



Does Preoperative Serum Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), and Lymphocyte to Monocyte Ratio (LMR) Predict Prognosis Following Radical Surgery for Pancreatic Adenocarcinomas? Results of a Retrospective Study

Vikas Gupta¹ · Vikram Chaudhari¹ · Shailesh V. Shrikhande¹ · Manish S. Bhandare¹ 

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Abstract

Background Pretherapy serum neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) have been shown to predict prognosis in patients with pancreatic ductal adenocarcinoma (PDAC). However, the published literature is conflicting; hence, we aimed to evaluate their role in predicting survival outcomes in operated patients of PDAC.

Methods A retrospective analysis was performed in all operated cases of PDAC who underwent curative resection between 2011 and 2018. The pretherapy NLR, PLR, and LMR were calculated and analyzed with respect to pathological and survival outcomes

Results One hundred thirty-four operated patients were included. The median overall survival for NLR of less than 2, 2.7, and 5 was 30.8, 27.2, and 27.5 months and for NLR of more than 2, 2.7, and 5 was 22.9, 21.6, and 21.5 months, respectively, and was statistically insignificant (p -value—0.32, 0.91, 0.34, respectively). Similarly, the PLR was not significant for a cutoff of 150 (p -value—0.27), and LMR was not significant for a cutoff of 2.8 (p -value—0.13) and 4.8 (p -value—0.11). On univariate analysis age, CA 19–9 levels, perineural invasion, margin positivity, lymph node positivity, and TNM stage were found to have a significant correlation with overall survival. However, on multivariate analysis, only TNM stage was found to be significant.

Conclusion The NLR, PLR, and LMR do not correlate with overall survival in operated patients with PDAC in this study. A combination of inflammatory markers or their dynamic testing might probably achieve prognostic significance.

Keywords Pancreatic cancer · Serum neutrophil to lymphocyte ratio (NLR) · Platelet to lymphocyte ratio (PLR) · Lymphocyte to monocyte ratio (LMR)

Introduction

With a continuous progress in development of newer and effective cancer-related therapies, much improvement in survival has been achieved in many cancers. However, there has been hardly any headway when it comes to pancreatic ductal adenocarcinoma (PDAC), and it is still one of the most fatal cancers, with a 5-year survival rate of 5–10% [1]. The main

hindrance being difficulty is in its early detection, as most patients are asymptomatic in early stages of cancer and the inherent aggressive tumor biology of PDAC. At the time of diagnosis, 10–20% of tumors are operable; 30–40% are borderline resectable (BRPC), while remaining are either locally advanced or metastatic [2]. For advanced disease, palliative chemotherapy and/or radiotherapy remain the only treatment option.

Operable pancreatic cancers are generally divided into resectable and borderline resectable depending upon radiological features and relation to surrounding vessels, predicting the risk of margin positivity. This distinction is important, in order to offer neoadjuvant treatment in BRPCs, which has shown to increase the percentage of R0 resections and reduce lymph node positivity, thus reducing the

✉ Manish S. Bhandare
manishbhandare@gmail.com

¹ Gastrointestinal and Hepato-Pancreato-Biliary Service, Department of Surgical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute, Mumbai 400012, Maharashtra, India

risk of local recurrence [3]. A prognostic marker which can predict margin positivity in a seemingly upfront resectable tumor will help in deciding the criteria of resectability and need of neoadjuvant chemotherapy in this patient population. However, this requires that patients are risk stratified before starting treatment. Radiological evaluation is not entirely accurate in distinguishing resectable from borderline tumors, as radiological findings do not always correlate with intraoperative findings and histopathological parameters. Contrast-enhanced computed tomography (CECT) has poor sensitivity (77%) to predict vascular invasion, and endoscopy ultrasound (EUS) has high false positives or negatives (33%) to predict resection [4, 6].

A number of systemic inflammation-based prognostic markers and scores have been studied to predict cancer-specific survival in several digestive cancers [5]. Out of these, CA19-9 has been most commonly used in pancreatic cancers. However, use of CA 19-9 may not be accurate as few patients are non-secretors (10–15%); also, some patients with obstructive jaundice will have spuriously elevated CA 19-9 levels [6]. Previous studies concluded that the level of serum neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) might be associated with prognosis in several tumor types, including pancreatic cancers [7–12]. Although they are easy to measure, the number of neutrophils, monocytes, and lymphocytes is influenced by the immune status of body, which in turn is activated by host of other factors like active infection, chronic inflammatory diseases, and lifestyle-related habits [13]. In the present study, we aimed to assess the value of inflammation-based markers, namely, NLR, PLR, and LMR in predicting prognosis of operated PDAC patients.

Materials and Methodology

Data was collected from a prospectively maintained surgical database of patients who underwent curative pancreatotomy for PDAC, between January 2010 and June 2019. Inclusion criteria were patients with histologically proven PDAC with imaging findings consistent with resectable or borderline resectable pancreatic cancers as per the AHPBA criteria [14], documented patient Eastern Cooperative Oncology Group (ECOG) performance status score of < 2, who underwent curative intent surgery, either upfront or after neoadjuvant therapy. Exclusion criteria included patient with metastatic disease on presentation, patients lost to follow-up, patient who died in the immediate post-operative period, and those in whom data was not available on pre-treatment NLR, LMR, and PLR. Each patient was reviewed by multidisciplinary joint team (MDT) comprising of HPB surgeon, medical oncologist, radiation oncologist, radiologist, and pathologist,

for planning treatment. Patients with borderline resectable cancers were offered neoadjuvant chemotherapy/chemoradiation or upfront surgery as per discretion of MDT.

The NLR was calculated from the differential leucocyte count by dividing the absolute neutrophil count by the absolute lymphocyte count. Similarly, the PLR (platelet count by the absolute lymphocyte count) and the LMR (absolute lymphocyte count by the absolute monocyte count) were also calculated. The ratios were then divided into two groups using cutoff values; for NLR, we used cutoff values of 2.7 (mean NLR), 2, and 5. For PLR, 150, and for LMR, 2.8 and 4.8 were used as cutoffs. These cutoffs were based on literature review of previous large studies which have shown difference in survival using these values [7–12]. Patients who were upfront resectable had their blood samples collected within 1 month before surgery, and those planned for NACT had their values obtained from blood sample taken just before starting chemotherapy. All patients who were planned for neoadjuvant chemotherapy or chemoradiation or surgery showed no signs of systemic inflammation or infection as noted at the time of laboratory testing. For patients having obstructive jaundice, all blood test results were re-assessed after procedures such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous trans-hepatic biliary drainage (PTBD), once jaundice had resolved, before planning surgery.

Statistical Test

Continuous variables were compared using Student's *t*-test and categorical variables were compared using the chi-squared test. Survival curves were calculated using the Kaplan–Meier method and compared using log-rank test to evaluate difference in survival. Survival curves were compared using the cutoff values already mentioned. P values less than 0.05 were considered statistically significant. The factors associated with OS in univariate analysis were used for the performance of the multivariate Cox-regression analysis. The statistical analyses were performed with the Statistical Package of the Social Sciences (SPSS), version 17.0.

Results

Overall, 1144 patients underwent surgery between 2010 and 2018 for pancreatic and periampullary tumors. Seven hundred eight patients had tumors of periampullary origin, and 260 were of non-adenocarcinoma histology. Follow-up data was not available for 20 patients, and pretherapy blood parameter records were not available of 5 patients. There were 17 post-operative deaths. After excluding these cases, 134 patients were available for final analysis who underwent curative resections for pancreatic

Table 1 Laboratory tests of resected patients

Variable	Median (min, max)
ANC ($10^9/l$)	5 (2, 10)
AMC ($10^9/l$)	0.4 (0.1, 1.2)
ALC ($10^9/l$)	1.9 (0.1, 5.3)
Platelets ($10^9/L$)	288 (77, 674)
Serum albumin (g/dL)	3.9(2.7–5.2)
Neutrophil/lymphocyte ratio	2.7(0.38–76)
Platelet/lymphocyte ratio	196.8(20.8–2440)
Lymphocyte/monocyte ratio	4.8 (0.27–17)

adenocarcinoma. All patients underwent either pancreaticoduodenectomy (PD) or radical antegrade modular pancreatico-splenectomy (RAMPS).

There were slightly more females than males, and most of the cancers were pancreatic head adenocarcinomas (85.8%). Seventy-six patients (56.7%) were upfront resectable, and 58 (43.3%) were borderline resectable according to radiological evaluation. Forty (29.9%) patients received neoadjuvant therapy (37—chemotherapy, 3—chemoradiation). Adjuvant chemotherapy was given to 110 patients (82.1%). Thirty-two (24.3%) out of 132 patients had margin positivity. Most patients were T3 (43.3%), and there were an almost equal number of node-positive (54.5%) and node-negative (45.5%) patients (Tables 1 and 2).

The mean absolute lymphocyte, monocyte, neutrophil, and platelet counts were $1.9 \times 10^9/l$, $0.4 \times 10^9/l$, $5 \times 10^9/l$, and $288 \times 10^9/l$, respectively, and the mean NLR, LMR, and PLR values were 2.7, 195, and 4.8, respectively. Kaplan–Meier method was used to calculate survival curves, and survival was compared using log-rank test. Age more than 65 years ($p=0.008$), CA 19–9 more than 200 U/mL ($p=0.002$), presence of perineural invasion ($p=0.036$), margin positivity ($p=0.044$), lymph node positivity ($p=0.039$), and higher TNM stage ($p=0.002$) were found to have worse OS (Fig. 1). On univariate analysis stage of disease ($p=0.001$, HR—3.54, 95% CI 1.69–7.44), age with cutoff of 65 years ($p=0.010$, HR—2.03, 95% CI 1.18–3.49), CA 19–9 for a cutoff 200 U/mL ($p=0.016$, HR—1.83, 95% CI 1.31–2.96) perineural invasion ($p=0.040$, HR—0.59, 95% CI 0.36–0.97), and lymph node positivity ($p=0.04$, HR—0.60, 95% CI 0.37–0.98) were found to have significant correlation with overall survival. However, on multivariate analysis, only TNM stage ($p=0.02$, HR—2.97, 95% CI 1.13–0.7.77) was found to be significant. None of the inflammation-based markers, namely, NLR, PLR, and LMR were found to correlate with overall survival (Table 3).

Table 2 Clinical, operative, and pathological features of resected patient

Characteristics	Number (percentage)
Age, years (range)	56 (22–80)
< 65	108 (80.6)
> 65	26 (19.4)
Gender	
Male	81 (60.4)
Female	53 (39.6)
Location of tumor	
Head of pancreas	115 (85.8)
Body/tail of pancreas	17 (12.7)
Neck of pancreas	2 (1.5)
CA19-9 (U/mL)	
< 200	81 (60.4)
> 200	53 (39.6)
Type of resection	
Pancreaticoduodenectomy	114 (85)
Distal pancreatectomy	12 (8.95)
Total/subtotal pancreatectomy	8 (5.9)
Neoadjuvant therapy	40 (29.9)
Chemotherapy	37 (27.6)
Chemoradiation	3 (2.2)
Adjuvant therapy	
Chemotherapy	110 (82.1)
Observation	24 (17.9)
Pathologic features	
Histological differentiation	
Moderate	104 (77.6)
Poor	30 (22.4)
Perineural invasion present	73 (54.4)
Lymphovascular invasion present	54 (40.3)
Margin positivity ($n=132$)	
R0	100 (75.7)
R1	32 (24.3)
AJCC/TNM 8th Ed	
pT stage	
T1	17 (12.7)
T2	43 (32.1)
T3	58 (43.3)
T4	16 (11.9)
pN stage	
N0	61 (45.5)
N1	53 (39.6)
N2	20 (14.9)
Stage	
IA	16 (11.9)
IB	19 (14.2)
IIA	26 (19.4)
IIB	41 (30.6)
III	32 (23.9)

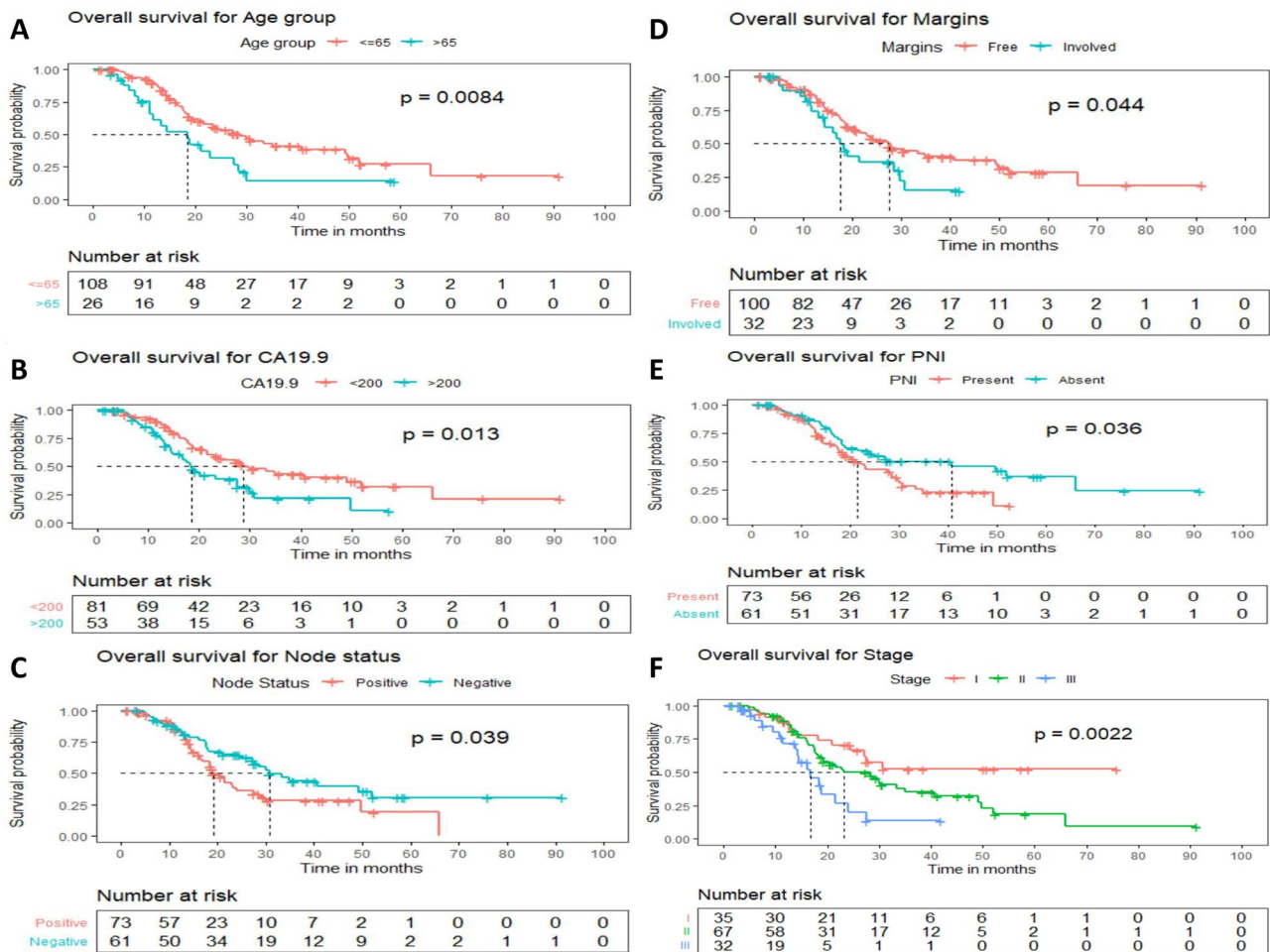


Fig. 1 Kaplan–Meier survival analysis demonstrated worse OS for patients who had aged more than 65 years (A), had CA 19–9 more than 200 (B), were node-positive (C), had margin positivity (D), had perineural invasion (E), and those with higher stage (F) ($p < 0.05$)

Discussion

There is a significant difference in the biological behavior and prognosis of pancreatic cancers, with patients within same stage also having varied final outcomes. To identify some markers which can predict survival may help us further prognosticate these patients and ultimately assist in decision-making. An ideal prognostic marker should give us information on the long-term prognosis of patients, help us in making a comprehensive treatment plan including sequencing of surgery, chemotherapy, and or radiotherapy and also in predicting margin and lymph nodal status before surgery [2]. The prognostic marker should best correlate with the pathological and clinical stage of disease. The most accurate information on outcomes following surgery are obtained from post-operative histological parameters like tumor size, nodal status, margin status, and pathological stage of the disease [15]. However, to make an effective treatment plan,

patients need to be risk stratified before surgery [7]. In the present study age, CA19-9, perineural invasion, margin positivity, lymph node positivity, and TNM stage of disease were found to have a significant association with overall survival. None of the inflammation-based marker ratios, namely, NLR, PLR, or LMR was found to have correlation with overall survival.

Inflammation is one of the hallmarks of carcinogenesis and plays an important role in tumor progression [16]. Neutrophils are among the first cells to migrate to site of inflammation. They, in turn, release chemokines and protease which further recruit other effector cells [17]. On the other hand, lymphocyte count correlates with the systemic immune response that the host can mount, and tumor-infiltrating lymphocytes (specifically T cells) are responsible for mounting the antitumor response within the microenvironment [18]. As far as platelets and cancer cells are concerned, they are known to interact with each other during tumorigenesis. Cancer cells bring about platelet adhesion,

Table 3 Univariate and multivariate Cox proportional hazards analysis of patient and tumor-related factors for overall survival

Variable	Univariate				Multivariate				
	Hazard ratio	95.0% CI		<i>P</i> Value	Hazard ratio	95.0% CI		<i>P</i> Value	
		Lower	Upper			Lower	Upper		
Patient-related factors									
Age	≤ 65								
	> 65	2.036	1.187	3.493	0.010	1.64	0.93	2.89	0.088
Sex	Male								
	Female	1.058	0.652	1.718	0.820				
CA19-9	< 200								
	> 200	1.831	1.131	2.965	0.014	0.63	0.379	1.078	0.093
NLR-2.7	< 2.7								
	> 2.7	0.975	0.609	1.563	0.918				
NLR-2	< 2								
	> 2	1.307	0.769	2.222	0.323				
NLR-5	< 5								
	> 5	1.400	0.694	2.824	0.348				
PLR-150	< 150								
	> 150	0.767	0.477	1.234	0.275				
LMR-4.8	< 4.8								
	> 4.8	0.673	0.409	1.108	0.119				
LMR-2.8	< 2.8								
	> 2.8	0.666	0.388	1.142	0.139				
Neoadjuvant therapy	Yes								
	No	1.442	0.843	2.467	0.181				
Tumor-related factors									
Tumor Differentiation	MDAC								
	PDAC	0.610	0.850	2.956	0.140				
LVE	Absent								
	Present	0.813	0.460	1.217	0.242				
PNI	Absent								
	Present	0.595	0.364	0.971	0.038	0.72	0.42	1.23	0.229
Margins	Free								
	Involved	1.721	1.007	2.942	0.047	1.11	0.59	2.09	0.751
LN status	Negative								
	Positive	0.606	0.375	0.980	0.041	1.17	0.60	2.26	0.652
pT stage	T3, T4 versus T1, T2	1.577	0.618	4.020	0.340				
TNM stage	III versus I and II	3.54	1.690	7.443	0.001	2.97	1.13	7.77	0.027

MDAC moderately differentiated adenocarcinoma, PDAC poorly differentiated adenocarcinoma, LVE lymphovascular emboli, PNI perineural invasion, LN lymph node

platelet activation, and degranulation with resultant pro-survival and pro-angiogenic signals which may promote cancer spread [19, 20]. Literature on use of these blood cell-based markers is inconsistent with few studies showing either no or some implication [15, 21–26] while others concluding their usefulness in prognostication of disease [6–8, 27, 28]. Although most studies including meta-analysis have shown favorable outcomes with the use of pro-inflammatory markers for prognosis, there is considerable variation in the type of marker used, timing of blood sample collection, and the cutoff value of marker.

In a recently published retrospective study assessing the role of NLR and PLR for resectable pancreatic cancers, no significant association was found between these markers and survival for a range of cutoff values [21]. Similarly, prospective study by Jamieson et al. studying the prognostic value of tumor and patient-related factors in patients undergoing potentially curative surgery for PDACs did not find either NLR or PLR to be associated significantly with survival for cutoff values of 5 and 150, respectively [15]. Other studies assessing multiple parameters have shown survival to

be unrelated to at least one or more of these markers (NLR, PLR, or LMR). In one of the studies with 74 resected pancreatic cancers, NLR was found to be significantly associated with disease-free survival at a cutoff of 5, but no difference was seen with C reactive protein (CRP) or PLR [22]. One of the larger retrospective studies found significant association between NLR (cutoff of 5) and overall survival for both resected and inoperable pancreatic cancers. However, no significance was seen for PLR (cutoff of 150) [27]. Likewise, retrospective cohort study by Sierzega et al. (442 patients) found NLR and LMR to be associated with survival, but no relation was seen with PLR [29] (Table 4).

There are at least 3 meta-analyses conducted to look into the prognostic significance of these markers [10–12]. One of the initial meta-analyses by Yang et al. (11 studies and 1804 patients) had a diverse patient population with few studies consisting of locally advanced cancers treated with chemotherapy, others having resected pancreatic cancer, and others still having a combination of both

resected and locally advanced patients [11]. Another meta-analysis of 1519 patients with 8 studies [12] which looked into only resected pancreatic cancers found a significant association between NLR (cutoff values ranging from 2 to 5) and survival. Nevertheless, most of these were studies conducted in Asian population, and this may be a confounding factor in validating the outcomes of this analysis into other population groups. A recently published larger meta-analysis of 8252 patients [10] consisting of heterogeneous study groups also found a significant association between NLR and survival. Even the subgroup analysis of surgery alone trials, as also analysis based on ethnic origin of the patients, showed positive results. Again, the surgery alone trials were predominantly conducted in Asian countries, and the subgroup of Caucasian trials predominantly involved non-surgical treatment, thus making comparison between study groups debatable. Surgery alters the natural course of disease process; thus, it might not be correct to club resected and inoperable patients

Table 4 Published literature on prognostic applications of NLR, LMR, and PLR in resected pancreatic cancer

Study	Year	Number	Variable	Cutoff	Cohorts	Median overall survival (months)	(<i>p</i> Value), Significance	
Clark et al. [25]	2007	44	NLR	<5/≥5	40/4	10.5/8.9	(0.16), NS	
Bhatti et al. [34]	2010	84	NLR	≤4/>4	71/13	14/7.1	(0.004), S	
				≤3/3–4/>4	55/17/12	13.7/17/5.9	(0.016), S	
Garcea et al. [22]	2011	74	NLR	<100/100–200/>200	35/39/10	14.4/10.3/8	(0.642), NS	
				<5/>5	-	52/12 (DFS)	(0.0057), S	
Jamieson et al. [15]	2011	135	PLR	-	-	-	NS	
				NLR	<5/≥5	105/30	20.9/25.7	(0.510), NS
La Torre et al. [24]	2012	101	PLR	<150/≥150	42/93	26.7/20.7	(0.21), NS	
				NLR	≤5/>5	81/20	21/17	(0.13), NS
Sanjay et al. [26]	2012	51	NLR	≤5/>5	38/13	16.2/9.1	(0.272), NS	
				PLR	<150/150–300/>300	16/25/10	15.9/15/4.1	(0.532), NS
Smith et al. [35]		110	NLR	Continuous	Continuous	-	(0.14), NS	
				PLR	<150/150–300/>300	48/43/19	19.7/13.7/5.8	(0.0001)
Stotz et al. [27]	2013	110	NLR	<5/>5	73/37	-	(0.006), S	
				PLR	<150/≥150	28/82	-	(0.458), NS
Hamed et al. [23]	2013	85	NLR	<5/≥5	67/18	20.6/11.3	(0.15), NS	
Sierzega et al. [29]	2017	442	NLR	<5/>5	323/119	25/12.6	(0.012), S	
				LMR	<3/≥3	247/195	13.1/29.2	(0.026), S
Onoe et al. [9]	2019	165	NLR	<3.2/≥3.2	117/48	-	(0.046), S	
				PLR	<250/≥250	132/33	-	(0.014), S
				LMR	<2.8/≥2.8	25/140	8.7/18.5	(0.015), S
Current study	2020	134	NLR	<2/≥2	35/99	30.8/22.9	(0.91), NS	
				<2.7/≥2.7	66/68	27.2/21.6	(0.32), NS	
				<5/≥5	122/12	27.5/21.5	(0.34), NS	
			PLR	<150/≥150	59/75	24/27.2	(0.27), NS	
			LMR	<4.8/≥4.8	79/55	21.5/30.8	(0.11), NS	
				<2.8/≥2.8	29/105	20.3/27.5	(0.13), NS	

NLR neutrophil to lymphocyte ratio, PLR platelet to lymphocyte ratio, LMR lymphocyte to monocyte ratio, NS not significant, S significant (*P* < 0.05)

together as a common cohort while analyzing the results of the study. Moreover, the cutoff value of NLR and sample size of included cohorts varied from 2 to 5 and 28 to 474, respectively.

With considerable improvement in survival over past decades and corresponding decrease in morbidity [30], identification of prognostic markers should help us in further improving patient outcomes. However, our study did not find any significant association between these markers and overall survival and, although the survival was better with low NLR and high LMR for all cutoffs, it did not reach statistical significance. One of the reasons for this may be that, although, individually, this test may not be predictive of survival, a combination of two or more of these variables may be a better marker to assess prognosis. The systemic immune-inflammation index (SII), calculated with lymphocyte, neutrophil, and platelet counts, has been shown to be an independent negative predictor of disease-free survival in resectable PDAC [31] as well as OS when evaluated as a continuous variable rather than preoperative value in patients given neoadjuvant chemotherapy [32]. It has also been shown to be better than neutrophil-to-lymphocyte ratio (NLR) or the platelet-to-lymphocyte ratio (PLR) for prediction of OS in patients with resectable PDAC [33]. Also, as inflammatory markers are dynamic, they may change during the treatment course. Thus, instead of assessing these variables at a point in time, looking at change of values over the course of treatment might be a better way of utilizing their potential. This may be of significance as neoadjuvant approach is being increasingly used to treat borderline resectable pancreatic cancers. Glazer et al. in their study of BRPCs did not find NLR value alone (pre- and post-chemo) as predictive of survival, but an increase in values over course of chemotherapy to be associated with poor survival post-resection [28].

The main limitation of our study is its single-center, retrospective design with a relatively small sample size. Larger, multicenter studies will give a better answer to the applicability of these markers. To summarize, although literature is replete with studies that have shown correlation of survival with proinflammatory markers, their applicability is still contentious. Many of the studies had heterogeneous population groups with regards to management (surgical or non-surgical), cutoff value used, the timing of sample collection, presence of associated inflammatory condition, and tumor stage. Thus, there is still an ambiguity involved in using these markers for the purpose of prognostication. Further larger trials using combination of markers measured preoperatively for upfront resectable patients or assessing response of these markers following neoadjuvant treatment for BRPC are needed. Till robust data on their use is available, it may be counterproductive if these markers are used for definitive decision making.

Conclusion

The NLR, PLR, and LMR were not found to correlate with overall survival in operated patients with pancreatic ductal adenocarcinomas in our study. A combination of inflammatory markers or their dynamic testing might probably achieve prognostic significance.

Author Contribution VG, MB VC, and SS were involved in the conception and design of the work. VG and MB are involved in acquisition, analysis, interpretation of data, and manuscript preparation. MB, VC, and SS are involved in manuscript editing, manuscript review. All authors read and approved the manuscript.

Declarations

Ethical Approval The data of the present study were collected in the course of common clinical practice, and accordingly, the signed informed consent was obtained from each patient for any surgical and clinical procedure. The study protocol was in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments. Because this was a retrospective study, formal consent for this study is not required, and no approval of the institutional research committee was needed.

Conflict of Interest The authors declare no competing interests.

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