



RELEVANCE OF PREOPERATIVE INFLAMMATORY BIOMARKERS IN PATIENTS UNDERGOING PANCREATODUODENECTOMY

Surgery

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ABSTRACT

Background: A high level of inflammatory biomarker may predict a worse perioperative outcome and can be an indirect evidence of a bad tumour biology which may possibly help to change the treatment plan from an upfront surgery to neoadjuvant therapy. We aim to study the relationship between inflammatory biomarkers with postoperative outcome and histopathological features. **Methodology:** This is a retrospective observational study. Data of patients who underwent pancreaticoduodenectomy in our institution from 2015 to 2022 were taken for analysis from a prospectively maintained database. Whipple with distal pancreatectomy, evidence of active infection with TC > 12000, deep vein thrombosis, vascular or inflammatory disorder, previous history of malignancy, chemoradiotherapy and benign pathology were excluded. The preoperative NLR, PLR and dNLR were calculated and statistical significance was assessed with the pathological features and morbidity. ROC curves were plotted to get the cut-off values of the same. **Results:** 105 patients were taken up for pancreaticoduodenectomy of which 88 were taken for analysis after satisfying the exclusion criteria. A statistically significant relationship was noted between PLR, NLR and dNLR with Lymph node involvement (P value = 0.021, 0.005, and 0.008 respectively), dNLR and NLR with Perineural invasion (P value : 0.12 and 0.019) and lympho-vascular invasion (P value : 0.003 and 0.002). An increasing PLR showed a statistically significant increased risk of POPF (P value = 0.031). **Conclusion:** Preoperative Inflammatory biomarkers may help to predict the pathological features and clinical outcome in patients undergoing pancreaticoduodenectomy.

KEYWORDS

Inflammatory Biomarkers ; Pancreatico-duodenectomy ; Pathological outcome

INTRODUCTION

Periampullary carcinoma is a broad term that incorporates a diverse group of neoplasms with varying pathological and prognostic characteristics. They include distal bile duct tumors, carcinoma head of the pancreas, duodenal tumors, and ampullary tumors (1). Carcinoma head of the pancreas accounts to be the most common among the group and shows cases the worst prognosis. Pancreaticoduodenectomy with or without pylorus preservation is the treatment of choice for periampullary tumors. The postoperative morbidity following pancreaticoduodenectomy remains very high and previous studies have shown that pre-operative inflammatory biomarkers (PIB) have a relation with the same (2). An elevated preoperative inflammatory biomarker may also act as an indirect evidence of worse pathological and clinical stages which is not commendable in routine imaging. Neutrophil Lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) are two inflammatory biomarkers that can be obtained from routine workups of these patients and proving their clinical significance can alter the treatment plan in these groups of patients.

AIMS AND OBJECTIVES

- To assess the role of preoperative inflammatory biomarkers in predicting the postoperative pathological outcome
- To assess the relation between Preoperative inflammatory biomarkers and postoperative morbidity

METHODOLOGY

This is a retrospective observational study undertaken in the Department of surgical gastro-enterology, Medical College Trivandrum. Data of patients who underwent pancreaticoduodenectomy from 2015 to 2022 were collected from a prospectively stored computerized database and were used for analysis. Whipple

with distal pancreatectomy, patients with active infection with total count >11000 or with leukopenia < 4000, Chronic liver disease, Hematologic disease, vascular or inflammatory disorders, deep vein thrombosis, patients with a history of prior chemotherapy, radiotherapy and benign pathology were excluded.

Patient demographics including age, sex and comorbidities were gathered. CBC with differential counts including absolute neutrophil counts (ANC $\times 10^9/L$), absolute lymphocyte counts (ALC $\times 10^9/L$), and absolute platelet counts (APC $\times 10^9/L$) were collected at the time of admission for surgery. Preoperative CA 19.9 values were also collected. Intraoperative factors like surgical procedure (pancreaticoduodenectomy or pylorus-preserving pancreaticoduodenectomy), duration of the procedure, and intra operative transfusion details were also collected. Pancreas specific post-operative complications post-operative pancreatic fistula (POPF), delayed gastric emptying (DGE) and post-operative pancreatic hemorrhage (PPH) were assessed according to the ISGPS guidelines —(35). Surgical site infection was assessed by Southampton grading system. Overall morbidity was assessed using the Clavian Dindo grading (CD) with grades 3, 4 and 5 taken as significant post-operative morbidity (6). The final pathological stage of the tumor according to the TNM 8th edition staging system including the lymph node involvement (LNI), perineural invasion (PNI) and lymphovascular invasion (LVI) were also collected from the specimen report.

NLR and PLR were calculated by division of ANC and APC by ALC measured in peripheral complete blood count. Derived NLR (dNLR) is calculated by dividing the ANC by the value obtained from subtracting ANC from WBC count.

Statistical Analysis

Qualitative variables were reported as proportions. The differences among groups were calculated using chi square test. Continuous variables (PLR, NLR, dNLR) were reported as median and differences were tested with the Mann-Whitney's U test due to data distribution (non-parametric according to the Shapiro-Wilks test for Normality). Receiver operating characteristic (ROC) analysis was performed among independent variables to define the cut-off point for NLR, dNLR, PLR, values to predict postoperative complications and pathological T stage, Lymph node involvement and PNI / LVI. Data was analyzed using SPSS 27 software.

RESULTS

Out of 105 patients who had undergone pancreaticoduodenectomy during the study period, 88 patients were taken for analysis after fulfilling the inclusion and exclusion criteria. 17 patients were excluded among which 3 patients underwent concomitant distal pancreatectomy, 6 patients had active infection, 2 patients had previous malignancy history, 3 patients received neo adjuvant therapy, and 3 patients had benign pathology in the final histopathology report.

The patients belonged to the age group from 32-77 years with a mean age of 56. Males (52%) had a slight predominance compared to the female population. Among the patients taken up for surgery median values of PLR, NLR and dNLR were 121, 2 and 1.7 respectively. 20 out of 88 patients had positive lymph nodes, 23 had PNI and 24 had LVI. 46 patients were of T1-T2 stage while 42 patients were T3-T4 stage.

Table 1 Demographic Data

Age	56Y(32-77)
Gender distribution	Male 46(52%) Female 42(46%)
PLR	121(median), 69.8(IQR)
NLR	2(median), 2(IQR)
dNLR	1.7(median), 1(IQR)
LNI	20/88(22.75%)
PNI	23/88(26%)
LVI	24/88(27.3%)
T Stage	T1 - T2 46 (52%) T3 - T4 42(47%)

Table 2 Pathological Diagnosis

Ampullary carcinoma	23
Duodenal carcinoma	20
Carcinoma head of pancreas	17
Distal cholangiocarcinoma	12
Neuroendocrine tumor	11
IPMN	5

IPMN-Intraductal papillary mucinous neoplasm

Table 3 Statistical Significance Of PIB With Post Operative Pathological Features

	PLR	NLR	dNLR
LVI	NS	P=0.003	P=0.002
PNI	NS	P=0.012	P=0.019
LNI	P=0.021	P=0.005	P=0.008
T stage	NS	NS	NS

LVI-Lymphovascular invasion: PNI-Perineural invasion: LNI-Lymph node involvement

Table 4 Statistical Significance Of PIB With Post Operative Complications

	PLR	NLR	dNLR
POPF	.013	NS	NS
PPH	NS	P=0.041	NS
DGE	NS	NS	NS

Among the patients, 23 patients had ampullary carcinoma, 20 duodenal carcinoma, 17 carcinoma head of pancreas, 12 distal cholangiocarcinoma, 11 NET and 5 IPMN. Clinically significant grade B/C POPF were seen in 17 and 2 patients respectively. DGE grade A, B and C were seen in 27, 15 and 2 patients respectively. PPH was seen in 6 patients. Majority of the patients had CD grade 1 and 2. Higher CD grade with more than 3 was seen in 14 patients in which 3 had post operative mortality. 36 patients had surgical site infection.

PLR (P=0.021), NLR (P=0.005) and dNLR (P=0.008) showed a

statistically significant relation with LNI. ROC curves were plotted with PLR, NLR and dNLR with LNI and cut offs obtained were PLR - 125 (sensitivity - 75%, Specificity - 58%, AUC - 0.67) (Fig 1a), NLR - 2.95 (sensitivity - 60%, Specificity - 79.4%, AUC - 0.70) (fig 1b), dNLR - 1.95 (sensitivity - 67%, Specificity - 71%, AUC - 0.710).

NLR and dNLR showed a statistically significant relation with PNI and LVI. ROC curves were also plotted for the same and cut offs obtained were NLR (PNI) (fig.2a) - 2.1 (sensitivity - 56%, Specificity - 73%, AUC - 0.72), NLR (LVI) (fig.2b) - 2.1 (sensitivity - 62%, Specificity - 76%, AUC - 0.69) and dNLR (PNI) (fig.3a) - 1.47 (sensitivity - 82%, Specificity - 47%, AUC - 0.74), dNLR (LVI) (fig.3b) - 1.47 (sensitivity - 87%, Specificity - 50%, AUC - 0.71). PLR, NLR and dNLR didn't show any statistically significant relation with T stage.

When the relation between POPF and PLR was assessed, it was found that patients with no POPF had a median PLR value of 104 while grade B and C POPF had values above 140 (P value = 0.013). NLR was also shown to have a statistically significant relation with PPH (P value = 0.041) and ROC curve showed a cutoff value 2.1 (AUC - 0.043).

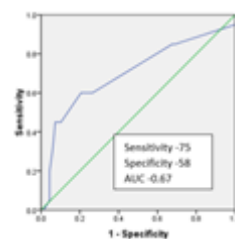


Fig 1 (a) PLR with LNI

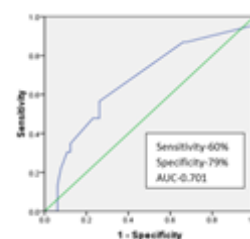


Fig 1 (b) NLR with LNI

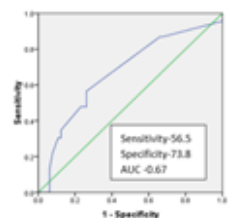


Fig 2 (a) NLR with PNI

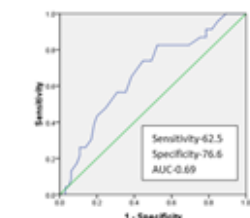


Fig 2 (b) NLR with LVI

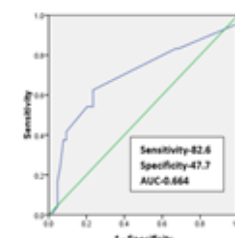


Fig 3 (a) dNLR with PNI

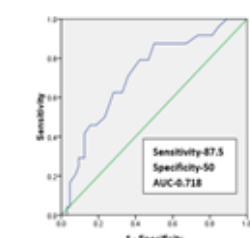


Fig 3 (b) dNLR with LVI

DISCUSSION

Inflammation is thought to play a major role in development of multiple cancer types. Inflammation induced carcinogenesis can be of different processes like DNA adduct formation, increased angiogenesis and altered anti apoptotic signalling (7). Inflammation can be assessed by various biochemical markers like cytokines (IL 6, IL11), acute phase proteins (CRP), immune related factors (NLR/PLR), reactive oxygen and nitrogen species, prostaglandins etc. Recently PLR and NLR were studied regarding its relation with various cancer types and possible involvement in the progression as well as prognosis of the disease. The value of PLR and NLR are well proven in the prognosis of colorectal cancer (8), gastric cancer (9), cholangiocarcinoma (10) and esophageal malignancies (11). Easy availability and low cost have made them very popular among the inflammatory biomarkers.

Pancreaticoduodenectomy is a major procedure which has a high morbidity (12), and the final result of the whole surgery will depend on R0 resection with N0 involvement. The prediction of the same can alter the management from an upfront surgery to neoadjuvant therapy in potentially resectable periampullary lesions. Neo adjuvant therapy is a proven and internationally followed modality in rectal cancers (13) and

upper GI malignancies(14) in potentially resectable lesions, while in case of periampullary lesions it still not advocated . Multiple trials are going on at the present for a neo adjuvant protocol in the management of carcinoma pancreas with in a potentially resectable lesion(15).

A study done by Nebi Serkan Demirci et al. on assessment of prognostic role of NLR and PLR in operable cases of ampullary carcinoma have found that a high NLR > 3 had a lower disease free survival (DFS) and overall survival OS(16). In our study, higher PLR, NLR and dNLR is shown to be statistically significant relation with LNI. LNI is one of the most important prognostic factors in periampullary lesion. The ROC curve plotted showed a cut off value of 2.95 for NLR in predicting LNI similar to Nebi Serkan Demirci et al. study. NLR and dNLR showed statistically significant association with PNI and LVI. Both PNI and LVI are bad histopathological factors that can adversely affect the prognosis. All these features may not be well assessed in a preoperative routine imaging. Previous studies in esophagus and other malignancies have shown that neoadjuvant therapy can downstage the disease and thereby improve the DFS and OS. A high CA 19.9 level above 500 is considered as a biochemical indicator of borderline resectable cancer and thus advised for neoadjuvant therapy even though tumour is resectable(17). Similarly, PIB can act as an indirect indicator of a bad pathological disease and hence thereby giving an option for neoadjuvant therapy. A study by Hasegawa et al. have showed in pancreatic cancer patients, NLR>2.2 responded better with neoadjuvant chemoradiotherapy(18).

Another important aspect of pancreatoduodenectomy is the post operative morbidity. POPF is an important complication which contributes to this and it depends on the independent factors like soft pancreas, amount of blood loss during the procedure, the histological diagnosis and a small pancreatic duct diameter(19). But apart from this, an inflammatory milieu may increase the chance for the post operative events . Hence identification of such patients may benefit the physicians to plan the post operative management protocol. A study by Coppola et al. have showed that the PIB can play a role in predicting the postoperative morbidity and thereby change the post operative protocol from an ERAS to a more cautious and slower approach(2). In our study we found a significant association between PLR and POPF. The median value of patients who had POPF where above 140. In the study by Coppola et al NLR was associated with PPH with a cut off value of 1.65. In our observation we found a significant association between NLR and PPH with a P value of 0.041 and a cut off value of 2.1.

CONCLUSION

Preoperative inflammatory biomarkers like NLR, PLR and dNLR are an easily available and cost effective investigations that can aid in the preoperative preparation of the patient. Our study has shown their implication over the post operative pathological outcome as well as the post operative complications. Wider and multicentre study are required for the further validation of the same which may help in identifying patients who would benefit from neoadjuvant therapy.

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