Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios inversely correlate to clinical and pathologic stage in patients with resectable pancreatic ductal adenocarcinoma

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Background: Post-surgical pathology (SP) staging correlates with long-term survival. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been shown to predict prognosis and extent of tumor in patients with metastatic pancreatic ductal adenocarcinoma (PDAC). This study aimed to correlate NLR and PLR to radiological clinical staging (CS), carbohydrate antigen (CA) 19-9 tumor marker and SP staging in patients with resectable-PDAC (R-PDAC); and to investigate NLR and PLR as potential markers to guide neoadjuvant therapy.

Methods: Data were collected retrospectively from R-PDAC patients who received upfront surgery from November 2011 to December 2016. NLR and PLR values on the day of diagnosis and surgery were collected. SP, tumor size, location, resected margins (RM), lymphovascular/perineural invasion (LVI/PNI), lymph node involvement, and AJCC/TNM 8th Edition staging were obtained. Associations were assessed using linear, ordinal logistic, and poison regressions or Kruskal Willis Rank Sum Test per the nature of outcome variables, with statistical significance at p-value <0.05.

Results: Fifty-five patients were identified with resectable stage I (61%) and II (38%). They had a mean age of 66 years (48–87 years) and were 47.2% male, 83.6% white, 90.9% non-Hispanic and 89% with ECOG 0-1. NLR/PLR at diagnosis for R0, R1 and R2 were 6.7/241, 4.8/224, and 2.9/147 (P=0.01/0.002), respectively. NLR/ PLR for N0 and N1 were 5.1/212 and 2.7/138.3 (P=0.03/0.009) at diagnosis. No other significant association was detected.

Conclusions: These findings suggest that NLR/PLR inversely correlates with RM and lymph node status in patients with R-PDAC, but require prospective evaluation in clinically defined scenarios.

Keywords: Neutrophil-to-lymphocyte; platelet-to-lymphocyte; ratio; pancreatic ductal adenocarcinoma (PDAC); outcomes

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer related death in the United States and its incidence rates continue to increase, now 3% of all new cancers (1). At the time of diagnosis about 10% of patients have localized disease, and another 29% have disease that has spread to regional lymph nodes; although surgical resection with curative intent is a possibility, their 5-year survival are 34.3% and 11.5%, respectively (2). The National Cancer Comprehensive Network (NCCN) defines PDAC as resectable, borderline resectable, or unresectable based primarily on vasculature-defined criteria from imaging findings (3). Furthermore, approximately 80% of PDAC patients who undergo radical surgery will have a recurrence despite adjuvant therapy (4). Neoadjuvant treatment has been shown to improve survival in borderline resectable pancreatic cancer by increasing the percentage of R0 resection and lowering lymph node rates therefore reducing local recurrence (5). As per NCCN guidelines, neoadjuvant treatment is recommended for resectable cases with high-risk features (e.g., high risk suspicious imaging findings, very highly elevated carbohydrate antigen (CA) 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, extreme pain), and for borderline resectable cases (3). Hence, it is of most importance to achieve an accurate PDAC evaluation that will clearly define patients eligible for upfront resection with curative intent and those who may benefit from perioperative treatments. It is equally important to have a biomarker that guides either continued perioperative chemotherapy versus referral for surgical resection.

Although different imaging modalities can be used to evaluate whether a patient with PDAC is a surgical candidate, each has potential challenges, e.g., triple-phase staging contrast-enhanced computed tomography (CT) has poor sensitivity (77%); diagnosing vascular invasion and endoscopy ultrasound (EUS) has 33% false positive or negative resectability interpretations (6). Magnetic resonance imaging (MRI) has added preoperative accuracy on resectability and occult liver metastasis for patients for whom upfront surgery is planned (7). CA 19-9 has been shown to be predictive of survival and resectability for PDAC (8). Nevertheless, the utility of CA 19-9 is limited by the fact that approximately 10–15% of patients are non-secretors and a concerning 25% of patients have normal serum levels in a retrospective study with early stage PDAC (9). Therefore, early pancreatic cancer stage continues to have a need for more sensitive and specific biomarkers that can more accurately identify early stage PDAC patients who can benefit from surgical resection.

Multiple retrospective findings have associated different serological pro-inflammatory biomarkers, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with poor cancer outcomes. A meta-analysis has suggested that NLR has a significant correlation with Ca 19-9 level and tumor metastasis extension as well an association with overall survival independent of surgery or chemotherapy of pancreatic adenocarcinoma (10). Pre-operative NLR >3 and PLR >225 was shown to be an independent risk factor of poor survival after upfront surgery of resectable or borderline resectable PDAC (11). Other PDAC retrospective studies have also shown that relatively higher NLR is a predictive marker of poor outcome for: invasion in pre-malignant intraductal papillary mucinous neoplasm (NLR >2.5) (12), pathological response to preoperative chemoradiotherapy (NLR >2.2) (13), survival after neoadjuvant chemotherapy (NLR >2.5) (14), and disease-free survival post upfront curative resection (NLR >5) (15). PLR above 150 was analyzed by systemic review and meta-analysis and demonstrated to be a significant independent prognostic factor of increased likelihood metastatic disease and poor overall survival for pancreatic cancer (16). Likewise, multiple retrospective PLR studies have shown that a higher PLR correlated with: poor disease-free survival after upfront surgical resection (PLR >150) (17), poor survival of resectable cancers (PLR >140) (18), and poor outcomes of locally advanced peri-operative treatments (PLR >149) (19). NLR and PLR have become both independent and complementary novel potentially reliable prognostic factors for PDAC at different clinical stages.

Independent imaging and tumor serum markers have failed to accurately assess risk of which PDAC patients may benefit from upfront surgical resection or which may benefit from added neoadjuvant chemotherapy. Complete blood counts (CBCs) and differential including neutrophil, lymphocyte and platelet absolute are routinely available at diagnosis, staging and preoperative steps. NLR and PLR ratios are easily available and evaluable in every day clinical practice. The aim of this study was to correlate NLR and PLR to clinical staging (CS), CA 19-9, and surgical pathology (SP) outcomes in patients with R-PDAC; and to investigate NLR/PLR as a potential marker to guide neoadjuvant therapy.

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Methods

A retrospective chart review of patients with R-PDAC who underwent upfront surgery (Whipple) between November 2011 and December 2016 at the University of Arizona Cancer Center was conducted. We obtained prior to initiating research an Institutional Review Board approval Protocol Number: 1804508070 and further obtained a waiver of personal health information authorization [45 CFR 164.512(i)(2)(ii)]: as the use or disclosure of protected health information involves no more than minimal risk to the individuals and the research could not practicably be conducted without the waiver. Inclusion criteria were: (I) histologically proven PDAC, (II) available radiological evaluation with contrast-enhanced CT or magnetic resonance of a resectable tumor not involving the celiac axis, superior mesenteric artery, and/or common hepatic artery, <180 contact with superior mesenteric vein or portal vein, regardless of size and no distant metastasis including non-regional lymph nodes (3), (III) documented patient Eastern Cooperative Oncology Group (ECOG) performance status score of <2 and appropriate comorbidity profile for surgery, and (IV) available perioperative electronic medical record documentation. Exclusion criteria were: (I) patient with another malignancy not related to PDAC, (II) pre-operative cancer therapy including systemic chemotherapy, radiation therapy and clinical trials, (III) surgical intervention aborted, (IV) other documented infectious or autoimmune active disease, and (V) no available complete medical documentation.

Patient's demographics including age, sex, race, ethnicity and comorbidities were collected. CBC with differential including absolute neutrophils counts (ANC $\times 10^9$/L), absolute lymphocyte counts (ALC $\times 10^9$/L) and absolute platelet counts (APC $\times 10^9$/L) were gathered on the day of diagnosis (biopsy date or closest date before or after) and on the day of surgery (pre-surgical evaluation or closest day prior). A preoperative level of the serum tumor marker carbohydrate antigen 19-9 (CA 19-9; also called cancer antigen 19-9 reference interval 0–37 U/mL) was included when available. Clinical radiological stage by tumor size (cm, cT1-4), regional lymph node status (cN0-2), and final clinical stage TNM 8th Edition Staging System group (cIA-III) were assessed by our Imaging Department. The tumor location, histology and differentiation grade (well, moderate, and poor), size (cm, pT1-T4), lymph node involvement (ratio, pN0-2), resection margins (R0, R1, R2), lymphovascular/perineural invasion (LVI/PNI), and pathological stage (pIA-III) were obtained from the SP specimen report.

Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were calculated by division of ANC and APC by ALC measured in peripheral CBC. Means, medians, ranges and other descriptive statistics were calculated to summarize the data. A paired two-tailed *t*-test was used to compare the means of two groups. Associations were assessed using linear, ordinal logistic, and Poisson regressions or Kruskal Wallis Rank Sum Test per the nature of outcome variables. Statistical significance was considered at P value less than 0.05.

Results

Our search of the tumor registry yielded a total of 82 patients; in which 55 fulfilled inclusion criteria and 27 patients were excluded due to other malignancy (n=8), preoperative therapy (n=8), metastatic disease at laparoscopy (n=3) and incomplete data analysis (n=8). Our analysis included patients with median age of 66 years old at diagnosis (range, 48–87), with 52.8% female, 83.6% white, and 90.9% non-Hispanic. Of these 69.1% had at least one cancer risk factor, the most common clinical presentation, 43.3% with painful jaundice, 61.8% had biliary stent placement, and 56.3% with ECOG of 1 (*Table 1*).

Median laboratory values at diagnosis and surgery were ANC 4.4/4.7, ALC 1.4/1.7, APC 252/255, ($\times 10^9$/L) respectively (all prior, unpaired *t*-test non-significant), and preoperative CA 19-9 median was 63 U/mL. Median ratios at diagnosis/surgery were 3.1/3.1 and 172.7/152.5 for NLR and PLR, respectively (all prior, unpaired t-test non-significant). Clinical radiology showed a median tumor size of 2.4 (0.5–8) cm, 23.6% with lymph node positive (N1), and stage cI (58%), cII (40%), cIII (1.8%). Common pathology reports featured: tumor at head of pancreas (83.6%), moderate histological differentiation (65.4%), tumor size 3.5 (0.2–15) cm, PNI (72.7%), LVI (47.2%), Lymph node positive (N1) (74.5%), positive resection margins (76.3%), and stage pI (21.9%), pII (67.2%) and pIII (10.9%) (*Table 2*). Postoperatively, 70.9% of patients received systemic therapy and had median overall survival of 20 months (1–79 months) (*Table 1*).

Paired t-test analyses for NLR and PLR (NLR/PLR) showed no statistical difference between the data collected at the day of diagnosis and the day prior to surgery, thus we decided to evaluate outcomes to the values measured at day of diagnosis. NLR/PLR at diagnosis correlated inversely

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Table 1 Patients with resectable pancreatic ductal adenocarcinoma characteristics

Characteristics	Value
Patients included, n (%)	55 (100%)
Age at diagnosis [years]	66 [48–87]
>65 years old, n (%)	30 (54.5)
Gender	
Male	26 (47.3)
Female	29 (52.7)
Race	
White	46 (83.6)
Black	1 (1.8)
Asian	2 (3.6)
Native American	3 (5.5)
Unknown	3 (5.5)
Ethnicity	
Hispanic	5 (9.1)
Non-Hispanic	50 (90.9)
Pancreatic risk factors	
None	17 (30.9)
Smoking	20 (36.4)
Diabetes mellitus/obesity	14 (25.5)
Personal/family cancer history	9 (16.4)
Non-hereditary chronic pancreatitis	6 (10.9)
Presenting symptom	
Abdominal pain	28 (50.9)
Jaundice	24 (43.6)
Weight loss	14 (25.5)
Painless Jaundice	3 (5.5)
Other	4 (7.3)
Biliary stent placement	34 (61.8)
Performance status ECOG score	
0	18 (32.7)
1	31 (56.4)
2	6 (10.9)
Laboratory values, median (range)	
At day of diagnosis	
ANC	4.4 (1.6–19.7)
ALC	1.4 (0.5–5.9)
Hgb	13.6 (8.2–16.8)
APC	252 (121–408)
NLR	3.1 (0.8–24.02)
PLR	172.7 (55.4–504)
At day of surgery	
ANC	4.7 (1.7–12.1)
ALC	1.7 (0.4–3.7)
Hgb	13.0 (7.3–17.3)
APC	255 (121–582)
NLR	3.1 (0.8–19.0)
PLR	152.5 (52.2–606)
Preoperative CA 19-9 median U/mL (range)	63 [1–2,595]
Adjuvant therapy, n (%)	39 (70.9)
Median overall survival (months)	20 [1–79]

ECOG, Eastern Cooperative Oncology Group; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Hgb, haemoglobin; APC, absolute platelet count; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CA 19-9, carbohydrate antigen 19-9.

with positive resection margins (RM) pathology report; mean NLR/PLR for R0, R1 and R2 were 6.7/241, 4.8/224, and 2.9/147, respectively (P=0.01/0.002). Likewise, NLR/PLR was inversely associated with the radiological lymph node (LN) status; values for N0 and N1 were 5.1/212, and 2.7/138.3, respectively (P=0.03/0.009), although not significant for pathological LN status (P=0.46/0.98). No other significant association with clinical stage (cT/N/M), pathological stage (pT/N/M), including differentiation grade, PNI/LVI, laboratory tumor marker CA 19-9 or overall survival with either NLR or PLR levels from diagnosis or surgery day were detected (*Table 3*). Established prognostic factors were evaluated and correlated to our

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Table 2 Clinical and pathological pancreatic ductal adenocarcinoma characteristic table

Characteristics	n (%)
Clinical stage AJCC/TNM 8th Ed	
IA	13 (23.6)
IB	19 (34.5)
IIA	8 (14.5)
IIB	14 (25.5)
III	1 (1.8)
Location	
Head	46 (83.6)
Body	3 (5.5)
Tail	2 (3.6)
Overlap	4 (7.3)
Histological differentiation	
Well	6 (10.9)
Moderate	36 (65.5)
Poor	13 (23.6)
Perineural invasion	40 (72.7)
Lymphovascular invasion	26 (47.3)
Lymph node	
N1	41 (74.5)
Pathological stage AJCC/TNM 8th Ed.	
IA	6 (10.9)
IB	6 (10.9)
IIA	9 (16.4)
IIB	28 (50.9)
III	6 (10.9)
Resection margins	
R0	13 (23.6)
R1	20 (36.4)
R2	22 (40.0)

AJCC/TNM 8th Ed., American Joint Committee on Cancer/ Tumor, Node, Metastasis Eight Edition.

patient survival cohort, demonstrating a worse survival outcome if Stage T3 (P=0.01 *vs.* <T2), N1-2 (P=0.001 *vs.* N0), R1-2 (P=0.01 *vs.* R0), and positive PNI (P=0.03 *vs.* negative), although not seen with LVI or CA 19-9 level (P>0.05).

Discussion

Systemic inflammatory response by the innate immune cells is recognized as an enabling characteristic of tumors that promotes the ability to acquire hallmark capabilities (20). Increasing evidence has shown that inflammation caused by the hematological cells can influence solid tumor progression by providing bioactive molecules into the microenvironment and could foster other hallmark-facilitating programs. Neutrophils promote angiogenesis, tumorigenesis, metastasis, and tumor cell proliferation and survival and can also protect tumor cells from immune mediated destruction (21-23). Lymphocytes counts have shown to predict the immune systemic response of the host, and furthermore, tumor-infiltrating lymphocytes (and specifically T cells) are responsible for mounting the antitumor response within the microenvironment (24). Suppression of antitumor immunity is another hallmark capability, described by the recruitment of regulatory T cells resulting in an unopposed tumor progression (20). Platelets are well-known reservoirs of critical cytokines that regulate tumor angiogenesis, proliferation, migration, and metastasis (25). Notably, PDAC has proven to have a unique and complex immune dysfunction with immunosuppressive cell types, tumor-supportive immune cells and defective inflammatory cells (26).

Contrary to the expected hypothesis and data trend, our study demonstrated that pre-operative NLR and PLR at diagnosis exhibited a statistically significant inverse correlation with resection margins and lymph nodes status on the pathology pancreatic cancer specimen report. The majority of prior meta-analyses on the prognostic role of NLR and PLR for PDAC have shown a positive correlation of higher NLR and PLR with poor outcomes (10,16,27,28). It is worth noting that previous authors acknowledged the limitations of their meta-analyses and weakness due to intrinsic heterogeneity, including but not limited to small sample size, variability in cut off levels used, variation in demographic patient population, difference in interventions, large spectrum of clinical stage included, endpoint criteria, and retrospective nature of study (10,26). Most importantly there is a recognized publication bias due to inclusion of studies with positive results and possible exclusion of non-published negative results (29,30) Therefore, we urge caution when evaluating both (NLR and PLR) novel biomarkers from our retrospective review of resectable pancreatic adenocarcinoma patients in order to

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Table 3 Association analysis per the nature of outcome variables

Coding	Outcome	NLR (at Dx)	PLR (at Dx)
W, M, P[1]	Differentiation grade	0.8324	0.8029
pT1, T2, T3, T4[1]	Tumor (T)	0.8402	0.4060
pContinuous[2]	Tumor size (cm)	0.9630	0.7095
cN0, N1, N2[3]	Regional lymph nodes	0.0381*	0.0099*
pN0, N1, N2[3]	Regional lymph nodes	0.4637	0.9858
pCount[4]	# of + lymph nodes	0.1810	0.0360
Yes/No[3]	Lymphovascular invasion	0.9732	0.2447
Yes/No[3]	Perineural invasion	0.3165	0.1564
pIA, IB, IIA, IIB, III[1]	AJCC/TNM stage	0.7849	0.7470
R0, R1, R2[1]	Resection margins	0.0146*	0.0023*
Continuous[2]	Months to last contact	0.7632	0.5685
Yes/No[3]	CA19-9 <>37	0.8619	0.9384

*, statistically significant at P value less than 0.05. [1], ordinal logistic regression; [2], linear regression; [3], Kruskal-Wallis rank sum test; [4], Poisson regression; [5], logistic regression. W, well; M, moderate; P, poor; P, pathology; T, tumor; N, node; R, resection; CA 19-9, carbohydrate antigen 19-9; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Dx, diagnosis; AJCC/TNM, American Joint Committee on Cancer/Tumor, Node, Metastasis.

avoid potential controversy.

Our literature review showed three studies that evaluated NLR association with surgical outcomes and prognosis of upfront surgery for resectable PDAC patients concluded that higher NLR correlated with poor outcomes (31-33). Worth noticing, all patients included were from Asian populations [N: 138 Japanese (31), N: 219 Chinese (32), N: 81 Koreans (33)] differing from our mostly Caucasian patients from the United States. Our population appeared to be more symptomatic than comparison groups, i.e., 44% with jaundice versus none 85% of patients, respectively. Likewise, the populations differed on baseline CA19-9 level >39 U/mL with 61% versus 73%, in previous meta-analyses and our retrospective review, respectively. Furthermore, on other studies most patients included had earlier stage (< IIA 88%) and less node positive disease (LN+ 66%) than ours with predominantly > IIA 78% and LN+ 74%. Thus, we could expect a difference in results influenced by the patient population and cancer stage.

The major limitations of our study are a single center, retrospective review, small sample size with about 10 % of patients excluded because of lack of data. Although our study was not designed to corroborate AJCC/TNM prognostic factors with survival prognosis, we were able to provide further validation by upholding T3, LN+, and RM+ to worse outcomes. In conclusion, our study demonstrated that pre-operative NLR and PLR at diagnosis day are inversely associated with RM and LN status in patients undergoing resection for PDAC. Our findings indicate a potential utility for using NLR <3–6> and PLR <150–250> together (NLR/PLR >6/250 proceed to surgery and <3/150 continue neoadjuvant therapy) on clinical trials or standard of care to guide neoadjuvant therapy and should be investigated further in prospective studies.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ apc.2019.06.01). The authors have no conflicts of interest to declare.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The authors obtained prior to initiating research an Institutional Review Board approval Protocol Number: 1804508070 and further obtained a waiver of personal health information authorization [45 CFR 164.512(i)(2)(ii)]: as the use or disclosure of protected health information involves no more than minimal risk to the individuals and the research could not practicably be conducted without the waiver.

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