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Research Article

In Patients with Metastatic Pancreas Cancers, Evaluation of the Relationship Between Neutrophil Lymphocide Ratio, Trombocyte Index, Systemic Immune-inflamation Index and Clinical, Pathologic and Prognostic Factors

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Abstract

Objectives: In this study, we aimed to determine whether integrated markers that better reflect local immune response and systemic inflammation and based on clinically available peripheral neutrophil, lymphocyte and platelet counts are associated with treatment response and survival in pancreatic cancers.

Methods: We retrospectively evaluated the clinical, pathological and prognostic features of 75 patients who were diagnosed with metastatic pancreatic adenocarcinoma and who treated between January 1, 2012 and September 1, 2019 at Trakya University Medical Faculty, Medical Oncology Department. Since systemic inflammation markers did not have agreed threshold values in the literature, we determined the median values to be used as threshold values in our study.

Results: In our study; We found that the overall survival was longer in patients with lower than NLR median value (<3) (p=0.001). We determined that the high platelet count (≥235.10^3) was related to longer progression-free survival (p=0.02) and similarly, higher PCT (≥0.22) was related to longer progression-free survival (p=0.01). We found that the overall survival of patients with an ECOG score of 0-1 was longer than that of patients with an ECOG score of 2 (p=0.003). We determined that the overall survival in patients with the first series of disease control was longer than those without disease control (p=0.002).

Conclusion: Our study showed that NLR may be an independent marker predicting overall survival in patients with metastatic pancreatic cancer, and progression-free survival is associated with platelet count and PCT.

Keywords: Metastatic pancreatic cancer, SII, neutrophil lymphocyte ratio, platelet, PCT

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Pancreatic cancer is one of the most aggressive types of cancer. Surgical resection is the only curative treatment option; however, gemcitabine-based chemotherapy or FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) have prolonged the survival time of patients. Despite this, most patients with pancreatic cancer do not respond to treatment, and only a small percentage achieve disease stabilization or a partial response. Therefore, identifying a tool that can predict the prognosis of patients is essential.

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The importance of systemic inflammation in cancer progression and patient survival is well established. The relationship between cancer and chronic inflammation dates back to nearly a century ago when Rudolf Virchow first identified leukocytes in tumor tissue.[1,2] Since then, many studies have shown that chronic inflammation in tumor tissue, as a host response, affects tumor development, metastasis, prognosis, and response to treatment. Systemic inflammation involves immune cells, cytokines, and small inflammatory proteins, and can be detected in the systemic circulation. One of the routine indicators of systemic inflammatory response is hemogram parameters. Recent studies have shown the relationship between the degree of systemic inflammation and cancer, with parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune index (SII) being evaluated as systemic inflammation markers. Leukocyte and platelet counts, including neutrophils, lymphocytes, and monocytes, have been found to have prognostic value in various cancers, including pancreatic cancer: SII (Neutrophil × Platelet / Lymphocyte), Neutrophil / Lymphocyte ratio (NLR).

Systemic inflammation is a key promoter of tumor cell proliferation, invasion, and metastasis. The relationship between SII and prognosis in advanced pancreatic cancer stems from high SII values caused by thrombocytosis, neutrophilia, and lymphopenia, indicating increased inflammatory status and reduced immune system response. Increasing evidence has shown a positive correlation between neutrophilia and thrombocytosis with cancer. Neutrophils not only increase cancer cell proliferation and metastasis but also aid in immune evasion by cancer cells. In pancreatic cancer, platelets support the adhesion of tumor cells to evade immune surveillance. Circulating tumor cells (CTCs) are neoplastic cells shed into the bloodstream, associated with tumor metastasis. Platelets can also induce the epithelial-mesenchymal transition of CTCs during circulation. Conversely, lymphocytes play a crucial role in tumor defense by inducing cell death and inhibiting cell proliferation and migration. Lymphopenia, which indicates immune surveillance failure, is also seen in pancreatic cancer and is reported to be associated with poor survival in some malignant tumors.[3,4] Recently, SII has been used to obtain prognostic information in patients with various malignancies, including hepatocellular carcinoma, esophageal squamous cell carcinoma, and gastric cancer.[5-9]

Systemic inflammation may also affect a patient's response to chemotherapeutic agents. A study in a mouse model revealed that systemic inflammation induced resistance to gemcitabine in pancreatic cancer tissue, particularly through tumor-associated macrophages (TAMs).[10] Systemic inflammation can alter the response to chemotherapeutic agents in metastatic pancreatic cancer and affect patient survival. Therefore, the relationship between systemic inflammatory response and post-chemotherapy survival in pancreatic cancer patients has also been investigated. This study aimed to determine whether integrated markers based on clinically available peripheral neutrophil, lymphocyte, and platelet counts, which may better reflect local immune response and systemic inflammation, are correlated with treatment response and survival in pancreatic cancer patients.

Methods

Data Collection

The study was conducted after obtaining approval from the Scientific Research Ethics Committee of Trakya University Faculty of Medicine, dated November 6, 2019, with the approval number 18/24 (EK-1). Patients diagnosed with metastatic pancreatic adenocarcinoma at the Department of Medical Oncology, Trakya University Faculty of Medicine, between January 1, 2012, and September 1, 2019, were included in the study. The patients' files and hospital automation system records were reviewed retrospectively.

Data Analysis

For the 75 patients whose data were analyzed:

Clinical and demographic characteristics; age, sex, comorbidities, stage at presentation, histopathological type, ECOG performance status, metastasis sites and numbers, chemotherapy regimens, progression times, diagnosis, and death dates.

Before the first chemotherapy; CA 19-9 levels, neutrophil-lymphocyte ratio (NLR), platelet indices, including parameters such as mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), platelet count (PLT), Systemic immune index parameters; neutrophil, lymphocyte, platelet data were collected for further analysis.

Statistical Methods

The values of neutrophil-lymphocyte ratio, platelet indices, and systemic immune inflammation index were calculated based on the values at the time of diagnosis. Since there is no consensus on the optimal cut-off values of systemic inflammation markers in the literature, ROC analysis was used to determine the cut-off values for this study. The marker variables were tested in ROC analysis according to survival status variables. In the absence of statistical significance, median values were determined as cut-off values for this study. Overall survival (OS) was calculated as the time from diagnosis to death, and progression-free survival (PFS) as the time until the first progression. Statistical evaluation was performed using SPSS (Statistical Package for Statistical Sciences). Univariate and multivariate analyses were

performed. Data are presented as standard deviation (±). The comparison of parametric variables between groups was made using the independent t-test. The relationships of non-parametric variables with each other were assessed using the Chi-square test. Survival analyses were conducted using Kaplan-Meier analysis. Multivariate analysis was performed using Cox regression. A confidence interval of 95% and a p-value <0.05 were considered statistically significant.

Results

In our study, a total of 75 patients with metastatic pancreatic cancer were analyzed. The demographic and clinical characteristics of the patients are presented in Table 1, and their distributions are shown in Figures 1-5.

Table 1. Clinical and Demographic Characteristics of the Patients

Age (years, Mean±SD	62±10
Gender, n (%)	
Female	26 (34.7)
Male	49 (65.3)
ECOG Performance Score, n (%)	
0	27 (36.0)
1	40 (53.3)
2	8 (10.7)
Metastasis site, n (%)	
Liver	42 (52.5)
Lung	13 (16.2)
Lymph node	12 (15.0)
Adrenal	5 (6.2)
Peritoneum	4 (5.0)
Bone	4 (5.0)
First-line chemotherapy regimen, n (%)	
Gemcitabine-based regimen	61 (81.3)
Fluoropyrimidine-based regimen	13 (17.3)
Other	1 (1.3)
Second-line chemotherapy regimen, n (%)	
Gemcitabine-based regimen	7 (9.3)
Fluoropyrimidine-based regimen	23 (30.7)
Paclitaxel	1 (1.3)
Third-line chemotherapy regimen, n (%)	
Gemcitabine-based regimen	5 (6.7)
Fluoropyrimidine-based regimen	1 (1.3)
Irinotecan	2 (2.7)
Paclitaxel	1 (1.3)
Disease control, n (%)	
Achieved	26 (35)
Not achieved	49 (65)
Final Status, n (%)	
Deceased	72 (96)
Alive	3 (4.0)

SD: Standard Deviation; ECOG: Eastern Cooperative Oncology Group.

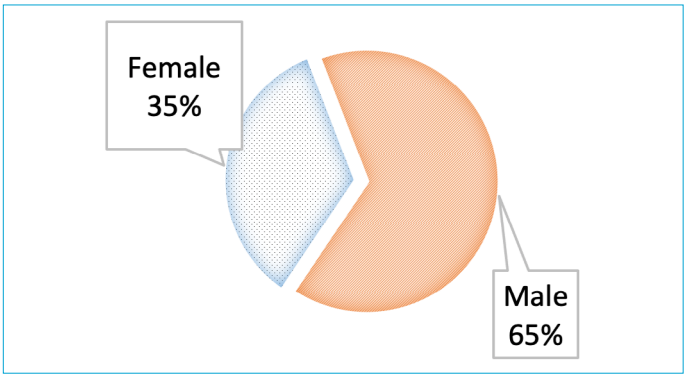

Figure 1. Gender distribution.

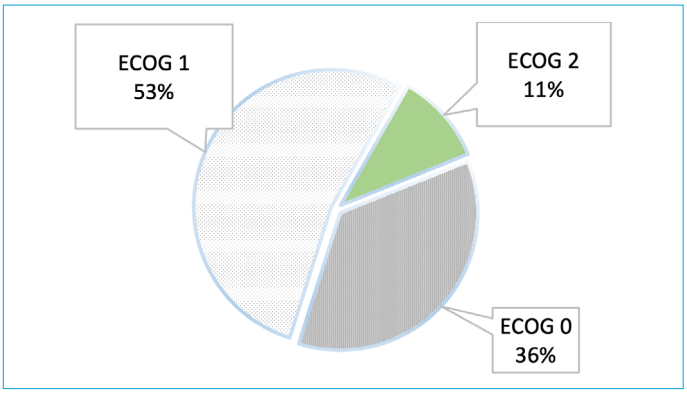

Figure 2. Performance Score (ECOG) distribution.

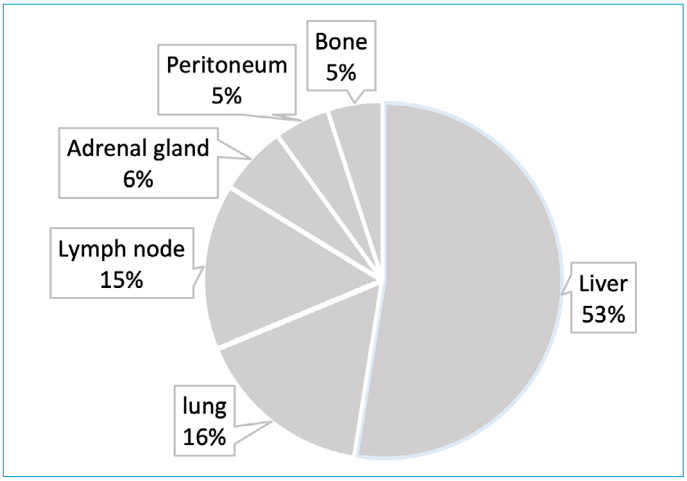

Figure 3. Distribution of Metastasis Locations.

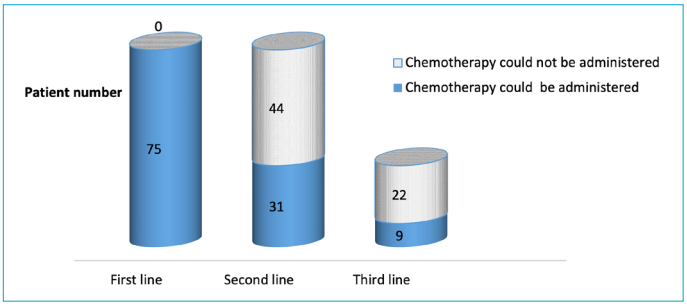

Figure 4. Patient-Chemotherapy Administration Distribution.

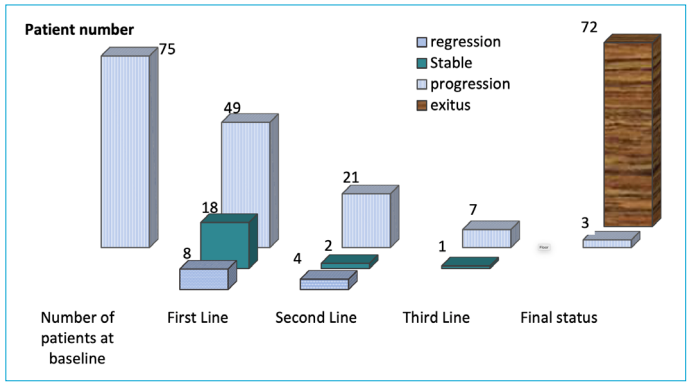

Figure 5. Distribution of Response to Chemotherapy Administration.

As statistical significance was not reached in the ROC analysis, it was decided that the identified cut-off values would not be used in our study. Instead, the median values of systemic inflammation markers were determined and used as cut-off values in our study. The median values of systemic inflammation markers are presented in Table 2.

Evaluation of the Relationship between Demographic and Clinical Characteristics and Progression-Free Survival

The relationship between demographic and clinical characteristics and median progression-free survival (PFS) was evaluated using univariate progression-free survival analysis (Table 3). The median PFS for the entire group was calculated as 2.9 months (95% CI 1.9–3.7 months).

According to this analysis: In patients with a platelet count <235,000/μL, the PFS was 2.1 months (1.4-2.8), whereas in patients with a platelet count ≥235,000/μL, the PFS was 3.7 months (3.3-4.1). The difference in PFS between the two groups was statistically significant (p=0.02).

Table 2. Median (Interquartile) Values of Systemic Inflammation Markers

Marker	Median	Mean±SD	Minimum-Maximum
CA19.9, U/ml	524	2269±7504	2-49584
NLR	3.0	4.48±4.62	1.24-27.80
Platelet, 10^3/μL	235	262±121	87-697
MPV, fL	9.28	9.45±1.43	6.29-12.60
PCT, (%)	0.22	0.24±0.12	0.07-0.74
PDW, fL	16.90	21.40±15.48	9.50-95.30
SII	768	1224±1396	176-8281

SD: Standard Deviation; CA19.9: Carbohydrate Antigen 19-9; NLR: Neutrophil to Lymphocyte Ratio; MPV: Mean Platelet Volume; PCT: Platecrit; PDW: Platelet Distribution Width; SII: Systemic Immune Inflammation Index.

In patients with PCT less than 0.22, the PFS was 2.1 months (1.6–2.5), whereas in patients with PCT of 0.22 or higher, the PFS was 3.6 months (3.3–4.0). The difference in PFS between the two groups was statistically significant (p=0.01).

Table 3. Relationship Between Demographic and Clinical Characteristics and Progression-Free Survival

Characteristics	Median PFS (months)	95% Confidence Interval	p
Age			
≤60	2.8	1.5-4.0	0.35
>60	2.9	2.2-3.5	
Gender			
Male	2.8	2.0-3.7	0.36
Female	2.4	0.8-4.0	
ECOG Performance score			
0	3.4	2.2-4.6	0.06
1	2.8	1.9-3.8	
2	1.1	0.2-2.1	
Metastasis location			
Liver (Met+)	2.7	1.5-3.9	0.74
Liver (Met-)	2.4	1.7-3.0	
Lung (Met+)	2.2	1.8-2.7	0.86
Lung (Met-)	2.7	1.2-4.2	
Lymph Node (Met+)	2.7	1.5-3.2	0.95
Lymph Node (Met-)	2.7	1.6-3.9	
First-line Chemotherapy Regimen			
Gemcitabine-based	2.7	1.6-3.8	0.31
Fluoropyrimidine-based	3.6	1.0-3.8	
CA 19.9			
Normal	3.2	2.4-4.0	0.32
Elevated	2.7	1.8-3.7	
NLR			
< 3	3.2	2.2-4.2	0.1
≥ 3	2.3	1.6-3.0	
Platelet Count			
< 235.103	2.1	1.4-2.8	0,02
≥235.103	3.7	3.3-4.1	
MPV			
<9.28	2.2	1.0-3.4	0.32
≥9.28	3.4	2.5-4.3	
PCT			
< 0.22	2.1	1.6-2.5	0.01
≥ 0.22	3.6	3.3-4.0	
PDW			
<.16.90	2.7	1.8-3.7	0.75
≥ 16.90	2.8	1.8-3.9	
SII			
< 768	2.8	1.5-4.2	
≥ 768	2.7	1.4-4.1	

PFS: Progression-Free Survival; ECOG: Eastern Cooperative Oncology Group; PCT: Platecrit; CA 19.9: Carbohydrate Antigen 19-9; NLR: Neutrophil-to-Lymphocyte Ratio; MPV: Mean Platelet Volume; PDW: Platelet Distribution Width; SII: Systemic Immune Inflammation Index.

Evaluation of the Relationship between Demographic and Clinical Characteristics and Overall Survival

The comparison of demographic and clinical characteristics with median OS was performed using univariate survival analysis (Table 4). The median OS for the entire group was found to be 7.0 months (95% CI 5.5-8.5 months).

According to this analysis:

According to the ECOG performance score, OS was 8.4 months (6.1-10.8) in patients with ECOG-0, 6.9 months (4.4-9.5) in patients with ECOG-1, and 3 months (1.1-4.9) in patients with ECOG-2. The difference between the groups was statistically significant (p=0.003).

At the first line, patients with disease control had a longer OS of 9.7 months (7.9-11.5), while patients without disease control had a shorter OS of 5.3 months (4.2-6.4). The difference between the groups was statistically significant (p=0.002).

In patients with NLR (Neutrophil-to-Lymphocyte Ratio) less than 3, the OS was 10.2 months (7.9-12.5), while in patients with NLR greater than or equal to 3, the OS was 5.6 months (4.0-7.1). The group with a low NLR had a significantly longer OS, and the difference was statistically significant (p=0.001).

The Relationship between Neutrophil-to-Lymphocyte Ratio and Demographic and Clinical Characteristics

In our study, patients with NLR (Neutrophil-to-Lymphocyte Ratio) greater than or equal to the median value (3.0) and patients with NLR less than the median value (3.0) were compared based on age, gender, ECOG performance score, metastasis site, and first-line disease control. No statistically significant difference was found between the two groups, and consistent results were obtained within each group (Table 5).

The Relationship of Platelet Count with Demographic and Clinical Factors

In our study, patients with a platelet count greater than or equal to the median value (235,103) were compared with those with a platelet count smaller than the median value (235,103) in terms of age, gender, ECOG performance score, metastasis location, and first-line disease control. No statistically significant differences were found (Table 6).

The Relationship of PCT with Demographic and Clinical Characteristics

In our study, patients with a PCT greater than or equal to the median value (0.22) were compared with those with a PCT smaller than the median value (0.22) in terms of age, gender, ECOG performance score, metastasis location, and

Table 4. Relationship between demographic and clinical characteristics and overall survival

Characteristics	Median PFS (months)	95% Confidence Interval	p
Age			
≤60	7.0	4.2 - 9.8	0.15
>60	6.99	4.3 - 9.6	
Gender			
Male	7.0	4.8 - 9.3	0.57
Female	6.76	4.1 - 9.4	
ECOG Performance score			
0	8.4	6.1 - 10.8	0.003
1	6.9	4.4 - 9.5	
2	3.0	1.1 - 4.9	
Metastasis location			
Liver (Met+)	5.7	3.7 - 7.7	0.77
Liver (Met-)	5.6	3.0 - 8.2	
Lung (Met+)	7.3	2.5 - 12.1	0.99
Lung (Met-)	5.6	4.1 - 7.1	
Lymph Node (Met+)	7.0	4.2 - 9.9	0.82
Lymph Node (Met-)	5.6	4.1 - 7.0	
First-line Chemotherapy Regimen			
Gemcitabine-based	7.8	6.0 - 9.6	0.91
Fluoropyrimidine-based	6.8	4.9 - 8.7	
Second-line Chemotherapy Regimen			
Gemcitabine-based	6.8	5.4 - 8.1	0.21
Fluoropyrimidine-based	10.2	9.5 - 10.9	
Disease Control			
Achieved	9.7	7.9 - 11.5	0.002
Not Achieved	5.3	4.2 - 6.4	
CA 19.9			
Normal	8.4	5.9 - 10.9	0.46
Elevated	6.8	5.1 - 8.5	
NLR			
< 3	10.2	7.9 - 12.5	0.001
≥ 3	5.6	4.0 - 7.1	
Platelet Count			
< 235.103	5.5	4.4 - 6.7	0,34
≥235.103	8,1	6.4 - 9,8	
MPV			
< 9.28	5.7	3.8 - 7.6	0.42
≥ 9.28	8.8	5.6 - 11.9	
PCT			
< 0.22	5.6	3.5 - 7.8	0.28
≥ 0.22	8.4	7.4 - 9.4	
PDW			
<.16.90	8.8	6.6 - 10.9	0.14
≥ 16.90	6.3	4.5 - 8.0	
SII			
< 768	8.4	5.9 - 11.0	0.15
≥ 768	6.8	3.5 - 10.1	

OS: Overall Survival; ECOG: Eastern Cooperative Oncology Group; CA19.9: Carbohydrate Antigen 19-9; NLR: Neutrophil-to-Lymphocyte Ratio; MPV: Mean Platelet Volume; PCT: Platecrit; PDW: Platelet Distribution Width; SII: Systemic Immune Inflammation Index.

Table 5. The Relationship Between NLR Ratio and Demographic and Clinical Characteristics

Characteristics	NLR<3.0	NLR≥3.0	p
Age, years			
Mean±Standard deviation	62±9	62±10	0.73
Gender, n			
Male/Female	21/15	28/11	0.13
ECOG Performance score, n (%)			
0	14 (39)	13 (33)	0.77
1	19 (53)	21 (54)	
2	3 (8)	5 (13)	
Metastasis location, n (%)			
Liver	26 (51)	16 (55)	0.66
Lung	10 (20)	3 (10)	
Lymph node	5 (10)	7(24)	
Adrenal	4 (7)	1 (3)	
Peritoneum	3 (6)	1 (3)	
Bone	3 (6)	1(3)	
Disease Control, n (%)			
Achieved	15 (42)	11 (28)	0.22
Not Achieved	21 (58)	28 (72)	

NLR: Neutrophil-to-Lymphocyte Ratio; ECOG: Eastern Cooperative Oncology Group.

Table 6. The Relationship of Platelet Count with Demographic and Clinical Characteristics

Characteristics	PLT<235.10³	PLT≥235.10³	p
Age, years			
Mean±SD	63±9	62±11	0.5
Gender, n			
Male/Female	24/13	25/13	0.93
ECOG Performance score, n (%)			
0	15 (40)	12 (32)	0.69
1	18 (49)	22 (58)	
2	4 (11)	4 (10)	
Metastasis location, n (%)			
Liver	22 (54)	20 (51)	0.86
Lung	5 (12)	8 (21)	
Lymph node	7 (17)	5 (13)	
Adrenal	3 (7)	2 (5)	
Peritoneum	2 (5)	2 (5)	
Bone	2 (5)	2 (5)	
Disease Control, n(%)			
Achieved	10 (27)	16 (42)	0.17
Not Achieved	27 (73)	22 (58)	

PLT: Platelet; ECOG: Eastern Cooperative Oncology Group.

first-line disease control. Similar trend results were obtained between the two groups, but no statistically significant differences were found (Table 7).

Table 7. The Relationship of PCT with Demographic and Clinical Characteristics

Characteristic	PCT<0.22	PCT≥0.22	p
Age, years			
Mean±SD	64±9	62±10	0.2
Gender, n			
Male/Female	20/13	25/13	0.65
ECOG Performance score, n (%)			
0	12 (36)	13 (34)	0.56
1	16 (49)	22 (58)	
2	5 (15)	3 (8)	
Metastasis location, n (%)			
Liver	18 (53)	20 (53)	0.17
Lung	2 (6)	9 (24)	
Lymph node	6 (18)	5 (13)	
Adrenal	1 (3)	3 (8)	
Peritoneum	4 (12)	0 (0)	
Bone	3 (9)	1 (3)	
Disease Control, n (%)			
Achieved	7 (29)	17 (71)	0.03
Not Achieved	26 (55)	21 (45)	

PCT: Platecrit; ECOG: Eastern Cooperative Oncology Group.

When the relationship between PCT and first-line disease control in metastatic pancreatic cancer patients was analyzed, statistically significant results were obtained (p=0.03). According to this, in patients who achieved disease control, 7 (29%) had a PCT smaller than 0.22, and 17 (%71) had a PCT greater than or equal to 0.22. In patients who did not achieve disease control, 26 (55%) had a PCT smaller than 0.22, while 21 (45%) had a PCT greater than or equal to 0.22.

Multivariate Analysis of Factors Predicting Overall Survival

In our study, a multivariate analysis of factors predicting overall survival was performed using the Cox regression method (Tables 8 and 9). Survival graphs (Figs. 6-8) were drawn according to the factors.

Discussion

Pancreatic cancer is one of the most common malignancies worldwide. The prognosis of pancreatic cancer is poor. Therefore, ongoing research is focused on identifying new predictive factors that influence prognosis, treatment response, and survival, to aid in the early diagnosis and treatment of patients.

ECOG performance status is useful in assessing a patient's ability to tolerate chemotherapy and in evaluating prognosis. Regardless of age, patients with lower performance

Table 8. Multivariate Analysis of Demographic and Clinical Characteristics Predicting OS

Characteristics	HR	%95 Confidence Interval	p
A			
<60			
≥60	1.42	0.87-2.28	0.15
Gender			
Male/Female	0.87	0.52-1.42	0.50
ECOG Performance score			0.01
0	1.34		0.006
1	4.28	0.81-2.23	0.26
2		1.75-10.49	0.001
Metastasis location			
Liver	0.43	0.06-3.23	0.30
Lung	0.90	0.39-2.05	
Disease Control			
Achieved	0.46	0.27-0.76	0.002
Not Achieved			

HR: Hazard ratio; ECOG: Eastern Cooperative Oncology Group.

Table 9. Multivariate analysis of systemic inflammation markers predicting OS

Variables	HR	95% Confidence Interval	p
CA 19.9			
Normal	1.28	0.66-2.45	0.45
Elevated			
NLR (< 3)			
< 3	2.23	1.37-3.65	0.001
≥ 3			
Platelet count			
< 235.103			
≥235.103	0.80	0.50-1.27	0,35
MPV (< 9.28)			
< 9.28			
≥ 9.28	0.82	0.49-1.35	0.43
PCT (< 0.22)			
< 0.22			
≥ 0.22	0.77	0.47-1.25	0.29
PDW (< 16.90)			
<.16.90			
≥ 16.90	1.43	0.88-2.32	0.15
SII (< 768)			
< 768			
≥ 768	1.41	0.88-2.25	0.15

HR: Hazard Ratio; CA19.9: Carbohydrate Antigen 19-9; NLR: Neutrophil-Lymphocyte Ratio; MPV: Mean Platelet Volume PCT: Plateletcrit; PDW: Platelet Distribution Width; SII: Systemic Immune-Inflammation Index.

scores typically have poorer chemotherapy tolerance and shorter overall survival.[11] In our study, we obtained results in line with the literature. We found that the overall survival (OS) time significantly decreased across patient groups with ECOG performance scores of 2, 1, and 0 (p=0.003). The OS times were 8.4 months (6.1-10.8) for patients with an ECOG-0 score, 6.9 months (4.4-9.5) for those with an ECOG-1 score, and 3 months (1.1-4.9) for those with an ECOG-2 score.

In patients who achieved disease control in the first-line treatment, the OS was longer, at 9.7 months (7.9-11.5), while it was shorter, at 5.3 months (4.2-6.4), in patients with disease progression. The difference between these groups was statistically significant (p=0.002).

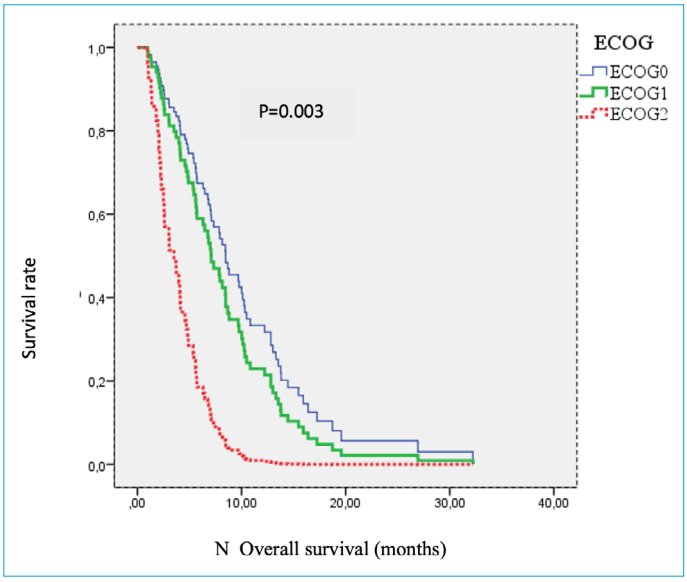

Figure 6. ECOG Performance Score - Overall Survival Graph.

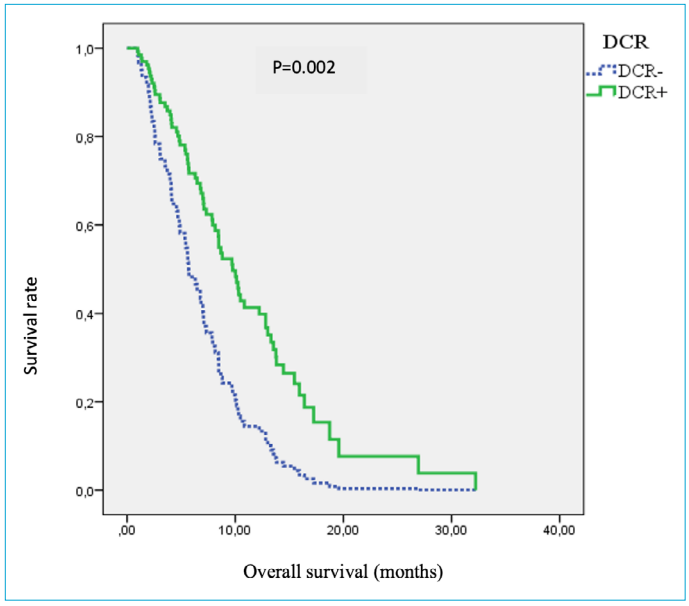

Figure 7. Disease Control - Overall Survival Graph.

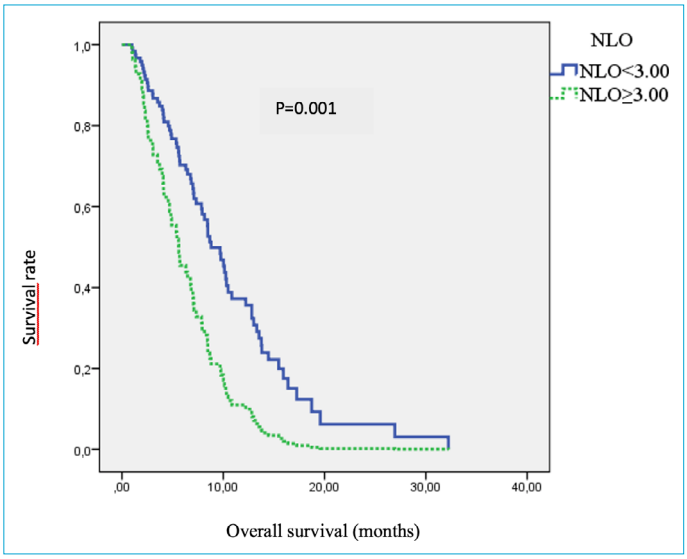

Figure 8. Neutrophil-Lymphocyte Ratio - Overall Survival Graph.

It is well known that the inflammatory microenvironment plays a critical role in cancer development and progression, angiogenesis, metastasis, and tumor resistance to systemic treatments.[12]

An increase in the neutrophil-to-lymphocyte ratio (NLR), which is thought to reflect systemic inflammation, is considered an indicator of pro-tumoral inflammation and has been recognized as a poor prognostic factor in various types of cancer.[13] An increase in NLR is due to either an elevation in neutrophil count or a decrease in lymphocyte count, with this imbalance shifting towards a pro-tumoral inflammatory state. Conversely, an increase in lymphocyte count or a decrease in neutrophil count reverses this balance, favoring an anti-tumoral immune response. Therefore, an elevated NLR is considered a poor prognostic indicator, while a decrease in NLR is associated with a better prognosis.[14] Another study has confirmed that a high NLR (NLR≥3) is associated with shorter survival.[15] In pancreatic cancer, it has been shown that a neutrophil-to-lymphocyte ratio (NLR) of 5 or higher is associated with shorter overall survival and progression-free survival.[16] In a study by Martin et al.,[17] 124 patients with metastatic (n=84) and locally advanced unresectable (n=40) pancreatic cancer were retrospectively analyzed. The median survival was found to be 2.6 months for patients with an NLR of 5 or higher, and 8.5 months for patients with an NLR less than 5. A study conducted on patients with locally advanced and metastatic pancreatic cancer showed that patients with a high baseline NLR (3 or higher) had a shorter survival time.[18] In our study, consistent with the literature, we found that the overall survival (OS) time was significantly longer in patients with an NLR below the median value,[3] with a median of 10.2 months (7.9-12.5), while it was shorter in patients with an NLR equal to or above the median value,[3] with a median of 5.6 months (4.0-7.1) (p=0.001). Although the progression-free survival (PFS) time did not show a statistically significant difference (p=0.1), we observed a similar trend, with a median of 3.2 months (2.2-4.2) in patients with an NLR less than 3 and 2.3 months (1.6-3.0) in patients with an NLR of 3 or higher. We identified that a high NLR (≥3) is an independent risk factor that reduces overall survival (OS) time and is therefore associated with poor prognosis. This finding suggests that NLR could be a useful marker for detecting poor prognosis.

In our study, the PFS duration was 2.1 months (1.4-2.0) in patients with a platelet count below the median value (235,103), while it was longer at 3.7 months (3.3-4.1) in patients with a platelet count at or above the median value. The difference between the two groups in terms of PFS duration was statistically significant (p=0.02). For PFS duration, patients with a PCT value below 0.22 had a duration of 2.1 months (1.6-2.5), whereas those with a PCT value above or equal to 0.22 had a PFS duration of 3.6 months (3.3-4.0). The difference in PFS duration between these two groups was statistically significant (p=0.01). Similarly, in OS duration, patients with a platelet count below 235,103 had a median of 5.5 months, while those with a platelet count of 235,103 or higher had a median of 8.1 months. However, the difference in OS duration between the two groups was not statistically significant (p=0.34).

Platelets are blood cells that are associated with chronic inflammation, a key factor in cancer development.[19] Therefore, numerous studies have been conducted on the prognostic value of platelets in cancer patients. A study published in 2016, involving 311 patients with pancreatic cancer, revealed that thrombocytosis at diagnosis was significantly associated with a reduced risk of death in a multivariable Cox proportional hazards model.[20]

In another study, the preoperative platelet counts of patients with pancreatic ductal adenocarcinoma who underwent potentially curative pancreaticectomy procedures between 1988 and 1999 were evaluated to assess the effect of platelet count on postoperative recovery and survival. It was observed that platelet counts were not related to disease stage, tumor size, weight loss, bilirubin concentration, non-surgical treatment, or other hematologic and pathological indices. The median survival for patients with platelet counts less than 300×10^9/L was 9.7 months, while for those with counts greater than 300×10^9/L, it was 24.3 months (p=0.03).[21]

In metastatic pancreatic adenocarcinoma patients, the first-line myelosuppressive chemotherapeutic regimens commonly used for treatment, particularly gemcitabine,

can often lead to anemia, neutropenia, and thrombocytopenia. In locally advanced cancers, invasion of the portal vein or splenic vein, liver dysfunction due to metastasis, and hypersplenism can also be contributing factors to thrombocytopenia. Additionally, whether an increased platelet count and, consequently, better survival reflect the antiangiogenic properties of platelets in this disease, or whether low platelet counts indicate megakaryocyte inhibition as a reflection of advanced undetectable disease stages, remains uncertain.

Moreover, the anticancer tendency of platelets has been noted in several in vitro studies. In the early 2000s, Ahmad and colleagues demonstrated that upon appropriate activation, human platelets could induce apoptosis of tumor cells.[22] Recently, Wang and Zhang observed that murine platelets directly inhibited the growth of tumor cells.[23] These findings suggest that the role of platelets in cancer progression may not be as straightforward as previously predicted. Platelets play a crucial role in tumor development and metastasis. They initiate tumor growth by inducing angiogenesis through the VEGF pathway. Additionally, it has been shown that during the circulation of tumor cells, they adhere to other tumor cells and platelets. This interaction may have a significant role in tumor cell aggregation and the survival of tumor cells.[24]

In pancreatic cancer research, as in other common cancers, contradictory results have been observed. Some studies indicate that thrombocytosis is negatively correlated with survival,[25-27] while others show the opposite or report no relationship at all.[21,28]

It is possible that the anti-cancer tendency of platelets plays a role in the inverse relationship between thrombocytopenia and pancreatic cancer survival. However, this hypothesis needs further validation.[20] Genetic and acquired factors such as race, age, smoking status, alcohol consumption, and physical activity can influence platelet count and MPV.[29,30]

The most important of the platelet indices, MPV (Mean Platelet Volume), is considered a parameter indicating inflammation and is used for the early detection of platelet activation.[31] It has been shown that platelets with a higher MPV, meaning larger in size, are metabolically more active and enzymatically richer compared to smaller platelets.[32] Larger platelets contain more granules and synthesize higher amounts of vasoactive and prothrombotic substances such as Tx A2 and ADP. Studies have shown that platelets with larger volumes are more active, which facilitates thrombus formation in the vascular bed.[33] There are many publications in the literature examining the relationship between MPV and cancer. In patients with endometrial cancer, the MPV value was found to be higher compared to patients with endometrial hyperplasia and the control group.[34]

In our study, for patients with an MPV value below the median value (9.28), the PFS duration was 2.2 months (1.0-3.4), and the OS duration was 5.7 months (3.8-7.6). In contrast, for patients with an MPV value above or equal to the median value (9.28), the PFS duration was 3.4 months (2.5-4.3), and the OS duration was 8.8 months (5.6-11.9). However, the difference in both OS (p=0.42) and PFS (p=0.32) durations between the two groups was not statistically significant.

In our study, for PFS duration, patients with an SII value below 768 had a PFS duration of 2.8 months (1.5-4.2), whereas those with an SII value above or equal to 768 had a PFS duration of 2.7 months (1.4-4.1). There was no statistically significant difference in PFS duration between the two groups (p=0.91). For OS duration, patients with an SII value below the median (768) had a OS duration of 8.4 months (5.9-11.0), while those with an SII value above or equal to 768 had a OS duration of 6.8 months (3.5-10.1). The difference in OS duration between the two groups was not statistically significant (p=0.15).

SII is a newly defined inflammation-associated index and is a comprehensive combination based on peripheral lymphocyte, neutrophil, and platelet counts. Numerous studies have been conducted that support our findings regarding the components of this combination. NLR is often related to the increased neutrophil count in the blood and the accompanying lymphocytopenia. A high neutrophil count may contribute to the formation of a tumor microenvironment where various growth factors are released, which can support the development and progression of neoplasms.[35] In addition, due to relative lymphocytopenia, the immune response that should be directed towards cancer cells via lymphocytes is impaired, which may lead to an increase in recurrence rates. This can be explained by the tumor cell being deprived of the immune response generated by tumor-infiltrating lymphocytes.[36] It has been shown that when the number of lymphocytes in peripheral blood decreases, an immune-tolerant microenvironment forms around the tumor, and lymphopenia thus has a negative prognostic effect.[3] In patients with pancreatic ductal adenocarcinoma, it has been shown that as the T stage increases, the numbers of CD3, CD4, and CD8 lymphocytes decrease in correlation with the stage of pancreatic cancer.[37] In a study investigating the importance of lymphocyte levels in patients with pancreatic cancer, it was found that the lymphocyte count of pancreatic cancer patients was lower compared to the control group and patients with

chronic pancreatitis. Lymphocyte count was also found to be lower in Stage II B-IV pancreatic cancer patients compared to those in Stage 0-II A.[38] Platelets play an important role in inflammation.[39] Chronic inflammation is one of the factors involved in the etiology of pancreatic cancer. In fact, pancreatic cancer is the cancer most notably associated with lymphopenia when compared to other gastrointestinal system cancers. It is believed that the disruption of balance and coordination within the lymphocyte system and immune system in pancreatic cancer may play a role in poor prognosis and tumor progression.[40] Data has been obtained proving the crucial role of lymphocytes in immune response against tumors.[41]

Conclusion

Our study demonstrated that the neutrophil-lymphocyte ratio (NLR) may serve as an independent predictor of overall survival in patients with metastatic pancreatic cancer, while progression-free survival was associated with platelet count and thrombocytocrit. Further prospective randomized controlled trials with larger sample sizes are required to investigate the relationship between systemic immune-inflammation indices (SII), particularly platelet-related parameters, and pancreatic cancer outcomes.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with the Princİples of the Declaration of Helsinki. The Ethics Committee of Trakya University approval was granted before the study (TUTF-BAEK 2019/356) Ethics Committee (Date: 06.11.2019 decision no: 18-24).

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