ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

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Opere Olmuş Pankreas Kanseri Hastalarında Periferik Kandaki İnflamasyon Parametrelerinin Sağkalım Üzerine Olan İlişkisi

The Relationship of Peripheral Blood Inflammation Parameters to Survival in Operated Pancreatic Cancer Patients

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ÖZET

GİRİŞ ve AMAÇ: Bu çalışmada, nötrofil-lenfosit oranı (NLO), platelet-lenfosit oranı (PLO), C-reaktif protein (CRP)/lenfosit oranı (CLO) ve CRP/albümin oranı (CAO) gibi inflamasyon belirteçleri ve tümör belirteçlerinin (karbonhidrat antijeni 19-9 [CA19-9] ve TNM evresi) opere olmuş pankreas kanseri hastalarında sağkalımı öngörmede kullanılabilirliğinin araştırılması amaçlandı.

YÖNTEM ve GEREÇLER: Bu retrospektif çalışmaya, opere olmuş 54 pankreas kanseri hastası dahil edildi. Hastaların demografik özellikleri, tanı anındaki TNM evresi ve tanı öncesi 1 ay içindeki inflamasyon belirteçleri (NLO, PLO, CLO ve CAO) ve CA 19-9 değerleri ve sağkalım sonucu kaydedildi. Klinikopatolojik parametreler ve inflamasyon belirteçleri genel sağkalım süresi ve mortalite riski ile ilişkileri açısından tek-değişkenli ve çok-değişkenli Cox-regresyon analizleri ile değerlendirildi.

BULGULAR: Toplam popülasyonda genel sağkalım süresi 13 ay (%95 GA 0.80-25,1 ay) olarak bulundu. Ileri yaş (HR 2,21, %95 GA 1,10-4,42, p=0,019) ve ileri T evresi (HR 2,33, %95GA 1,07-5,06, p=0,033) tek-değişkenli analizde mortalite riskinde artışla ilişkisi gösterilen tek parametreler iken, çok-değişkenli analizde bu iki parametrenin sağkalım üzerindeki anlamlı öngördürücü etkisi doğrulanamadı (sırasıyla, p=0,071 ve p=0,083). CA 19-9, NLO, PLO, CLO ve CAO dahil olmak üzere tümör veya inflamasyon belirteçlerinin hiçbirisinin sağkalım süresi veya mortalite riski üzerine anlamlı etkisi saptanmadı

TARTIŞMA ve SONUÇ: Sonuç olarak, bulgularımız opere olmuş pankreatik adenokarsinoma hastalarında, preoperatif olarak ölçülen inflamasyon belirteçlerinin (örn. NLO, PLO, CLO ve CAO) veya CA 19-9 düzeylerinin sağkalım üzerine anlamlı bir etkisi olmadığı yönündedir.

Anahtar Kelimeler: inflamasyon belirteçleri, CA19-9, tümör evresi, sağkalım sonuçları, opere pankreatik kanser

ABSTRACT

INTRODUCTION: This study aimed to investigate the utility of inflammation-based markers including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP)/lymphocyte ratio (CLR), CRP/albumin ratio (CAR) and tumor markers (carbohydrate antigen 19-9 [CA19-9] and TNM stage) in predicting survival outcomes among patients with operated pancreatic cancer.

METHODS: A total of 54 patients with operated pancreatic adenocarcinoma were included in this retrospective study. Data on patient demographics, TNM stage at diagnosis, the inflammation-based markers (NLR, PLR, CLR and CAR) and CA 19-9 values within 1 month prior to diagnosis and the final survival outcome were recorded. Clinicopathological parameters and inflammation-based markers were evaluated with respect to overall survival (OS) time and mortality risk using univariate and multivariate Cox-regression analyses.

RESULTS: OS time was 13 months (95% CI 0.80 to 25.1 months) in the overall study population. Older age (HR 2.21, 95% CI 1.10 to 4.42, p=0.019) and advanced T stage (HR 2.33, 95% CI 1.07 to 5.06, p=0.033) were the only factors associated with increased risk of mortality in the univariate analysis, whereas multivariate analysis did not confirm their predictive role on survival (p=0.071 and p=0.083, respectively). None of tumor or inflammation-based markers including CA 19-9, NLR, PLR, CLR and CAR had significant impact on survival time or mortality risk.

DISCUSSION AND CONCLUSION: In conclusion, our findings in patients with operated pancreatic adenocarcinoma revealed that none of the preoperatively determined inflammation-based marker ratios (i.e., NLR, PLR, CLR and CAR) or CA 19-9 had significant impact on survival outcome

Keywords: inflammation-based markers, CA19-9, tumor stage, survival outcome, operated pancreatic cancer

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INTRODUCTION

Pancreatic adenocarcinoma is associated with poor prognosis and a high recurrence rate after surgery despite the advanced surgical techniques and option of perioperative chemotherapy (1-5).

Most patients are already at an advanced stage or metastatic at the time of diagnosis, and chemo/radiotherapy remains to be the only approach used to palliate symptoms and increase survival in these patients (3,5-7). The operable pancreatic cancers (10-15% of patients), particularly the borderline resectable patients, are considered an important subgroup due to increased likelihood of R0 resections and decreased risk of lymph node positivity and local recurrence with the neoadjuvant treatment (6-8). In this regard, proper clinical staging and identification of poor prognostic factors alongside the resectability and need of neoadjuvant chemotherapy before starting treatment are valuable in estimating survival outcomes and implementing appropriate treatment protocols in pancreatic cancer patients (4,6,7,9,10).

Although, tumor-related pathological factors are well-established prognostic markers in pancreatic adenocarcinoma, they are highly dependent on histological examinations and are only available for assessment after surgery (4,11). Moreover, radiological findings may not correlate with intraoperative or histopathological findings in pancreatic cancer (7,12,13).

Hence, there is a need for novel prognostic markers that are usable in the preoperative setting to predict survival outcome as well as the risk of recurrence and thus to help in risk stratification of pancreatic cancer patients who would benefit from surgery and to decide therapeutic strategies (4,5,14).

The systemic inflammation has become increasingly recognized as a critical factor in cancer pathogenesis (4,15,16). Various systemic inflammatory markers readily available in routine clinical practice are considered potent prognostic factors for cancer survival (4). Accordingly, in addition to tumor markers such as tumor stage and carbohydrate antigen 19-9 (CA19-9), several markers based on preoperative systemic inflammation and/or nutritional status such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), C-reactive protein (CRP)/lymphocyte ratio (CLR), CRP/albumin ratio (CAR), neutrophil/albumin ratio (NAR), platelet/albumin ratio (PAR), prognostic nutritional index (PNI) and albumin/globulin ratio (AGR) have been suggested to be useful in prediction of pancreatic cancer prognosis and survival (4,5,7,10,13,17-22). However, the published literature on utility of systemic inflammation-based markers remains controversial in the setting of pancreatic cancer prognostication (6,7,10,23,24).

Therefore, this retrospective study aimed to investigate the utility of inflammation-based markers (NLR, PLR, CLR, CAR) and tumor markers (CA19-9, TNM stage) in predicting survival outcomes among patients with operated pancreatic cancer.

METHODS

Study population

A total of 54 patients (median age: 63.5 years, 55.6% were males) operated with the diagnosis of pancreatic adenocarcinoma at a tertiary care center between January 2011 and December 2018 were included in this retrospective study. Patient underwent radical resection for pancreatic cancer who have postoperative histopathology confirmed pancreatic cancer and those without any antibiotic anti-inflammatory therapy, radiotherapy, chemotherapy, or other treatments before surgery; and those with complete clinical data and follow-up data available were included in this study. Presence of other malignant tumors or distant metastases, autoimmune or infectious diseases and recent history of treatment with glucocorticoid or other immunosuppressive drugs were the exclusion criteria of the study.

The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Date of Approval: 13/04/2022, Reference number /Protocol No: E-10840098-772.02-2389/345).

Data collection

Data on patient demographics (age, gender) and TNM stage of disease at diagnosis (via the AJCC8), the blood-based analysis including inflammation-based markers (NLR, PLR, CLR and CAR) and CA 19-9 values within 1 month prior to diagnosis, and the final survival outcome were recorded. Clinicopathological parameters and inflammation-based markers were evaluated with respect to overall survival (OS) time and mortality risk using univariate and multivariate Cox-regression analyses. The CA 19-9, NLR, PLR, CLR and CAR were calculated and evaluated with respect to cut-off values of <42.11, 2.5, 138.98, 5.88 and 2.70, respectively, based on the corresponding median values obtained in the overall study population.

Statistical analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp.,

Armonk, NY). Numerical data for non-normally distributed variables were analyzed via Mann-Whitney U test. Survival analysis was made via Kaplan Meier analysis and comparisons were made via Log-Rank test. Cox proportional hazard analysis was used to estimate the level of significance. Data were expressed as median (range), 95% confidence interval (CI) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and survival outcome

Median patient age at diagnosis was 63.5 (range: 53.0) years and 55.6% of patients were males. Most of patients had T3 (52.9%) and N0-N1 (88.2%) stage tumor at the time of diagnosis. Laboratory findings prior to surgery are provided in Table 1. Overall, 68.5% of patients survived (Table 1).

Table 1. Baseline Characteristics and Survival Outcome

Patient demographics	
Age (year), median(range)	63.5 (53.0)
Gender, n(%)	
Male	30 (55.6)
Female	24 (44.4)
Tumor pathology	
Tumor (T) stage, n(%)	
1	8 (15.7)
2	11 (21.6)
3	27 (52.9)
4	5 (9.8)
N Stage, n(%)	
0	20 (39.2)
1	25 (49.0)
2	6 (11.8)
Blood parameters prior to diagnosis, median(range)	
Hb (g/dL)	13.10 (10.96)
Hct (%)	40.30 (28.12)
CRP(mg/L)	9.50 (153.97)
Albumin (g/dL)	3.80 (2.37)
CA 19-9 (U/mL)	42.11 (11244.57)
Neutrophil (10^3/uL)	4.67 (12.30)
Lymphocyte (10^3/uL)	1.81 (4.35)
Platelet (10^3/uL)	276.70 (462.77)
MPV (fL)	9.20 (10.54)
NLR	2.50 (11.33)
PLR	138.98 (546.22)
CLR	5.88 (96.27)
CAR	2.70 (42.78)
Survival outcome, n(%)	
Non-survivor	17 (31.5)
Survivor	37 (68.5)

Hb: Hemoglobin; Hct: Hematocrit; CRP: C-reactive protein; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; CLR: CRP/lymphocyte ratio; CAR: CRP/albumin ratio

Study variables with respect to overall survival time

OS time was 13 months (95% CI 0.80 to 25.1 months) in the overall study population. Older age (≥63.5 vs. <63.5 years: 10(7.46-12.54) vs. 52 (0-108.46) months, p=0.017), advanced T stage (T3-4 vs. T1-T2 stage: 23(7.15-33.32) vs. 55.63 (35.06-76.20) months, p=0.023) and N stage (N1-N2 vs. N0 stage: 11 (8.19-13.81) vs. 52 (3.33-100.67) months, p=0.048) were associated with significantly shorter median OS time (Table 2, Fig 1).

Table 2. Study Variables with Respect to Overall Survival Time

		Overall survival time (month)	p value
		median (95% CI LB-UB)	
Total (n=54)		13(0.80-25.21)	
Age (year)	<63.5	52 (0-108.46)	**0.017**
	≥63.5	10 (7.46-12.54)	
Gender	Male	16 (3.34-28.65)	0.722
	Female	11 (0-24.74)	
T stage	1-2	55.63 (35.06-76.20)	**0.023**
	3-4	23 (7.15-33.32)	
N stage	0	52 (3.33-100.67)	**0.048**
	1-2	11 (8.19-13.81)	
Hemoglobin (g/dL)	<13.1	13 (2.16-23.84)	0.681
	>13.1	13 (0.96-25.04)	
Hematocrit (%)	<40.3	13 (0.93-25.07)	0.921
	>40.3	16 (2.67-29.33)	
Neutrophil (10^3/uL)	<4.67	13 (2.06-23.94)	0.968
	>4.67	23 (0-51.42)	
Lymphocyte	<1.81	13 (0-31.01)	0.943
	>1.81	12 (0-24.20)	
Platelet (10^3/uL)	<276.70	11 (7.74-14.26)	0.832
	>276.70	23 (8.20-37.80)	
MPV (fL)	<9.2	12 (8.74-15.26)	0.506
	>9.2	23 (9.56-36.44)	
CRP (mg/L)	<9.5	11 (7.87-11.13)	0.733
	>9.5	23 (11.40-34.60)	
Albumin (g/dL)	<3.8	13 (4.21-21.79)	0.690
	>3.8	20 (0.67-39.33)	
CA 19-9 (U/mL)	<42.11	23 (0-63.73)	0.116
	>42.11	11 (6.71-15.30)	
NLR	<2.5	10 (4.49-15.51)	0.456
	>2.5	20 (11.28-28.72)	
PLR	<138.98	10 (8.08-11.91)	0.277
	>138.98	23 (11.14-34.87)	
CLR	<5.88	11 (4.43-17.57)	0.699
	>5.88	16 (4.27-27.73)	
CAR	<2.70	10 (6.32-13.68)	0.828
	>2.70	22 (9.16-34.84)	

Hb: Hemoglobin; Hct: Hematocrit; CRP: C-reactive protein; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; CLR: CRP/lymphocyte ratio; CAR: CRP/albumin ratio; ref: reference; CI: Confidence interval, LB: Lower bound; UB: Upper bound. Log rank test. Values in bold indicate statistical significance (p<0.05)

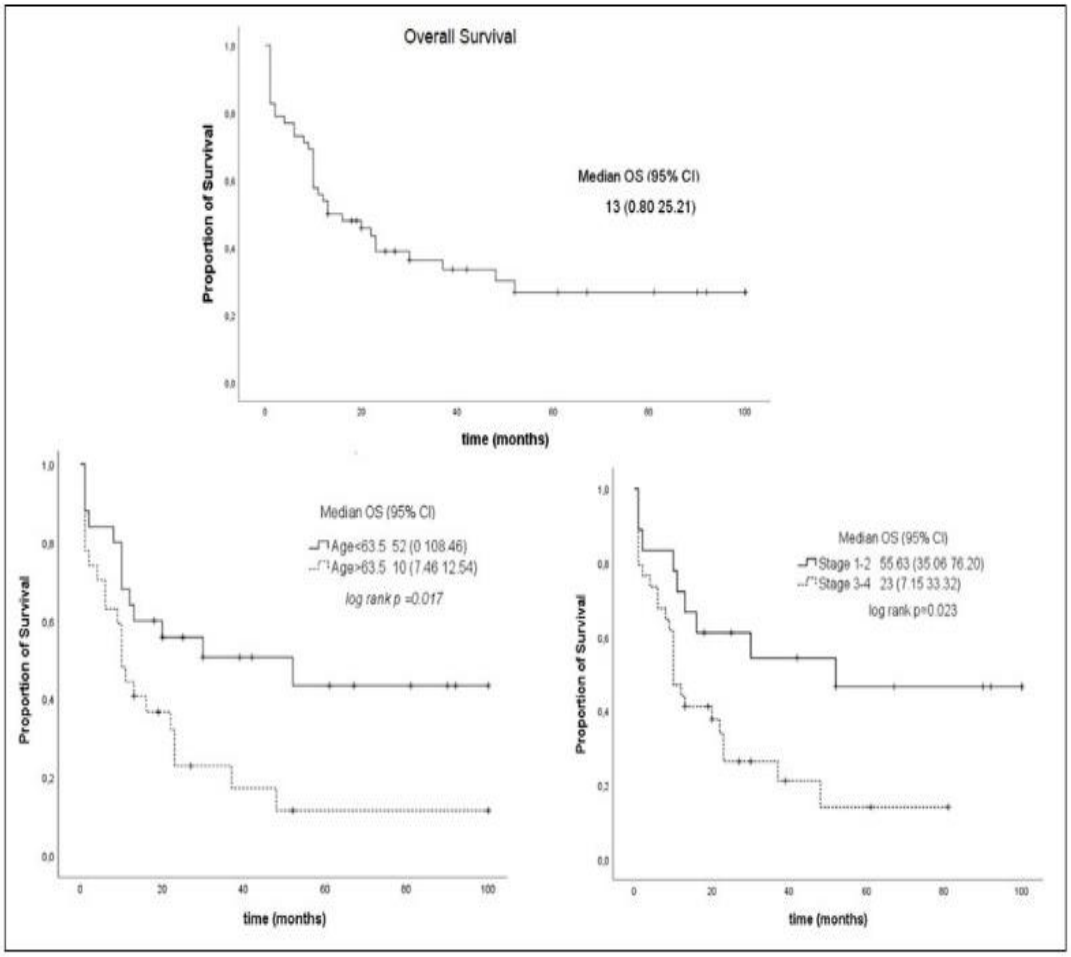

Fig 1. Kaplan-Meier Curves for Overall Survival in All Patients and According to Age at Diagnosis and TumorStage

None of the inflammation-based parameters including NLR, PLR, CLR and CAR, or the CA 19-9 had significant impact on survival time (Table 2).

Cox regression analyses of the factors affecting overall survival

Older age (≥63.5 vs. <63.5 years: HR 2.21, 95% CI 1.10 to 4.42, p=0.019) and advanced T stage (T3-4 vs. T1-T2 stage: HR 2.33, 95% CI 1.07 to 5.06, p=0.033) were the only factors associated with increased risk of mortality in the univariate analysis. In the ultivariate Cox regression analysis neither older age nor T stage were found to predict survival (p=0.071 and p=0.083, respectively) (Table 3).

None of the inflammation-based parameters including NLR, PLR, CLR and CAR, or the CA 19-9 had significant impact on the mortality risk in univariate analysis (Table 3).

Table 3. Univariate and Multivariate Cox Regression Analyses of the Factors Affecting Overall Survival

		Univariate analysis		Multivariate analysis	
		HR (95% CI LB-UB)	**p value**	**HR (95% CI LB-UB)**	**p value**
Variables					
Age	<63.5 (ref)	1	**0.019**	1	0.071
	≥63.5	2.21 (1.10 4.42)		1.92 (0.95 3.910)	
Gender	Male (ref)	1	0.732		
	Female	0.89 (0.45 1.75)			
T stage	1-2 (ref)	1	**0.033**	1	0.083
	3-4	2.33 (1.07 5.06)		2.02 (0.91 4.74)	
N stage	0 (ref)	1	0.061		
	1-2	2.06 (0.97 4.40)			
Hemoglobin	<13.1 (ref)	1	0.692		
	>13.1	0.88 (0.45 1.70)			
Hematocrit	<40.3 (ref)	1	0.924		
	>40.3	0.97 (0.50 1.88)			
Neutrophil	<4.67 (ref)	1	0.969		
	>4.67	0.98 (0.30 3.21)			
Lymphocyte	<1.81 (ref)	1	0.945		
	>1.81	0.98 (0.50 1.90)			
Platelet	<276.70 (ref)	1	0.838		
	>276.70	0.93 (0.48 1.81)			
MPV	<9.2 (ref)	1	0.523		
	>9.2	0.81 (0.41 1.57)			
CRP	<9.5 (ref)	1	0.743		
	>9.5	0.89 (0.46 1.76)			
Albumin	<3.8 (ref)	1	0.701		
	>3.8	0.88 (0.45 1.72)			
CA 19-9	<42.11 (ref)	1	0.135		
	>42.11	1.71 (0.85 3.44)			
NLR	<2.5 (ref)	1	0.475		
	>2.5	1.28 (0.65 2.53)			
PLR	<138.98 (ref)	1	0.299		
	>138.98	0.70 (0.36 1.37)			
CLR	<5.88 (ref)	1	0.710		
	>5.88	1.14 (0.57 2.30)			
CAR	<2.70 (ref)	1	0.834		
	>2.70	0.93 (0.47 1.84)			

Hb: Hemoglobin; Hct: Hematocrit; CRP: C-reactive protein; MPV: Mean platelet volume; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; CLR: CRP/lymphocyte ratio; CAR: CRP/albumin ratio; ref: reference; HR: Hazard Ratio; CI: Confidence interval, LB: Lower bound; UB: Upper bound.
Values in bold indicate statistical significance (p<0.05)

DISCUSSION

Our findings revealed no significant impact of CA 19-9, NLR, PLR, CLR and CAR detected within 1 month before the diagnosis on survival outcome in operated pancreatic cancer patients. In addition, while older age (≥63.5 years) and advanced T stage (T3-4) were the only factors associated with increased risk of mortality in the univariate analysis, multivariate analysis revealed no significant role of age or T stage in predicting survival outcome.

Several studies indicated the significant role of systemic immune inflammatory markers (i.e., NLR, PLR and LMR) in predicting survival outcome of pancreatic cancer patients (17,20,21,25,26). . However, their reliability as a prognostic factor for OS is considered questionable in resectable pancreatic cancer, and NLR and PLR are suggested not to predict survival in patients who underwent pancreatectomy for pancreatic cancer (7,27-29).

In a retrospective study among 134 operated cases of pancreatic ductal adenocarcinoma, the pretherapy NLR (for cut-off values of 2, 2.7 and 5), PLR (for a cut-off of 150), and LMR (for a cut-off of 2.8) were found not to be significantly associated with OS time, while the TNM stage was confirmed to be the only significant determinant of survival in the multivariate analysis (7). In a retrospective study with resectable pancreatic cancers, no significant association of NLR and PLR was found with the survival for a range of cut off values (28). Likewise, in a prospective study neither NLR (for cut-off of 5) nor PLR (for cut-off of 150) was reported to be associated significantly with survival in patients with resectable pancreatic ductal adenocarcinoma, (29).

In a study with 74 resected pancreatic cancers, NLR (for a cut-off of 5) was reported to be significantly associated with disease free survival (DFS), whereas no survival difference was noted for CRP or PLR (25). High NLR (for a cut off of 5) at the time of diagnosis was also reported to be associated with poor prognosis in patients with operable or inoperable pancreatic cancer (26,30), and to be superior to the PLR in patients who undergo resection for pancreatic adenocarcinoma following or not neoadjuvant CT/chemoradiation (10,31).

Indeed, significant association of some inflammation-based markers, particularly the NLR with the survival has also been reported in meta-analyses on the prognostic significance of systemic immune inflammatory markers in pancreatic cancer (21,32,33). However, these meta-analysis studies had a diverse patient population with considerable differences in the type of markers, time of blood sample collection and the cut off value of studied markers, along with analysis of resected and inoperable patients together, despite the likelihood of surgery to alter the natural course of disease process (7).

Notably, in a meta-analysis of 34 studies in 7105 pancreatic cancer patients, authors concluded the significant association of high NLR and PLR values with poor OS (6). However, in subgroup analyses, a high NLR was found to have a negative effect on OS except in patients who underwent chemo/radiotherapy and a high PLR had a negative effect on OS only in Asian patients and in those who underwent surgery plus chemo/radiotherapy (6). The authors emphasized the likelihood of NLR values to fluctuate based on neutrophil or lymphocyte changes during anti-cancer treatment and thus NLR after chemo/radiotherapy may not correlate with OS in pancreatic cancer patients (6,34). Besides, given the dynamic nature of inflammatory markers with likely changes during the treatment course, assessing their change over the course of treatment rather than at a single time point is considered more likely to reveal their potential (7,35). In this regard, our findings support that, systemic immune inflammatory markers (i.e., NLR, PLR, CLR, CAR) may not correlate with OS individually in operated patients with pancreatic adenocarcinoma, whereas a combined evaluation of inflammatory markers or a dynamic testing may reveal prognostic value (7,35).
Previous studies have confirmed that tumor stages 3-4 were risk factors affecting patient prognosis in pancreatic cancer, emphasizing the utility of TNM staging in evaluation of the resectability of the tumor before surgery (4,11). In the present study, tumor stage was found to correlate with OS only in the univariate analysis. Nonetheless, it should be noted that the biological behavior and prognosis of pancreatic cancers differ significantly along with varied final outcomes for patients even within the same tumor stage (3,7). This emphasizes the need for further preoperative prognostic markers to risk stratify the patients with pancreatic cancer before surgery for making an effective treatment plan (3,7,11,28).

Notably, in a study with 997 pancreatic cancer patients addressing the prognostic value of different combinations of inflammatory markers (NLR, PLR, CLR, CAR, NAR and PAR), authors reported that elevated CLR (cut-off value of 1.8) was an independent risk factor for poor survival and more accurate than the NLR, PLR, CAR, NAR and PAR in predicting survival (18). Similarly, in another study with 386 pancreatic ductal adenocarcinoma patients, an elevated CAR (a cut-off value of 0.180) was reported to be an independent factor for poor prognosis with significantly higher AUC values than PLR and similar AUC values to NLR, indicating the likelihood of CAR to serve as a significant and promising inflammatory prognostic score in pancreatic cancer (19). Also, in a study among 163 patients with resectable pancreatic cancer, the high CAR (for a cut-off value of 0.06), CA19-9 (for a cut-off value of 300 U/ml) and receipt of adjuvant chemotherapy were reported to be independent risk

factors for OS and DFS, while high CAR was also significantly associated with advanced T stage (5).

Our findings revealed no correlation of preoperative CLR (for a cut-off value of 2.70) with survival outcome in patients with operated pancreatic adenocarcinoma. Moreover, while high CA19-9 was reported to be associated with poorly differentiated tumor characteristics, a massive tumor size, and advanced stage of pancreatic cancer (36,37) and shown to be an independent predictor of survival in unresectable pancreatic cancer (38), metastatic pancreatic cancer (for a cut-off value of 1800 U/mL) (10) and clearly resectable pancreatic cancer (for a cut-off value of 1,000 U/mL) (39), our findings in operable pancreatic cancer patients revealed no significant correlation of CA 19-9 (for a cut-off value of 42.11) with postoperative survival outcome.

Limitations of the Study

Although conducted in a homogenous group of patients with resectable pancreatic adenocarcinoma, single center retrospective design seems to be the main limitation of the present study. In addition, assessment of inflammatory markers individually and at a single time point is another limitation given the likelihood of combined and dynamic evaluation of markers to extend the knowledge achieved in the current study.

Conclusion

In conclusion, our findings in patients with operated pancreatic adenocarcinoma revealed that none of the preoperatively determined inflammation-based marker ratios (i.e., NLR, PLR, CLR and CAR) or CA 19-9 had significant impact on survival outcome. The age at diagnosis and tumor stage were associated with OS only in the univariate analysis. Further larger scale studies in surgical and non-surgical groups of pancreatic cancer patients are needed to address the prognostic value of inflammation-based markers using combination of markers assessed preoperatively as well as a dynamic evaluation throughout the treatment period.

Ethics Committee Approval

The study was approved by the İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Date of Approval: 13/04/2022, Reference number /Protocol No: E-10840098-772.02-2389/345).

Authors' contributions

Ebru Karci: Concept, Design, Supervision, Data Collection and/or Processing, Literature Search, Writing Manuscript

Merve Tokocin: Resources, Materials, Analysis and/or Interpretation, Critical Review

Conflict of interest: The authors declare that they have no conflict of interest

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