11.96-18.04)	26.1±7.5	
Distal & Total pancreatectomy	9	3	40.75 (20.26-61.24)	*	75.0±15.3	
Spleen						0.893
Not-preserving	52	20	30.45 (20.85-40.05)	14 (8.1-19.9)	38.3±9.1	
Preserving	23	18	21.65 (15.04-28.27)	19 (11.17-26.83)	30.4±9.6	
Differentiation						0.102
Un-differentiated & poorly differentiated	25	13	14.56 (9.01-20.12)	10 (5.55-14.45)	11.5±9.9	
Moderately & highly differentiated	50	25	27.96 (19.77-36.15)	19 (10.61-27.4)	36.1±9.0	
Stage						0.736
Stage 1 & 2	49	25	25.64 (17.09-34.18)	15 (8.9-21.1)	31.1±8.8	
Stage 3	26	13	20.04 (14.48-25.60)	16 (7.51-24.49)	27.6±12.3	
Extracapsular invasion						0.209
No	61	29	27.06 (19.27-34.84)	19 (12.87-25.13)	34.8±8.5	
Yes	14	9	13.90 (9.16-18.64)	13 (8.58-17.43)	10.4±9.9	
Resectability (preoperative CT)						0.791
Resectable	48	26	25.13 (17.27-32.99)	16 (9.77-22.23)	26.7±8.5	
Borderline	27	12	19.90 (12.83-26.96)	14 (8.22-19.78)	38.2±12.4	
Perineural invasion						0.091
No	13	5	39.07 (22.56-55.58)	*	67.3±13.6	
Yes	62	33	18.88 (14.24-23.51)	14 (10.12-17.88)	19.7±7.2	
Lymphovascular invasion						0.684
No	23	11	29.86 (16.60-43.13)	19 (1.07-36.93)	46.3±12.7	
Yes	52	27	20.12 (15.03-25.20)	15 (12.37-17.63)	22.1±8.0	
Resection margin						0.162
R0	59	30	27.63 (20.01-35.26)	16 (10.44-21.56)	36.2±8.0	
R1	16	8	13.96 (8.65-19.28)	10 (4.61-15.39)	0.0±0.0	
Portal vein resection						0.142
No	63	35	22.88 (16.15-29.60)	14 (11.53-16.47)	22.7±7.3	
Yes	12	3	31.00 (21.72-40.28)	*	83.3±10.8	
Adjuvant chemotherapy						<0.001
No	16	12	7.85 (4.91-10.80)	9 (1.11-16.89)	11.5±10.0	
Yes	59	26	29.07 (21.35-36.79)	20 (12.03-27.97)	35.7±8.6	
Adjuvant radiotherapy						0.133
No	64	33	21.37 (14.52-28.22)	15 (12.07-17.93)	19.8±7.9	
Yes	11	5	29.65 (17.92-41.38)	*	58.3±16.1	
Leakage						0.536
No	61	29	25.30 (17.83-32.77)	16 (10.57-21.43)	30.7±8.4	
Yes	14	9	19.68 (9.36-29.99)	14 (10.9-17.1)	25.4±13.9	
Fistula						0.640
No	62	30	24.98 (17.67-32.28)	16 (11.22-20.78)	29.9±8.2	
Yes	13	8	20.24 (9.10-31.37)	15 (4.38-25.62)	27.7±15.0	
Postoperative infection						0.739
No	54	26	21.15 (15.92-26.39)	16 (9.9-22.1)	28.4±8.7	
Yes	21	12	26.45 (13.56-39.33)	14 (11.57-16.44)	30.8±12.6	
Recurrence						0.251
No	47	17	32.90 (22.44-43.35)	19 (1.06-36.94)	47.1±10.3	
Yes	24	17	17.27 (13.45-21.08)	15 (12.8-17.2)	15.5±9.5	

SE: Standard error, CI: Confidence interval, * Can not be calculated due to low number of exitus cases

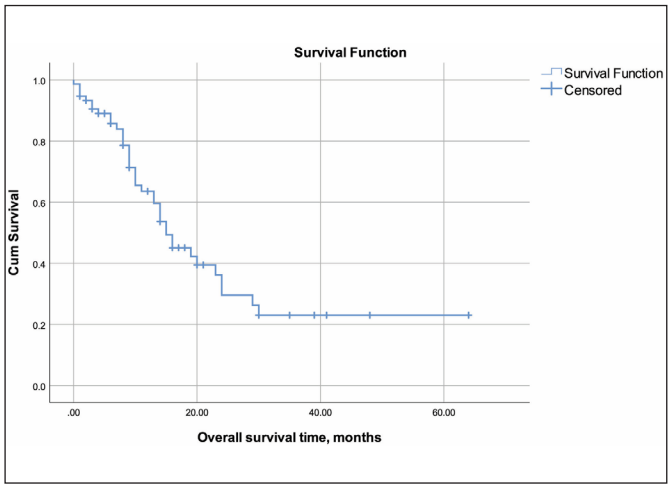

Figure 1. Overall survival plot

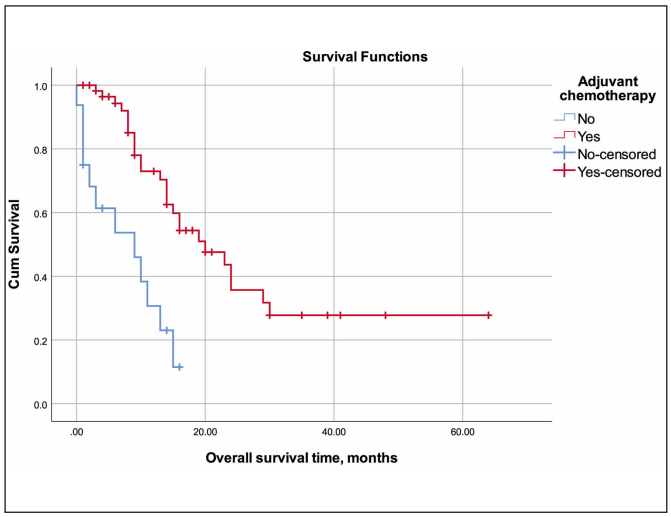

Figure 2. Overall survival plot with regard to adjuvant chemotherapy

We performed Cox regression analysis to determine significant prognostic factors associated with mortality. High total bilirubin level was a poor prognostic factor and adjuvant chemotherapy was a good prognostic factor. High total bilirubin level was associated with increased risk of death (p=0.045). Patients who received adjuvant chemotherapy had 4.049-fold lower risk of death than those without adjuvant chemotherapy (HR: 0.247, 95% CI: 0.118-0.519, p < 0.001). Other variables included in the model, age (p=0.621), sex (p=0.299), time between diagnosis and surgery (p=0.130), tumor size (p=0.084), number of metastatic lymph nodes (p=0.915), albumin (p=0.557), hemoglobin (p=0.093), RDW (p=0.143), CA 19-9 (p=0.253), NLR (p=0.971) and PLR (p=0.601) were found to be non-significant (**Table 6**).

DISCUSSION

Currently, there is no suitable preoperative blood test or analysis method enabling the prediction of morbidity and mortality in patients with PC (14). In this study, we aimed to evaluate many factors, with particular focus on PLR, NLR and RDW, to ascertain whether they were associated with the various characteristics of patients with PC and its prognosis. According to our results, PLR values of patients with poorly-differentiated and undifferentiated tumors were significantly higher than those with moderately and highly differentiated tumors. In addition, we observed that the PLR values increased significantly as the length of hospital stay was prolonged. There was a significant positive correlation between CA 19-9 levels and NLR and PLR. Regarding the effects of factors on survival, we observed that high bilirubin (poor prognosis) and receiving adjuvant chemotherapy (good prognosis) were the only factors independently associated with mortality.

Many researchers have investigated the role of inflammation and inflammatory markers/indices in predicting the postoperative prognosis of various tumors, including PC (1,5,8). The ability of platelets to protect cancer cells from the immune response and facilitate their attachment to the endothelium and the antitumor role of lymphocytes support the hypothesis that PLR may be valuable in predicting prognosis in cancer patients (10,15). The mechanism underlying the prognostic value of PLR in PC remains unclear. Platelets can also promote tumor growth, angiogenesis, metastasis, and cancer-associated thrombosis (2). Some researchers focusing on PC have found results showing that patients with high PLR may have shorter OS compared to patients with low PLR (16,17). In contemporary studies, results have shown that PLR value is significantly associated with OS in patients with PC, similar to the research outcomes concerning other cancers (2,4). In a multivariable analysis, greater PLR was found to be an independent risk factor for OS, along with important prognostic factors such as larger tumor diameter, positive microscopic surgical margin, and moderate or poor differentiation (16). A meta-analysis including 14 studies with 2743 patients showed that low preoperative PLR values were associated with better OS in patients with PC. Furthermore, in the aforementioned review, four studies with a total of 1062 patients reported results pertaining to disease-free survival (DFS). They demonstrated that low PLR appeared to be prognostic for better DFS, whereas high preoperative PLR had no

Table 6. Significant prognostic factors of the mortality, Cox regression analysis

	β coefficient	Standard Error	p	Exp(β)	95.0% CI for Exp(β)	
Adjuvant chemotherapy	-1.399	0.379	<0.001	0.247	0.118	0.519
Total bilirubin	0.053	0.027	0.045	1.055	1.001	1.111

CI: Confidence Interval

impact on OS (5). In another study, an optimal threshold value of 150 for PLR was associated with survival time in patients with resectable PC, while in another study, the same threshold value did not show prognostic value in patients with unresectable tumors (16,18). Another meta-analysis (including three studies) aiming to investigate the prognostic value of PLR found that PLR was not associated with OS in PC (19). Similar to the results of this study Kishi et al. (20) examined 65 patients with PC and concluded that PLR was not associated with the prognosis of these patients. We found a significant association between the presence of undifferentiated or poorly-differentiated PC and the level of PLR. We also observed that there was a significant relationship between CA 19-9 and PLR. While there was a statistically significant relationship between PLR and hospital stay, we did not find a significant association between PLR and survival or other morbidities. Although low PLR levels have the potential to be used as a predictor of better OS in patients with PC, current evidence does not support a role for PLR as a reliable prognostic factor for OS.

Similar to PLR, NLR is an inexpensive, easily available and widely used marker and has been found to be an important prognostic marker for many malignant tumors (3). Several studies have demonstrated the potential prognostic impact of NLR values in patients with PC (21,22). For instance, low NLR has been shown to be significantly associated with improved OS (22). On the other hand, interestingly, high NLR was reported as a surrogate marker in patients with resectable pancreatic adenocarcinoma (23). In another study conducted in China, preoperative NLR values were found to be an independent prognostic factor for OS in patients with early-stage PC (22). Similarly, preoperative serum NLR value in patients with operable pancreatic head cancer was found to provide prognostic information related to OS (24). In a meta-analysis of 34 studies involving 7105 patients with PC, NLR was shown to constitute new prognostic markers for predicting the prognosis of patients with PC, and high NLR value correlated with poor OS. In the same study, it was emphasized that NLR is a better predictor of the prognosis of patients with PC than PLR (1). A recent study investigating the prognostic predictive power of many important factors also found NLR to be an independent prognostic factor in PC, together with factors whose prognostic importance has been proven in many studies, such as CA 19-9, adjuvant chemotherapy, lymph node metastasis, and number of distant organ metastases (25). Hasegawa et al. (26) investigated the link between pretreatment NLR and response to neoadjuvant chemotherapy in PC patients and concluded that pretreatment NLR levels were independently associated with pathological response to treatment. In a study evaluating NLR and PLR together, patients with normal values for both NLR and PLR were found to have significantly better OS compared to those with elevated PLR or NLR values. Additionally, the authors suggested that NLR was superior to PLR as a prognostic marker in patients with PC (27). Finally, high NLR at preoperative assessment has also been found to be associated with poor survival in patients with metastatic PC (21,28,29). As a result of our study, in contrast to all these studies, we did not find a significant relationship between NLR value and any other tumor-related, patient-related, prognostic and survival-related factor, except for CA 19-9.

The RDW reflects the heterogeneity of the volume and size of circulating red blood cells and is a parameter readily available from routine blood tests (10). Previous studies have demonstrated that RDW may have diagnostic and prognostic value for various tumor types (14,15). In a study on PC, it was concluded that high RDW levels in patients with pancreatic masses may indicate malignancy (13). Studies have also reported that RDW could be used as an independent prognostic factor in patients with PC undergoing radical surgery. It was concluded that patients with high RDW may be at a more advanced stage of the disease and that the timing of surgery and the duration of neoadjuvant therapy can be determined by looking at the preoperative values of RDW (10), while other research has revealed that high RDW was associated with disease progress and longer postoperative hospital stay (30). In the present study, we did not find a prognostic value for RDW in operated PC patients.

CA 19-9 is a type of modified Lewis(a) blood group antigen and is recommended by the National Comprehensive Cancer Network guidelines for the diagnosis and follow-up of PC (31). Several reports have noted the usefulness of CA 19-9 in the monitoring of patients with PC.(32,33) Several studies have shown independent relationships between high levels of CA 19-9 and poor OS in advanced PC (7,25). However, in approximately 20% of patients with PC, CA 19-9 level may be normal before surgery (31) –which must be taken into account when evaluating patients in this respect. In our study, a significant correlation was found between NLR and PLR values and the level of CA 19-9; however, the possible relationships between these seemingly unassociated parameters require further research.

This study reports neoadjuvant chemotherapy and bilirubin levels as the only parameters independently associated with mortality in patients who underwent surgery for PC. It is understood that PC development leads to early systemic spread, and the majority of patients relapse soon after therapeutic surgery. Since the poor prognosis of PC is primarily determined by systemic

rather than local failure, it becomes clear that adjuvant treatment strategies need to be developed (34). Available data from randomized trials (35) and meta-analyses (34) showed that although receiving adjuvant chemotherapy significantly prolongs survival in patients with PC, no clear information is available for 5-year survival rate (34). Nonetheless, a recent study stated that receiving adjuvant chemotherapy was an independent good prognostic factor for PC (25), consistent with our findings.

Bilirubin is an endogenous antioxidant that plays a role in many physiological and pathological processes and also exhibits anti-carcinogenic effects (6). Increased bilirubin accumulation in the liver may be associated with PC and this condition can damage liver cells, causing liver dysfunction and even liver failure. These pathological processes may negatively affect survival in patients with advanced PC, resulting in poor prognosis (6). Nakata et al. (36) showed that, in patients with pancreatic head cancer, presence of obstructive jaundice at the time of diagnosis could predict unfavorable survival. Obstructive jaundice is a very common picture in patients with PC (37). Current discussions regarding the need for preoperative biliary drainage in these patients is another issue that should be taken into account (37). Previously, total bilirubin level has been identified as an independent prognostic factor in pancreatic body/tail cancer but not in pancreatic head cancer (25). A 10-year study of 5460 men and 4843 women revealed that high serum bilirubin (in the normal range) was associated with lower likelihood of cancer-related death (7). Supporting most of the literature, we found that high bilirubin was associated with poor prognosis in our group of patients with PC.

Study Limitations

Our study has some limitations. First, as this was retrospective single-center study, these results must be confirmed through unbiased prospective studies. Second, the number of investigated inflammatory markers was low, and the great range of variations in these parameters from patient to patient must be considered before attempting to generalize our findings. Third, the small number of patients may have affected the reliability of statistical evaluations. Finally, prognostic assessment in this study was directly based on mortality, and therefore, possible conclusions regarding associations with morbidity or quality of life cannot be drawn from our data.

CONCLUSION

Preoperative levels of NLR, PLR and RDW do not appear to have value as prognostic indicators for mortality in patients with PC. Nonetheless, our results demonstrate that the PLR elevation in patients with PC could be indicative of the presence of poorly differentiated & undifferentiated tumors. We also observed that greater PLR values were associated with prolonged hospital stay, indicating that PLR could be valuable in estimating hospital stay. Although CA 19-9 levels showed significant correlations with NLR and PLR, the correlation coefficients were too low to suggest a direct relationship between this tumor marker and inflammation. Most importantly, high bilirubin level was found to be associated with increased likelihood of death, while having received adjuvant chemotherapy reduced the likelihood of death. Large-scale prospective studies with greater patient numbers are needed to adequately evaluate the possible role of inflammatory markers in predicting prognosis in PC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ethics Committee of Osmangazi University Faculty of Medicine (Date: 15.06.2021, Decision No: 04).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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