High Systemic Immune-Inflammation Index Values Before Treatment Predict Poor Pancreatic Cancer Outcomes After Definitive Chemoradiotherapy

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ABSTRACT

BACKGROUND: The systemic immune-inflammation index (SII) is an effective tool for predicting the prognosis of patients with cancer. However, its value in patients with locally advanced pancreatic ductal adenocarcinoma (LA-PDAC) undergoing definitive chemoradiotherapy has yet to be addressed. Therefore, we aimed to retrospectively investigate the prognostic significance of the pretreatment SII on the survival outcomes of patients with unresectable LA-PDAC treated with concurrent chemoradiotherapy (C-CRT).

METHODS: The study included 163 patients with LA-PDAC who had received C-CRT. Using receiver operating characteristic (ROC) curve analysis, the utility of a pre-C-CRT cutoff that could stratify survival results was investigated. The primary and secondary endpoints were the correlations between SII levels and overall survival (OS) and progression-free survival (PFS).

RESULTS: At a median follow-up period of 15 months (range: 3.2-94.5), the median OS and PFS rates for the entire group were 15.7 months (95% confidence interval [CI]: 13.4-17.9), and 7.8 months (95% CI: 6.1-9.4), respectively. We divided the patients into 2 SII cohorts based on the ROC curve analysis (area under the curve [AUC]: 71.9%; sensitivity: 68.9%; specificity: 66.7%): SII $<$ 538 (N = 70) and SII $\geq$ 538 (N = 93). Comparative survival analysis showed significantly inferior median OS (13.0 vs 25.4 months; $P < .001$) and PFS (7.0 vs 15.2 months; $P = .003$) in patients with SII $\geq$ 538 compared with those with SII $<$ 538 before treatment. In multivariate analyses, the Eastern Cooperative Oncology Group (ECOG) performance of 2, N1-2 lymph node, CA 19-9 $>$ 90 U/mL, and SII $\geq$ 538 status emerged as independent prognosticators of inferior OS and PFS.

CONCLUSIONS: Present results indicate that patients with unresectable LA-PDAC who underwent C-CRT and had a pretreatment SII $\geq$ 538 had significantly worse OS and PFS outcomes compared with those with lower SII values.

KEYWORDS: Pancreas adenocarcinoma, prognosis, systemic-immune-inflammation index, concurrent chemoradiotherapy, survival outcomes

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Introduction

At the initial presentation, approximately 30% to 35% of all pancreatic ductal adenocarcinomas (PDACs) are classified as unresectable locally advanced (LA-PDACs).[1] For patients who are medically fit to receive curative-intent treatment, concurrent chemoradiotherapy (C-CRT) with or without induction chemotherapy is one of the current standards of care.[2-4] However, patients with LA-PDAC face a grim prognosis despite aggressive treatments, typically exhibiting a median overall survival (OS) of 1 year or less.[5,6]

Patients with LA-PDAC, who share similar performance status and tumor-node-metastasis stages, often exhibit varying response rates and outcomes when treated with standard therapies. These outcome variations suggest the need to identify new nonanatomic prognostic and predictive biomarkers to accurately categorize these patients for prognosis, which could ultimately inform treatment decisions. Cancer antigen (CA) 19-9 (CA 19-9) was the first biomarker to be established as a highly accurate predictor of survival outcomes for PDACs.[7,8] However, it is important to note that several other disorders, such as biliary diseases, chronic renal failure, or thyroid diseases, might cause an increase in CA 19-9 levels. Therefore, the prognostic value of CA 19-9 readings may be diminished in such situations, and it is

important to interpret these findings considering the unique clinical circumstances.

Systemic inflammation plays a pivotal role in the initiation, progression, and metastasis steps of PDACs.[9,10] Over the past 2 decades, there has been a concerted effort to explore inflammation-based prognostic scores for predicting disease outcomes in all stages of PDACs, akin to other solid tumors. Circulating cellular biomarkers, including neutrophils, lymphocytes, monocytes, and platelets, have emerged as valuable indicators of a patient's systemic inflammatory and immunological status and hold substantial prognostic significance. Of note is the systemic immune-inflammation index (SII), discovered first in hepatocellular carcinoma patients by Hu et al.[11] The prognostic value of SII has been studied in PDAC patients in different scenarios, such as preoperative, systemic chemotherapy, and immunotherapy settings, with varying degrees of success.[12-17] Nevertheless, the prognostic value of pretreatment SII in unresectable patients with LA-PDAC undergoing definitive C-CRT has yet to be explored. As a result, the primary objective of this retrospective cohort analysis was to ascertain whether SII could function as a dependable and practical prognostic biomarker in patients with LA-PDAC, which could enable clinicians to stratify these patients into distinct risk groups and customize treatment regimens accordingly.

Materials and Methods

Ethics, Consent, and Permissions

This study adhered to the Helsinki Declaration and Rules of Good Clinical Practice. The Institutional Ethical Committee review board of Baskent University Medical Faculty approved the study design before collecting data (Ethical Approval Number: DK-20-26). All patients provided written informed consent before treatment initiation to collect and analyze blood samples and pathological specimens and publish the outcomes, per our institutional standards.

Patients

A retrospective database survey was conducted between January 2007 and December 2019 on all patients with LA-PDAC who received C-CRT at the Baskent University Medical Faculty, Department of Radiation Oncology. At the time of referral, the patients with unresectable LA-PDAC (T4 stage) were identified using the American Joint Committee on Cancer's (AJCC) 8th edition staging framework. The study included patients who met the following criteria: (1) age between 18 and 80 years; (2) Eastern Cooperative Oncology Group (ECOG) performance status 0-1; (3) pathologically proven ductal adenocarcinoma histology; (4) no history of previous oncologic treatment (chemotherapy, radiotherapy, targeted therapies, or immunotherapy); (5) body mass index $> 20\,kg/m^2$ (6) available records of radiotherapy and chemotherapy; (7) adequate pre-C-CRT bone marrow, liver, and kidney functions; (8) available complete blood count and biochemistry test results obtained at the first day of C-CRT; and (9) available follow-up clinical, laboratory, and radiological records. The present study excluded patients with a medical history of chronic immunosuppressive medication or steroid usage within the past 30 days, chronic inflammatory diseases, active chronic or acute infections, radiation hypersensitivity syndromes, or blood transfusions within 90 days before the initiation of C-CRT.

Our institutional standards for the definition of technically unresectable LA-PDAC follow the most current AJCC staging system (8th edition for this study): involvement of the celiac axis and/or superior mesenteric artery, precisely stage III (T4N0-2M0) disease. The disease's extent was determined in all patients through radiological studies and laparotomy or laparoscopic examination, as necessary. The formal radiological procedure comprised the application of abdominal computerized tomography (CT) with contrast enhancement, magnetic resonance imaging (MRI), and/or MR-cholangiopancreatography. In addition, all patients underwent re-staging through the positron-emission tomography/CT (FDG-PET-CT) scans acquired for radiation therapy planning in the past week before the onset of C-CRT. As part of the standard institutional staging procedures for pancreatic adenocarcinomas (PACs), laparoscopic or laparotomic examinations were performed, and biopsy samples were obtained from the primary tumors for histological diagnoses. If enlarged or metabolically active regional lymph nodes or isolated single-organ metastasis are identified during laparotomy or laparoscopy or suspected radiologically, biopsies were also taken from them.

Concurrent Chemoradiotherapy

All eligible patients underwent a radical C-CRT protocol, consisting of a total radiation dosage of 45 Gy (1.8 Gy/fraction/day, for 25 days) encompassing the primary tumor and involved nodal regions.[18] According to our institutional standards for LA-PACs, elective nodal irradiation was not permitted for such patients. During RT, each patient additionally received a continuous infusion of 5-fluorouracil ($225\,mg/m^2/d$), followed by gemcitabine ($1000\,mg/m^2$ intravenous infusion) for 2 to 6 courses (on days 1 and 8, every 21 days). Supportive care measures, including antiemetic medications, hydration, and nutritional supplements, were provided as required.

Systemic-Immune-Inflammation Index Measures

We calculated the SII values for each patient before treatment by using the measurements of lymphocytes (L), platelets (P), and neutrophils (N) obtained from complete blood count tests on the first day of C-CRT. Hua and colleagues' original SII formula was employed to calculate SII: $SII = [(P \times N) \div L]$.[11]

Treatment Response Assessment and Follow-up

All patients were examined every 3 months for the first 2 years and then every 6 months after that. The FDG-PET-CT and

abdominal MRI scans were used to assess response following the European Organisation for Research and Treatment of Cancer's (EORTC) 1999 recommendations.[19] For follow-up assessments, we selected the following tools: complete blood count and biochemistry tests, serum CA 19-9 concentrations, chest x-rays, and abdominal MRI. Initially, FDG-PET-CT was used for the first response assessment visit, but abdominal MRI replaced it for patients who showed a complete metabolic response. Additional examinations such as abdominal ultrasonography, chest CT, cranial MRI, and bone scintigraphy were only conducted when deemed necessary.

Statistical Analysis

The primary objective of this study was the potential relationship between pretreatment SII measures and OS, defined as the interval between the first day of the C-CRT and the date of any cause of death or the last follow-up. The secondary objective was progression-free survival (PFS), defined as the interval between the first day of the C-CRT and the date of any tumor progression or death/last follow-up. Continuous variables were described using medians, whereas categorical variables were illustrated using frequency distributions. Fisher exact test, chi-square test, Student test, or Spearman correlation analyses were employed for intergroup comparisons based on their suitability and relevance to the research question. The accessibility of pre-C-CRT SII cutoffs, which might categorize the study cohort into 2 distinctive PFS and OS groups, was sought using receiver operating characteristic (ROC) curve analyses. Kaplan-Meier curves were generated for PFS and OS outcomes and compared with log-rank tests. The multivariate Cox proportional hazard model was used to examine potential interactions between the covariates and survival outcomes, with any 2-tailed $P \leq .05$ considered significant.

Results

The present retrospective cohort investigation comprised 163 eligible patients. Pretreatment patient and disease characteristics were as outlined in Table 1. The median age of the entire cohort was 57 (range: 39-77) years. The majority of patients were of the male sex (78%), with the head of the pancreas being the most common tumor site (79.1%). The nodal stage was categorized as N0 and N1-2 in 127 (77.9%) and 36 (22.1%) patients. Obstructive jaundice was present in 99 (66.9%) of the study cohort at the time of presentation. According to the CA 19-9 cutoff employed in the Charité Onkologie 001 (CONKO-001) study, 88 patients (54%) had CA19-9 measurements of ≥90 U/mL.[20]

The median follow-up time for the entire study group was 15 months (range: 3.2-94.5 months). The median OS rates at 2 and 4 years were 15.7 months (95% confidence interval [CI]: 13.4-17.9), 34.2%, and 25.3%, respectively, whereas the corresponding PFS rates were 7.8 months (95% CI: 6.1-9.4), 19.2%, and 13.1%, respectively.

The availability of an ideal pre-C-CRT cutoff of SII that significantly interacted with clinical outcomes was revealed using ROC curve analysis. For further intergroup comparisons, the ideal SII cutoff was determined to be 538 for OS (area under the curve [AUC]: 71.9%; sensitivity: 68.9%; specificity: 66.7%) and 536 for PFS (AUC: 69.5%; sensitivity: 69.1%; specificity: 65.2%) status (Figure 1). To enable comparative analysis, we categorized the patients into 2 groups using 538 as the standard cutoff value: the low SII group (L-SII; N = 70) and the high SII group (H-SII; N = 93). There were no notable disparities in baseline demographics and patient characteristics between the 2 SII groups, as shown in Table 1. The findings of the comparative survival analyses showed that the H-SII group had a substantially shorter median PFS (7.0 vs 15.2 months; $P = .003$) and OS (13.0 vs 25.4 months; $P < .001$) than the L-SII group, respectively (Figure 2).

Considering the carcinoembryonic antigen (CEA) and CA (CA-125), probably due to our study's small cohort size, ROC curve analysis did not yield cutoff values for CEA or CA-125. Nevertheless, we categorized our patients into 2 groups based on the maximum of the normal range used by our laboratory for these indicators: CEA: 2.9 ng/mL and CA 125: 35.0 U/mL.

In univariate analysis, we discovered that ECOG 2 performance status (compared with ECOG 0-1), CA 19-9 ≥ 90 (vs <90 U/mL), N1-2 node stage (vs N0), and H-SII (vs L-SII) had significantly lower OS and PFS results ($P < .05$ for each) (Table 2). Subsequent multivariate analysis results confirmed that ECOG 2 performance status, CA 19-9 levels ≥ 90 U/mL, N1-2 stage, and H-SII status were significant and independent factors associated with lower PFS ($P < .05$ for each) and OS rates ($P < .05$ for each) (Tables 2 and 3).

Discussion

The present retrospective study examined the prognostic significance of pretreatment SII in 163 patients with unresectable LA-PDAC who received definitive C-CRT in terms of OS and PFS outcomes. The results confirmed that a poor performance status (ECOG 2) before C-CRT, involvement of lymph nodes (N1-2), and elevated levels of CA19-9 (≥90 U/mL) are independent predictors of unfavorable outcomes. However, the most influential finding was the independent association between an SII ≥ 538 value and significantly reduced median OS (13 vs 25.4; $P < .001$) and PFS (7 vs 15.2; $P = .003$) durations in this patient group.

The SII, a composite measure derived from the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), integrates the 3 key hematological parameters: N, P, and L. Multiple retrospective cohort studies have investigated the prognostic value of SII in patients with PDAC. The consistent findings of these studies highlight a strong correlation between elevated SII values and unfavorable prognosis, corroborating the outcomes presented here. Notably, Bittoni et al[21] conducted a study encompassing 234 patients with LA-PDAC

Table 1. Baseline patient and disease characteristics for the entire study group and per systemic immune-inflammation index subgroups.

CHARACTERISTIC	ALL PATIENTS (N = 163)	SII < 538 (N = 70)	SII ⩾ 538 (N = 93)	*P* VALUE
Median age, years (range)	57 (39-77)	56 (39-68)	57 (39-77)	.97
Age group, y, No. (%)				
<65	133 (81,6)	58 (82.8)	75 (80.6)	.84
⩾65	30 (18.4)	12 (17.2)	18 (19.4)	
Gender, No. (%)				
Female	36 (22.1)	17 (24.2)	19 (20.4)	.57
Male	127 (77.9)	53 (75.8)	74 (79.6)	
ECOG performance, No. (%)				
0	127 (77.9)	57 (81.4)	70 (75.2)	.45
1-2	36 (22.1)	13 (18.6)	23 (24.8)	
Obstructive jaundice				
Absent	54 (33.1)	25 (35.7)	29 (31.2)	.68
Present	99 (66.9)	45 (64.3)	54 (68.2)	
Tumor location, No. (%)				
Head	133 (81.6)	57 (81.4)	76 (81.7)	.78
Body/tail	30 (18.4)	13 (18.6)	17 /18.3)	
Median tumor size, cm (range)	4.4 (2.9-9.7)	4.1 (2.9-9.1)	4.6 (3.1-9.7)	.71
Tumor size group				
<4.4 cm	79 (48.5)	34 (48.6)	45 (48.4)	.92
⩾4.4 cm	84 (51.5)	36 (51.4)	48 (51.6)	
N-stage, No. (%)				
0	84 (51.5)	40 (57.1)	44 (47.3)	.27
1-2	79 (48.5)	30 (42.9)	49 (52.7)	
CEA status, No. (%)				
⩽2.9 ng/mL	67 (41.1)	26 (37.1)	41 (44.1)	.32
>2.9 ng/mL	96 (58.9)	44 (62.9)	52 (55.9)	
CA 125 status, No. (%)				
⩽35.0 U/mL	61 (37.4)	24 (34.3)	37 (39.8)	.37
>35.0 U/mL	102 (62.6)	46 (65.7)	56 (60.2)	
CA 19-9 status, No. (%)				
⩽90 U/mL	75 (46.0)	35 (50)	40 (43)	.43
>90 U/mL	88 (54.0)	35 (50)	53 (57)	

Abbreviations: SII: systemic immune-inflammation index; ECOG: Eastern Cooperative Oncology Group; N-stage: nodal stage; CEA: carcinoembryonic antigen; CA 125; cancer antigen 125; CA 19-9: cancer antigen 19-9.

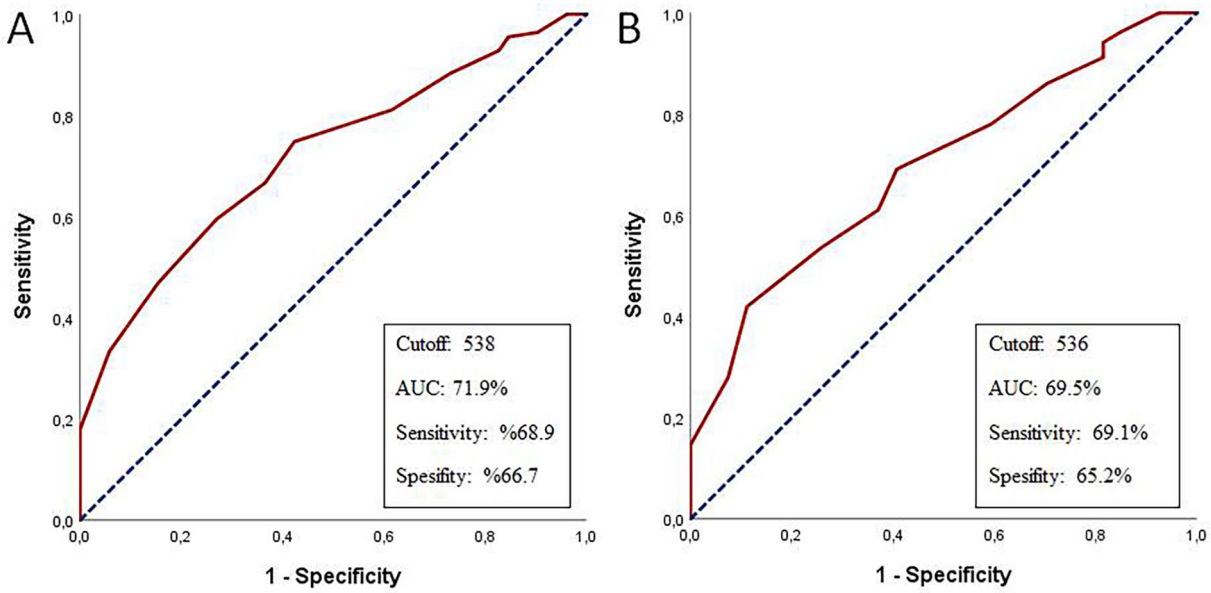

Figure 1. The results of receiver operating characteristic (ROC) curve analyses examining the connection between the systemic immune-inflammation index measures and survival outcomes: (A) overall survival and (B) progression-free survival.

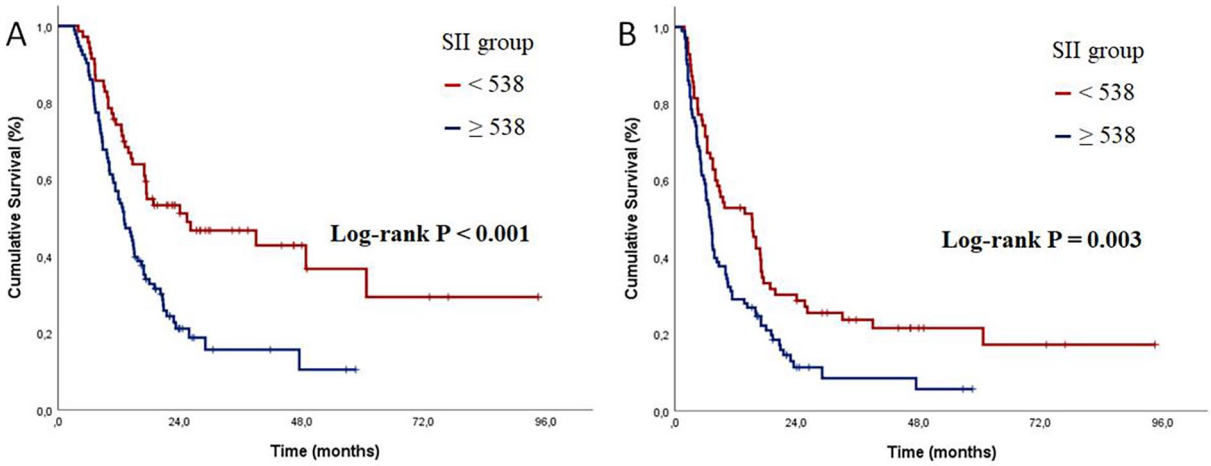

Figure 2. Survival outcomes per systemic immune-inflammation index (SII): (A) overall survival and (B) progression-free survival.

to assess the predictive utility of SII in clinical outcomes. Their results revealed a significant association between high SII values and reduced OS ($P = .003$) and PFS ($P = .008$) durations. This study's findings were further validated by Aziz et al,[12] who reported that a high SII value before surgery was one of the strongest predictors of poorer tumor-specific survival in a larger cohort of 590 patients with PDAC. An analysis of the data also indicated that a high SII value yielded a more pronounced prognostic impact than other inflammation indices. These findings were corroborated in another study by Xu et al,[22] which examined the outcomes of 135 patients who underwent the Whipple procedure for PDACs. In this study, high SII values before surgery were associated with poorer survival outcomes. In a study by Jomrich et al[13] encompassing 321 resectable PDAC patients, the SII emerged as an independent prognostic indicator for OS ($P < .01$). Moreover, Zhang et al[16] observed that irrespective of CA19-9 levels, patients with advanced PDACs and pretreatment SII > 440 cohorts exhibited significantly diminished OS compared with those with SII ≤ 440 cohorts. Several other studies have reported similar results for PDAC patients treated with chemotherapy and/or immunotherapy.[15,23-25] Although these previous studies supported the findings presented here, our study is distinguished by including a more homogeneous patient group, consisting solely of LA-PDACs treated with definitive C-CRT.

Three meta-analyses have previously evaluated SII's usefulness as a prognostic biomarker in PAC patients.[26-28] Although the outcomes of these meta-analyses affirm the efficacy of SII as a prognostic biomarker in pancreatic cancer patients, our study diverges significantly from these analyses. The patient cohort encompassed in the meta-analyses spans stages I to IV and incorporates diverse treatment modalities, including

Table 2. Outcomes of univariate and multivariate analysis.

FACTOR	OVERALL SURVIVAL			PROGRESSION-FREE SURVIVAL		
	UNIVARIATE *P*-VALUE	MULTIVARIATE *P*-VALUE	HR (RANGE)	UNIVARIATE *P*-VALUE	MULTIVARIATE *P*-VALUE	HR (RANGE)
Age group (< vs ⩾65 y)	.877	—	0.96 (0.63-1.42)	.17	—	0.87 (0.62-1.24)
Gender (F vs M)	.393	—	0.94 (0.72-1.34)	.866	—	0.90 (0.71-1.17)
ECOG (0-1 vs 2)	<.001	<.001	0.83 (0.77-0.91)	.001	.004	0.88 (0.82-0.96)
Obstructive jaundice (absent vs present	.51	—	0.92 (0.76-1.29)	.58	—	0.89 (0.68-142)
Tumor location (H vs B/T)	.84	—	0.92 (0.76-1.37)	.87	—	0.97 (0.69-1.53)
Tumor size group (<4.4 vs ⩾4.4 cm)	.23	—	0.93 (0.78- 1.12)	.27	—	0.92 (0.81-1.04)
N-stage (0 vs 1-2)	<.001	<.001	0.76 (0.64-0.89)	<.001	<.001	0.69 (0.49-0.83)
CEA (⩽ vs >2.9 ng/mL)	.18	—	0.86 (0.55-1.23)	.16	—	0.82 (0.61-1.08)
CA-125 (⩽ vs >35.0 U/mL)	.19	—	0.83 (0.67-1.04)	.15	—	0.82 (0.66-1.07)
CA19-9 (< vs ⩾90 U/mL)	<.001	<.001	0.79 (0.59-0.92)	.007	<.001	0.72 (0.60-0.85)
SII (< vs ⩾538)	<.001	<.001	0.46 (0.22-0.68)	.003	.027	0.53 (0.39-0.65)

Abbreviations: HR: hazard ratio; CI: confidence interval; ECOG: Eastern Cooperative Oncology Group; H: head; B/H: body/tail; N-stage: nodal stage; CA 19-9: cancer antigen 19-9; SII: systemic immune-inflammation index.

Table 3. Survival results according to the factors exhibiting independent prognostic significance in multivariate analyses.

ENDPOINT	ECOG STATUS			N-STAGE			CA 19-9 STATUS			SII STATUS		
	0-1	2	*P*-VALUE	0	1-2	*P*-VALUE	<90 U/M/L	⩾90 U/M/L	*P*-VALUE	<538	⩾538	*P*-VALUE
Overall survival												
Median, mo.	19.0	9.9	<.001	26.1	12.5	<.001	20.8	12.5	.001	25.4	13.0	<.001
2 years (%)	41.7	6.8		54.3	13.7		43.6	26.3		51.2	21.1	
4 years (%)	30.9	0		39.9	11.8		36.4	13.9		42.8	10.4	
Progression-free survival												
Median, mo.	11.3	4.6	<.001	14.3	6.4	<.001	11.3	6.7	.007	15.2	7.0	.003
2 years (%)	23.5	5.6		31.0	9.8		24.5	14.6		28.7	11.3	
4 years (%)	16.0	0		21.2	4.9		17.1	8.4		21.5	5.6	

Abbreviations: ECOG: Eastern Cooperative Oncology Group; N-stage: nodal stage; CA 19-9: cancer antigen 19-9; SII: systemic immune-inflammation index; mo: months.

radical surgery, radiotherapy alone, chemotherapy alone, and palliative chemotherapy. While their findings are noteworthy for discerning the general efficacy of SII as a prognostic biomarker, they are deficient in data pertinent to patients with technically unresectable locally advanced pancreatic cancer undergoing exclusive C-CRT. Consequently, our study represents the inaugural effort to appraise the prognostic significance of SII in this specialized patient cohort and delineates its substantial utility in this particular context.

The precise nature of the relationship between SII and disease prognosis in patients with LA-PDAC remains unknown. However, a thorough examination of the components of the SII formula and their functions in cancer development can help form logical hypotheses. First, neutrophils are known to secrete various cytokines and chemokines that promote tumoral neoangiogenesis, adhesion of circulating tumor cells, and distant metastasis.[12] Furthermore, elevated neutrophil counts can impede T-lymphocyte functions by releasing excessive

quantities of reactive oxygen and nitric oxide species. Consequently, these species can facilitate cancer cells' avoidance of the systemic immune response, thereby enhancing their survival, invasion, proliferation, and metastatic capabilities.[13-16] Platelets can help circulating tumor cells avoid immune detection by coming into direct contact with cancer cells, stimulating tumor cell migration, and assisting circulating tumor cells in spreading through the bloodstream. Platelets can help circulating tumor cells avoid immune detection by coming into direct contact with cancer cells, stimulating tumor cell migration, and assisting circulating tumor cells in spreading through the bloodstream.[17] Lymphocytes are vital components of the acquired immune system, defending and monitoring the body's immune response. Unlike neutrophils and platelets, circulating lymphocytes can improve the prognosis of cancer patients by producing specific cytokines and suppressing tumor growth.[19] However, cancer patients in advanced stages often experience a decrease in lymphocyte counts, leading to a weakened immune system. This weakened state creates a conducive environment for cancer cells to proliferate and disseminate locally and systemically.[20] Consequently, it is reasonable to propose that an elevated SII value, which correlates with an increased count of neutrophils or platelets and/or a decreased count of lymphocytes, may facilitate tumor angiogenesis, adhesion, and metastasis and weaken anticancer immunity, ultimately leading to inferior clinical outcomes. Our current findings, along with previously published research, suggest that patients diagnosed with a high SII may have more severe immunosuppression and a heavier tumor burden than those with a lower SII. If further research confirms these findings, SII could be used as an additional tool for selecting personalized treatments and improving prognosis.

There are some limitations to our study. First, it was a retrospective study conducted in a single center with a relatively small cohort size. This fact, familiar to any retrospective study, may have resulted in unpredictable selection biases. Second, although the SII is a dynamic biological marker that experiences significant fluctuations over time, we only analyzed measures obtained shortly before C-CRT initiation. Thus, the SII cutoff we determined may not necessarily reflect the most efficient cutoff value, implying the need for further studies to investigate the ideal cutoff value by calculating SII at different time points. Third, our study did not encompass patients with resectable or borderline resectable PACs, and none of the patients met the criteria for conversion surgery following C-CRT. Consequently, the findings presented in this study cannot apply to all PAC patients, necessitating further investigation in future research endeavors in these patient groups for its potential to represent all PAC patients. And fourth, unintended heterogeneities in salvage therapies, such as using different systemic therapy regimens or radiosurgery for recurrent primaries in certain patients, may have skewed the outcomes in favor of one group. Hence, meticulously designed future studies involving larger cohorts are imperative to unveil more robust findings and deduce definitive conclusions regarding the actual prognostic value of the SII in these specific patient cohorts. As a result, it is crucial to consider the current results as hypothetical, requiring validation through further comprehensive research.

Conclusions

Our research indicates that a pre-C-CRT SII value of ⩾538 is an independent and reliable indicator of poor prognosis for patients with LA-PDAC who undergo definitive C-CRT. Therefore, if confirmed by more extensive studies, SII can be used as a novel biomarker to improve the prognostic classification of patients with LA-PDAC and help select the most suitable personalized treatment options.

Author Contributions

ET, AK, DO, EEO, NKD, SS, US, and BP conceived the study, participated in the study's design, and performed clinical examination and statistical analysis. All authors contributed significantly and equal, and all authors approved the final form of the manuscript.

Availability of Data and Materials

The present data belongs to and is stored at the Baskent University Faculty of Medicine; it cannot be shared without permission. Researchers who meet the criteria for access to confidential data should contact the Baskent University Department of Radiation Oncology at adanabaskent@baskent.edu.tr.

Ethics Approval and Consent to Participate

This study adhered to the Helsinki Declaration and Rules of Good Clinical Practice. The Institutional Ethical Committee review board of Baskent University Medical Faculty approved the study design before collecting data ((Ethical Approval Number: DK-20-26). All patients provided written informed consent before treatment initiation to collect and analyze blood samples and pathological specimens and publish the outcomes, per our institutional standards.

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