Journal of Inflammation Research

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ORIGINAL RESEARCH

Low Pre-Chemoradiotherapy Pan-Immune-Inflammation Value (PIV) Measures Predict Better Survival Outcomes in Locally Advanced Pancreatic Adenocarcinomas

Erkan Topkan[1], Ugur Selek[2,3], Ahmet Kucuk[4], Berrin Pehlivan[5]

[1]Department of Radiation Oncology, Baskent University Medical Faculty, Adana, Turkey; [2]Department of Radiation Oncology, Koc University School of Medicine, Istanbul, Turkey; [3]Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Clinic of Radiation Oncology, Mersin Education and Research Hospital, Mersin, Turkey; [5]Department of Radiation Oncology, Bahcesehir University, Istanbul, Turkey

Correspondence: Erkan Topkan, Department of Radiation Oncology, Baskent University Medical Faculty, Adana, 01120, Turkey, Tel +90-533-7381069, Fax +90-322-3444452, Email docdretopkan@gmail.com

Objective: This study sought to determine whether pretreatment pan-immune-inflammation value (PIV) could be used to predict prognosis in patients with locally advanced pancreatic adenocarcinoma (LA-PAC) following definitive concurrent chemoradiotherapy (C-CRT).

Methods: The outcomes of 178 LA-PAC patients who received definitive C-CRT were analyzed retrospectively. For all patients, the PIV was calculated using the peripheral blood platelet (P), monocyte (M), neutrophil (N), and lymphocyte (L) counts obtained on the first day of C-CRT: PIV=P×M×N÷L. The optimum cutoff values for PIV connected to progression-free (PFS) and overall survival (OS) results were sought using receiver operating characteristic (ROC) curve analysis. The OS and PFS differences between the PIV groups constituted the primary and secondary endpoints, respectively.

Results: ROC curve analysis indicated that the ideal PIV cutoff was 464 (AUC: 75.9%, sensitivity: 74.1%, specificity: 71.9%), which categorized patients into two groups based on PFS and OS results: low PIV (L-PIV; N = 69) and high PIV (H-PIV; N = 109). According to comparative survival analyses, patients in the L-PIV group had significantly longer median PFS (14.3 vs 7.3 months; HR: 3.04; P<0.001) and OS (25.9 vs 13.3 months; HR: 2.86; P<0.001) than those in the H-PIV group. Although none of the H-PIV patients could survive beyond 5 years, the estimated 5-year OS rate was 29.7% in the L-PIV cohort. In multivariate analyses, besides the L-PIV, N_0 nodal stage, and CA 19–9 ≤ 90 U/mL appeared to be the independent predictors of better PFS (P < 0.05 for each) and OS (P < 0.05 for each) results.

Conclusion: The present results indicated that pre-C-CRT L-PIV measures were associated with favorable median and long-term PFS and OS results in LA-PAC patients, suggesting that the PIV is a potent and independent novel prognostic biomarker.

Keywords: pancreas cancer, pan-immune-inflammation value, biomarker, prognosis, survival

Introduction

Pancreatic adenocarcinoma (PAC) has one of the worst 5-year overall survival (OS) rates of any common solid tumor, owing primarily to PAC's resistance to virtually all systemic therapies and radiotherapy (RT).[1,2] Nearly one-third of all newly diagnosed PACs are locally advanced PACs (LA-PAC), which are surgically incurable because of the local invasion or encasement of significant veins and arteries. Due to the exceptionally high risk of distant metastasis (DM) in this population and the fact that nearly two-thirds of patients will never revert to a resectable disease state,[3,4] some experts recommend systemic chemotherapy alone as the best therapeutic option for such patients. Contrarily, local relapses may become the main reason for cancer deaths, particularly in patients who are still alive 15 months after

Received: 6 August 2022
Accepted: 10 September 2022
Published: 18 September 2022

diagnosis.[5,6] As evidence of the importance of local control for better outcomes, the results of the randomized LAP-07 study demonstrated that the addition of RT to chemotherapy reduced the local progression rate from 46% to 32% compared to chemotherapy alone.[7] Furthermore, in a series from Massachusetts General Hospital, C-CRT with efficient systemic agents produced exceptional R0 resection rates of 69%, with an outstanding median OS length of 33 months.[8] As a result, C-CRT has been acknowledged as a viable option for treating LA-PACs to enhance local control rates, which may benefit some patients' survival.[9,10]

According to the surgical series,[9] the patient's performance status, tumor size, degree of tumor differentiation, resection margins status, vascular and perineural invasion, invasion of neighboring structures, lymph node metastasis and number, and carbohydrate antigen (CA) 19–9 levels are all conventional prognostic factors for non-metastatic PACs. The majority of these characteristics serve as the framework for the current TNM (tumor-node-metastasis) staging system. However, these patients frequently have drastically different response rates and survival times after receiving standard therapies, even though their performance status, local and regional stages, and prognostic factors are nearly identical at presentation.[11] These clinically significant outcome variations among LA-PAC patients may be brought on by the current TNM staging framework's apparent disregard for the prognostic value of biological indicators. Such pronounced variations also highlight the critical requirement for novel biologic markers that may be invaluable in the more accurate prognostic stratification of LA-PAC patients.

The seventh cancer hallmark, persistent inflammation, has unquestionably been established to play a crucial role in every stage of carcinogenesis, from the onset of the illness to the development of invariably fatal widespread metastasis.[12] For instance, the risk of developing PAC is increased 13-fold in patients with chronic pancreatitis.[13] Similarly, growing evidence suggested that chronic systemic inflammation was a key factor underlying the variations in PAC prognoses following similar treatment regimens, regardless of whether the tested index was a single marker or a specific combination.[14–26] The pan-immune-inflammation index (PIV), a unique blend of circulating platelets, monocytes, neutrophils, and lymphocytes, is another recently developed biomarker. Previous research has found strong links between pretreatment levels of PIV and clinical outcomes in cancers such as colorectal, breast, esophageal, and small-cell lung cancers, Merkel cell carcinomas, and malignant melanomas.[27–38] Furthermore, a PIV variant, the PILE [combination of PIV, lactate dehydrogenase, and Eastern Cooperative Oncology Group (ECOG) performance status] score, as well as a recent meta-analysis by Guven et al, confirmed PIV's prognostic utility in various cancer types and disease stages.[39,40] The prognostic utility of PIV in unresectable LA-PAC patients has paradoxically never been questioned, even though a substantial amount of trustworthy basic and clinical evidence is readily available for other solid malignancies. These underlying motivations led us to retrospectively assess whether the calculated pre-C-CRT PIV measures had any prognostic implications in LA-PAC patients who underwent definitive C-CRT.

Patients and Methods

Ethics, Consent and Permissions

All patients signed written informed consent before the initiation of the C-CRT, either individually or via properly licensed representatives, for the gathering and processing of blood samples and pathologic specimens, as well as the publication of their results. The study was carried out in accordance with the Helsinki Declaration and the Good Clinical Practice Guidelines. Before any data collection, the research protocol was endorsed by the Baskent University Medical Faculty's Institutional Ethical Committee review board.

Patient Population

The current retrospective investigation was carried out by evaluating the medical records of patients with unresectable LA-PAC who had definitive C-CRT at the Baskent University Medical Faculty Department of Radiation Oncology between January 2007 and December 2020.The AJCC staging framework (8th ed.) was utilized as a standard strategy for initial staging, with only stage III ($T_4N_{0\text{-}2}M_0$) patients being included in our research. We defined an unresectable LA-PAC as: 1) >180° of celiac artery involvement, 2) solid tumor contacting celiac artery and aorta, 3) >180° of superior mesenteric vein involvement, and 4) impossible to reconstruct portal and/or superior mesenteric vein owing to tumor involvement or occlusion. Patients had to fulfill

the following additional requirements in order to be qualified: age 18 to 80 years, ECOG performance status 0–1, histological adenocarcinoma proof, no previous chemotherapy/RT history, available pre-C-CRT routine complete blood count and biochemistry records, an adequate bone marrow reserve (hemoglobin value of ≥ 10 g/dL, leucocyte of ≥ 4.000 μL, and thrombocyte of ≥ 100.000 μL), hepatic (aspartate aminotransferase or alanine aminotransferase of < 5 times the upper limit) and renal function (serum creatinine < 2 mg/dL), available CA 19–9 tests, body mass index (BMI)>20 kg/m^2, no weight loss > 10% at past 6 months, no history of immunosuppressive disease and medication history.

Concurrent Chemoradiotherapy

All patients received RT at a total dose of 45 Gy (1.8 Gy/fraction, 5 days/week, for 5 weeks) that covered only the specified planning target volume, with no elective nodal irradiation allowed. All patients were treated with continuously infused 5-fluorouracil (225 mg/m^2/day) while undergoing RT. Maintenance gemcitabine (1000 mg/m^2 intravenously on days 1 and 8, every 21 days) was administered to patients who could tolerate it in two to six courses. received by 103 patients.

Measurement of PIV

For each patient, the pretreatment PIV was computed using Fucà's original formula: P×M×N÷L, where P, M, N, and L indicate pretreatment platelet, monocyte, neutrophil, and lymphocyte counts acquired on the first day of C-CRT.[27]

Response Evaluation

Patients had planned follow-up assessments every 3-months for the first 2-years, then every 6-months or more regularly after that. The first response assessment was performed at 3-months after the C-CRT completion, utilizing restaging PET/CT and abdominal MRI/CT scans and following the EORTC 1999 recommendations. The patients were then monitored every 3-months for the first 2-years and every 6-months after that by total blood count and biochemistry tests, serum CA 19–9 concentrations, PET/CT scans (to the date when a complete metabolic response was substantiated), and abdominal MRI/CT scans in patients with an asserted complete metabolic response. Response evaluations were performed using the RECIST (Response Evaluation Criteria in Solid Tumors) 1.1. Additional chest CT, abdomen ultrasonography, cranial MRI, and bone scintigraphy investigations were carried out only when clinically or radiologically necessitated.

Statistical Analysis

The primary objective of this study was to see if a significant difference in overall survival (OS: time from the first day of C-CRT to the date of death or the last visit) could be achieved between high and low PIV patient groups, with progression-free survival (PFS: time from the first day of C-CRT to the date of first observation of disease progression or death or the last visit) as a secondary objective. Percentage frequency distributions were used to illustrate categorical variables. Quantitative variables were evinced using medians and ranges. Chi-square tests, Student's *t*-tests, and Spearman correlations were used to assess correlations between various groups. The accessibility of an ideal PIV cutoff that could arrange the research population into two groups with significantly divergent OS and PFS results was pursued using receiver operating characteristic (ROC) curve analysis. The likely influence of different risk factors on OS and PFS was explored using Kaplan-Meier estimates and Log rank tests. The multivariate Cox proportional hazard model was utilized to analyze the possible interactions between these variables and survival results, enclosing only the factors that demonstrated significance in univariate comparisons. Two-sided P-values of <0.05 were deemed significant for inter-group comparisons.

Results

The current retrospective analysis included 178 unresectable LA-PAC patients (N = 137; 77% male) with a median age of 57 (range: 26–79 years) years who received definitive C-CRT from January 2007 to December 2020. The pre-C-CRT patient and disease characteristics were as shown in Table 1. In 140 (78.7%) of the cases, the tumor was located in the head of the pancreas. A history of chronic pancreatitis was reported by 29 (16.3%) of the patients. According to the most

Table 1 Pretreatment Patient and Disease Characteristics

Characteristics	All Patients (N=178)	L-PIV (N=69)	H-PIV (N=109)	P-value
Median age, years (range)	57 (26–79)	56 (26–78)	59 (33–79)	0.55
Age group				
< 70	132 (74.2)	53 (76.8)	79 (72.5)	0.67
≥ 70	46 (25.8)	16 (23.2)	30 (27.5)	
Gender, N (%)				
Female	41 (23.0)	17 (24.6)	24 (22.0)	0.76
Male	137 (77.0)	52 (75.4)	85 (88.0)	
ECOG performance, N (%)				
0	70 (39.3)	29 (42.0)	41 (37.6)	0.39
1	108 (60.7)	40 (58.0)	68 (62.4)	
Obesity				
Yes	22 (12.4)	6 (8.7)	16 (14.7)	0.037
No	156 (87.6)	63 (91.3)	93 (85.3)	
Alcohol abuse				
Yes	141 (79.2)	56 (81.2)	85 (78.0)	0.86
No	37 (20.8)	13 (18.8)	24 (22.0)	
Tobacco consumption				
Yes	156 (87.6)	59 (85.5)	97 (89.0)	0.74
No	22 (12.4)	10 (14.5)	12 (11.0)	
Diabetes mellitus				
Yes	53 (29.8)	22 (31.9)	31 (28.4)	0.84
No	135 (70.2)	47 (68.1)	78 (71.6)	
Chronic pancreatitis				
Yes	29 (16.3)	7 (10.1)	22 (20.2)	0.009
No	149 (83.7)	62 (89.9)	87 (79.8)	
Tumor location, N (%)				
Head	140 (78.7)	52 (75.3)	88 (80.7)	0.26
Body/Tail	38 (21.3)	17 (24.7)	21 (19.3)	
Median largest tumor diameter, cm	4.6 (1.9–8.9)	4.2 (2.3–8.4)	5.1 (1.9–8.9)	0.16
Tumor size group, N (%)				
<4.6 cm	85 (47.8)	30 (43.5)	55 (50.5)	0.33
≥4.6 cm	93 (52.2)	39 (56.5)	54 (49.5)	
N-stage, N (%)				
0	88 (49.4)	41 (59.4)	47 (43.1)	0.014
1–2	90 (50.6)	28 (40.6)	62 (56.9)	
Median CA 19–9, U/mL (range)	94.8 (21.8–194.6)	64.2 (21.8–124.7)	116.8 (48.9–194.6)	<0.001
CA 19–9 group				
< 90U/mL	71 (39.9)	36 (52.2)	35 (32.1)	0.011
≥ 90 U/mL	107 (60.1)	33 (47.8)	74 (67.9)	

Abbreviations: L-PIV, Low pan-immune-inflammation-value; H-PIV, High pan-immune-inflammation-value; ECOG, Eastern Cooperative Oncology Group; N-stage, Nodal stage; CA 19–9, Cancer antigen 19–9.

recent AJCC staging system (8th ed.), 90 (50.6%) patients had lymph node involvement (stage $N_{1\text{-}2}$). One hundred seven (60.1%) of patients had a CA 19–9 level of >90 U/mL per the critical cutoff of the Charité Onkologie 001 (CONKO-001) randomized study.[41]

The C-CRT protocol was well tolerated, with 144 (80.9%) cases completing the entire course of treatment. Only 2 (1.1%) treatment-related fatalities were observed throughout the follow-up period: febrile neutropenia (N= 1) and duodenal fistula (N= 1) in the third and eighth months, respectively. All patients could receive continuously infused 5-fluorouracil (225 mg/m2/day) concurrent with RT. In addition, 103 patients could receive 2 to 6 courses of intravenous maintenance gemcitabine (1000 mg/m2 on days 1 and 8, every 21 days). After a median follow-up period of 17.9 months (range: 3.2–104.0), 52 (29.2%) patients were still alive, with 28 (15.7%) surviving disease-free. Uncontrolled widespread DM was the leading cause of death [104 (82.6%) of all 126 deaths]. The whole study cohort's median and 5-year PFS and OS times were 7.8 [95% confidence interval (CI): 5.7–9.9 months] and 10.2% and 15.7 months (95% CI: 13.5–17.9 months) and 15.3%, respectively.

The pretreatment PIV values of 469 (area under the curve [AUC]: 75.2%, sensitivity: 73.3%, specificity: 71.6%) and 464 (AUC: 75.9%, sensitivity: 74.1%, specificity: 71.9%) were identified by the ROC curve analyses as having a meaningful relationship with the respective PFS and OS results (Figure 1). Due to the numerical similarity of the two cutoff values, we adopted 464 as the common cutoff to divide patients into two groups for subsequent intergroup comparisons: Low-PIV (L-PIV; N= 69) and High-PIV (H-PIV; N= 109). Despite the fact that other factors were nearly evenly distributed, the L-PIV cohort had a lower prevalence of chronic pancreatitis history (10.1% versus 20.2%; P = 0.009), N_{1-2} nodal stage (40.6% versus 56.9%; P = 0.014), and CA 19–9 value >90 U/mL (47.8% versus 67.9%; P= 0.011). Comparative survival analysis indicated that the L-PIV group had significantly longer median PFS (14.3 versus 7.3 months; P < 0.001) and OS (25.9 versus 13.3 months; P < 0.001) than their H-PIV counterparts, as shown in Figure 2 and Table 2. Likewise, while none of the H-PIV patients could survive beyond five years, the 5-year PFS and OS rates in the L-PIV group were 22.3% and 29.7%, respectively (Table 2). Uncontrolled widespread DM was the leading cause of death in both the L-PIV (31 of 39 deaths: 79.5%) and H-PIV (83 of 87 deaths: 95.4%).

In univariate analysis comprising the factors in Table 1, the N_0 nodal stage (versus N_{1-2}), CA 19–9 ≤ 90 U/mL (versus > 90 U/mL), and L-PIV (versus H-PIV) all appeared as variables that predicted superior median PFS (P < 0:05, for each) and OS (P < 0:05, for each) outcomes (Table 3). After that, a multivariate Cox regression analysis confined to these factors indicated that each of the three variables maintained their unbiased significance for each survival endpoint (Table 3). As illustrated in Figure 3, patients presenting with an N_0 nodal stage, a CA 19–9 ≤ 90 U/mL measure, and an L-PIV had statistically meaningfully longer median PFS and OS durations than their N_{1-2}, CA 19–9 > 90 U/mL, and H-PIV matches.

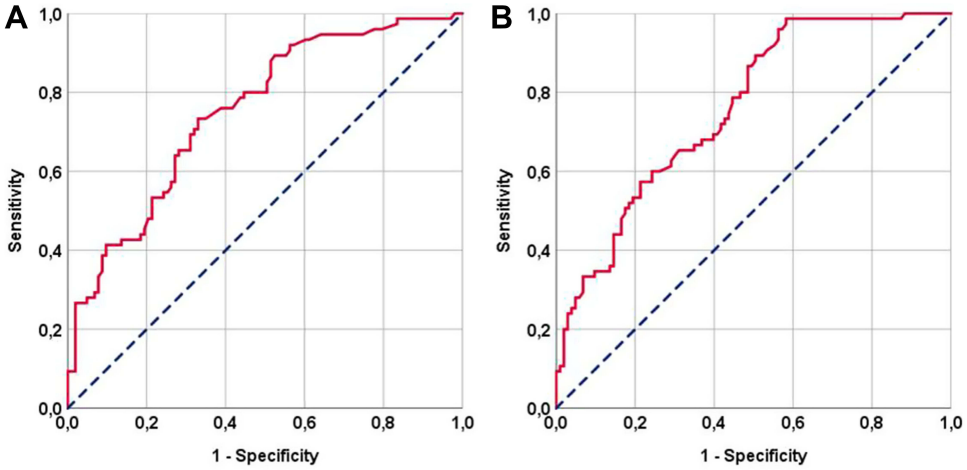

Figure 1 Outcomes of receiver operating characteristic curve analyses: (**A**) Progression-free survival (Cutoff: 469 (area under the curve [AUC]: 75.2%, sensitivity: 73.3%, specificity: 71.6%), (**B**) Overall survival (Cutoff: 464, AUC: 75.9%, sensitivity: 74.1%, specificity: 71.9%).

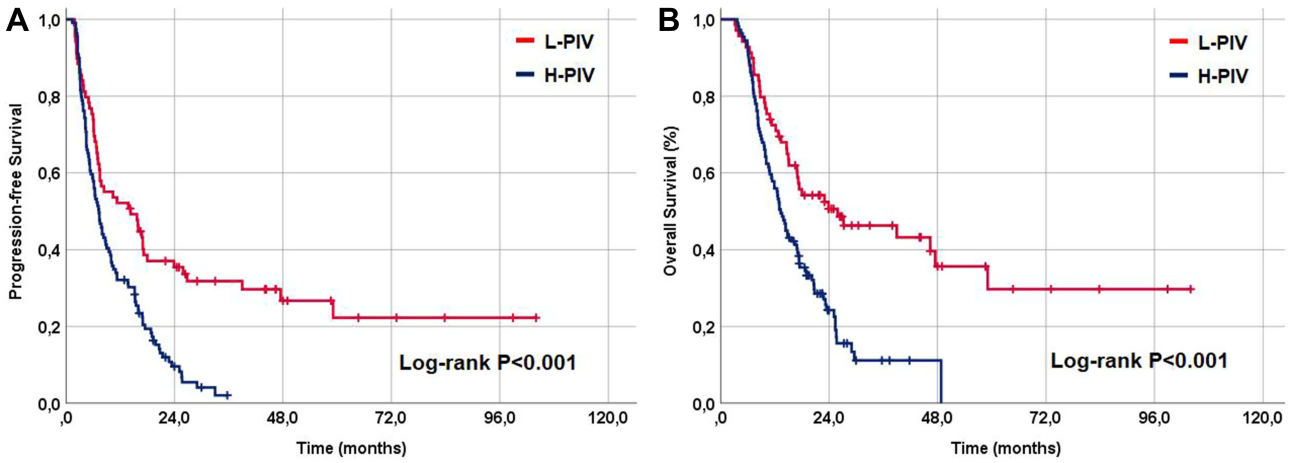

Figure 2 Comparative survival outcomes between the pan-immune-inflammation value groups. (**A**) Progression-free survival, (**B**) Overall survival.
Abbreviations: Red: L-PIV, Low pan-immune-inflammation value; Dark blue: H-PIV, High pan-immune-inflammation value.

Discussion

The current retrospective study sought to determine whether pretreatment PIV had any prognostic value in a cohort of 178 patients with unresectable LA-PAC who received definitive C-CRT. The novel result of multivariate Cox regression analysis was that pretreatment L-PIV measures were strongly and independently associated with significantly better median and long-term PFS and OS outcomes in this patient group, suggesting that PIV might be useful for more accurate stratification and individualized treatment of LA-PAC patients.

All PACs are distinguished by the presence of large numbers of immunological and fibroblastic cells in the tumor microenvironment (TME), which secrete proinflammatory cytokines and form a dense tumor stroma, indicating that inflammation is critical in tumor genesis, growth, and metastasis.[42] In support of this, it has been demonstrated that these inflammatory cytokines facilitate PAC growth and progression directly by stimulating tumor cells and indirectly by changing the TME.[42] Further, advances in tumor biology have shown a direct correlation between persistent local and systemic inflammation and the development of malignant clones resistant to currently available RT modalities and anticancer drugs.[12] In this regard, several systemic inflammatory response indexes have been researched for their prognostic utility in PAC patients due to chronic inflammation's detrimental effects on host immunity: ease of immune surveillance, inhibition of apoptosis, and promotion of neoangiogenesis, tumor aggressiveness, invasion capacity, and metastasis.[43] The results of such studies have essentially always confirmed the significant prognostic usefulness of such biological indicators, regardless of the chosen treatment approach.[14–26] The PIV, a newly discovered relevant indicator of

Table 2 Comparative Survival Results Between the Two Pan-Immune-Inflammation-Value Groups

Endpoint	All Patients (N=178)	L-PIV (N=69)	H-PIV (N=109)	P-value
Progression-free survival				
Median, mo. (95% CI)	7.8 (5.7–9.9)	14.3 (5.6–23.0)	7.3 (5.9–8.7)	<0.001
1-year (%)	39.9	52.2	32.1	
3-year (%)	14.6	31.8	2.1	
5-year (%)	10.2	22.3	0	
Overall survival				
Median, mo. (95% CI)	15.7 (13.5–17.9)	25.9 (4.7–47.1)	13.3 (11.5–15.1)	<0.001
1-year (%)	62.3	72.4	56.0	
3-year (%)	26.2	46.3	1.1	
5-year (%)	15.3	29.7	0	

Abbreviations: L-PIV, Low pan-immune-inflammation-value; H-PIV, High pan-immune-inflammation-value; CI, Confidence interval; mo, Months.

Table 3 Outcomes of Uni- and Multivariate Analysis

Characteristics	Overall Survival				Progression-Free Survival			
	Univariate P-value	Multivariate P-value	HR	95% CI	Univariate P-value	Multivariate P-value	HR	95% CI
Gender (female vs male)	0.89	-	-	-	0.81	-	-	-
Age group (<70 vs.≥70 years)	0.44	-	-	-	0.36	-	-	-
ECOG (0 vs.1)	0.94	-	-	-	0.97	-	-	-
Obesity (no vs.yes)	0.51	-	-	-	0.59	-	-	-
Alcohol abuse (no vs yes)	0.47	-	-	-	0.42	-	-	-
Tobacco consumption (no vs yes)	0.63	-	-	-	0.50	-	-	-
Chronic pancreatitis (no vs yes)	0.23	-	-	-	0.19	-	-	-
Tumor location (H vs B/T)	0.64	-	-	-	0.76	-	-	-
Tumor size group (< vs ≥4.6 cm)	0.43	-	-	-	0.37	-	-	-
Adjuvant chemotherapy (no vs yes)	0.27	-	-	-	0.23	-	-	-
Adjuvant chemotherapy cycles (< 4 vs ≥4)	0.19	-	-	-	0.17	-	-	-
LN status (N0 vs N1-2)	<0.001	<0.001	2.27	2.13–2.41	<0.001	<0.001	2.16	1.98–2.34
CA 19–9 (<vs ≥90 U/mL)	0.002	0.007	1.74	1.51–1.97	<0.001	0.004	2.02	1.77–2.27
PIV (L-PIV vs H-PIV)	<0.001	<0.001	2.86	2.58–3.14	<0.001	<0.001	3.04	2.87–3.21

Abbreviations: HR, Hazard ratio; CI, Confidence interval; ECOG, Eastern Cooperative Oncology Group; H, Head: Head of pancreas; B/T, Body/Tail of pancreas; LN, Lymph-node; CA 19–9, Cancer antigen 19–9; L-PIV, Low pan-immune-inflammation-value; H-PIV, High pan-immune-inflammation-value.

systemic immune-inflammation response that blends circulating platelets, monocytes, neutrophils, and lymphocytes, has been shown to accurately predict the prognosis in patients with colorectal, breast, esophageal, small-cell lung, non-small cell lung, and Merkel cell carcinomas, and malignant melanomas.[27–38] Despite the steadily growing body of basic and clinical data, it is interesting to note that the PIV has never been tested for its prognostic utility in LA-PAC patients undergoing radical CRT.

In PAC patients with any T-stage, the presence and number of lymph node metastases, a necessary component of the current TNM staging system, have repeatedly been shown to be a reliable predictor of clinical outcomes.[44] Similar to this, CA 19–9 is a trustworthy biomarker for accurately predicting pretreatment tumor stage and resectability status, as well as response to different anti-cancer therapies and survival outcomes.[41,45] In this respect, as did the majority of its

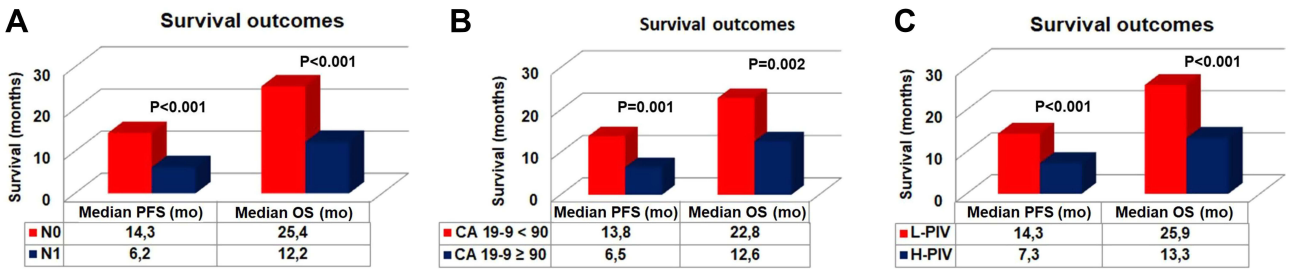

Figure 3 The bar chart demonstrating the comparative median progression-free survival (PFS) and overall survival (OS) results per (**A**) N-stages, (**B**) CA 19–9 measures, and (**C**) pan-immune-inflammation value (PIV) groups.

predecessors, the results of the current study supported the prognostic relevance of lymph node metastasis (stage N1-2) and higher CA19-9 levels (> 90 U/m/L) as predictors of poor PFS and OS in LA-PAC patients.

Representing a first for unresectable LA-PAC literature, we unveiled independent prognostic expediency for pretreatment PIV measures in such patients, where an H-PIV was linked to significantly inferior median PFS (7.3 versus 14.3 months for L-PIV; $P < 0.001$) and OS (13.3 versus 25.9 months for L-PIV; $P < 0.001$) durations after definitive C-CRTDue to the lack of LA-PAC research with a similar design, it is impossible to draw firm conclusions from the present notable results. Anyhow, these results seem to be consistent with the findings of earlier PIV studies in other tumor sites,[27–38] and a recently published systemic inflammation response index (SIRI) study in LA-PAC patients treated with radical C-CRT.[22] In the first-ever PIV study on digestive system tumors, Fucà et al[27] showed that pretreatment L-PIV values were associated with significantly better ($P < 0.001$) and OS ($P < 0.001$) outcomes in a cohort of 438 metastatic colorectal cancer patients receiving first-line therapy. In a recent study of 433 patients with esophageal cancer, Yoshifumi et al[34] found that L-PIV measurements significantly improved OS ($P = 0.0065$). In both studies, it was established that the prognostic significance of the PIV was unrelated to the other clinical factors ($P < 0.05$). Topkan et al recently published SIRI research in 154 LA-PAC patients treated with definitive C-CRT is of particular significance because PIV may also be formulated as: PIV = Platelets × SIRI.[24] The authors of this study reported that patients who presented with SIRI < 1.6 had significantly longer PFS (13.8 versus 6.7 months; $P < 0.001$) and OS (28.6 versus 12.6 months; $P < 0.001$) results than their SIRI ≥ 1.6 counterparts. The results presented here, which demonstrate that the novel PIV has a robust prognostic utility in the prognostic classification of the LA-PAC patients prior to the definitive C-CRT, seem reasonable given these clinical justifications.

Another impressive finding of the current study was that the H-PIV cohort had no 5-year survivors, similar to the tragic scenario of metastatic PAC patients, in contrast to the L-PIV cohort's 29.7% 5-year survivors. This finding is significant because it demonstrates the presence or emergence of malignant clones that are excessively aggressive, quickly metastatic, and resistant to anti-cancer treatments in the H-PIV group, an unpleasant but typical trait of the highly inflammatory and immune-suppressed tumor phenotypes.[26,46] Despite the fact that all eligible patients underwent an extensive initial staging workup that included FDG-PET-CT, abdominal MRI, and laparoscopic examination (if indicated), uncontrolled widespread DM was the cause of death in 83 (95.4%) of the 87 fatalities in this group. This finding implies that H-PIV patients had occult metastatic foci before the start of C-CRT, which were invisible to conventional staging techniques. The available research results appear to support this implication, which demonstrates that the underlying tumor's inflammation-induced chemoresistance and radiation resistance directly contribute to an increase in the incidence of occult DM.[47] These findings may have at least two significant clinical ramifications, although the underlying process is probably more complex. First, such data may emphasize the urgent requirement for more sophisticated staging tools to diagnose the occult metastatic disease before anti-cancer therapy. And second, the H-PIV group's significantly lower PFS and OS may call for the use of customized treatment algorithms, either to intensify therapy with brand-new therapeutic agents or to avoid ineffective aggressive C-CRT in this patient group. For a sizeable portion of patients, it may be possible to avoid the futile C-CRT regimens by starting treatment with chemotherapy and saving RT for those who do not experience disease progression during this time.

The inclusion of a relatively homogeneous patient population in terms of eligibility of only LA-PAC patients who were staged and treated similarly, as well as the identical timing of the PIV measurements, strengthens our current study. However, it is still limited by a number of factors. First, it was a retrospective study conducted by a single institution with a small cohort size, making it potentially susceptible to the unanticipated biases associated with such research. Second, the PIV is a dynamic biomarker that can fluctuate dramatically during and after C-CRT owing to changes in host immunity, systemic inflammatory response status, and tumor burden. Our findings, however, were based on a single time point snapshot, specifically pre-C-CRT PIV measurements. On the other hand, PIV variations may indicate tumor response or progression much earlier than the appearance of explicit radiographic abnormalities at any given time. As a result, future research should concentrate on PIV dynamics to define a more relevant cutoff that could be useful in the prognostic categorization of such patients. Third, since we selectively included only patients with good performance status (ECOG 0–1) in our study, the results may not fully describe all real-world outcomes in LA-PAC patients receiving radical C-CRT. Fourth, despite similar pretreatment and posttreatment characteristics, differences in adjuvant or rescue therapies may have unintentionally favored one PIV group over the other. Finally, due to a lack of patient categorization

per chemokines, lymphokines, interleukins, paracrine or autocrine factors such as TNF-α and TGF-β, apoptosis- and autophagy-related factors, we may have missed the opportunity to elucidate the actual relationship between the pre-C-CRT PIV measures and the patients' immune and/or inflammation status. Therefore, the findings presented here must be viewed as hypothetical and should be reiterated in subsequent studies to develop more convincing arguments about the prognostic relevance of PIV in this patient population.

Conclusion

The results of the present retrospective analysis revealed a clear and independent link between L-PIV measures and significantly more pleasing median and long-term PFS and OS outcomes in patients with unresectable LA-PAC who underwent definitive C-CRT. If additional research confirms this discovery, it might be helpful in more precise stratification and customized treatment of these patients as a complement to the respectable TNM staging system.

Data Sharing Statement

The datasets used and/or analyzed during the current investigation are available to researchers who satisfy the conditions for access to sensitive data via the Baskent University Department of Radiation Oncology Institutional Data Access (email address: adanabaskent@baskent.edu.tr).

Ethical Approval

The institutional review board approved the study design before collecting any patient data.

Consent

Each participant, either directly or via legally privileged representatives, provided written informed consent for the assemblage and analysis of blood samples and pathologic specimens, as well as the publication of the outcomes.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in relation to this work and that there are no conflicts of interest regarding the publication of this paper.

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