Published in final edited form as:

Pancreas. 2019 July ; 48(6): 832–836. doi:10.1097/MPA.0000000000001342.

Neutrophil-to-lymphocyte ratio as a predictor of invasive carcinoma in patients with intraductal papillary mucinous neoplasms of the pancreas

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Abstract

Background: Intraductal papillary mucinous neoplasms (IPMN) are cystic precursor lesions of pancreatic adenocarcinoma. Preoperative determination of the grade of dysplasia is difficult, yet necessary for optimal management. Previous data have suggested that serum Neutrophil-to-Lymphocyte Ratio (NLR) has an ability to predict invasive disease in patients with IPMN.

Methods: A prospectively maintained database was queried for consecutive patients who underwent resection of IPMN between 2000 and 2017. Exclusion criteria included recent diagnosis or treatment of non-pancreas associated cancer, immunosuppression, use of immunomodulatory medications, and infection or jaundice within one month of operation. All patients had a complete blood count (CBC) with differential within 30 days of operation for calculation of NLR.

Results: Within the study period, 446 patients underwent resection for IPMN and 348 patients (78%) met inclusion criteria. Low-grade dysplasia was present in 60 patients (17%), 137 patients (39%) had intermediate-grade dysplasia, 76 (22%) had high-grade dysplasia and 75 (22%) had invasive carcinoma. NLR was associated with invasive carcinoma as compared to non-invasive disease (3.00 vs 2.68, $p=0.039$). There was no difference in NLR between patients with high-risk (invasive and high-grade) lesions and low-risk (low-grade and intermediate-grade) lesions (2.80 vs 2.71, $p>0.95$). There was also no difference between patients with high-grade dysplasia and those with less than high-grade dysplasia (2.80 vs 2.43, $p=0.10$).

Conclusion: NLR was significantly higher in patients with IPMN-associated invasive carcinoma as compared to patients with non-invasive disease, however NLR was not helpful in differentiating between high-grade and low-grade lesions.

Introduction

Intraductal papillary mucinous neoplasms (IPMN) are cystic precursor lesions of pancreatic adenocarcinoma (PDAC) that are now being detected at an increased frequency. IPMN contain a spectrum of low-, intermediate- and high-grade dysplasia that can progress to invasive carcinoma. Pancreatectomy in patients with IPMN may be curative as resection can prevent the identified lesion from progressing to invasive cancer, yet pancreatic resection is associated with a high morbidity. Operative intervention is usually reserved for patients presumed to have high-grade dysplasia or invasive carcinoma on preoperative imaging, whereas patients with low- and intermediate-grade dysplasia are generally monitored with radiographic surveillance.

The Fukuoka Consensus Guidelines outlined clinical and radiographic features that are associated with an increased risk of high-grade dysplasia or invasive carcinoma in pancreatic cystic neoplasms, and it is suggested that these may help in identifying patients who should undergo resection.^{1,2} However, it has been shown that these guidelines have an overall sensitivity and specificity of 28% and 96%, respectively.³ Therefore, there exists a need for improved preoperative prediction of high-grade dysplasia and invasive carcinoma in IPMN to better determine which patients may benefit from pancreatic resection.

Serum Neutrophil-to-Lymphocyte Ratio (NLR) is a readily available marker that reflects systemic inflammation. The link between a systemic inflammatory response and cancer is well established,⁴ and NLR has been shown to have prognostic significance in multiple malignancies.⁵⁻⁷ In PDAC, a high preoperative NLR has been shown to be associated with worse disease-free and overall survival in patients who have undergone resection.⁸⁻¹⁰ Additionally, in the locally advanced and metastatic setting, elevated NLR has been associated with worse progression-free and overall survival.¹¹⁻¹³ Studies have investigated the use of NLR as a biomarker in pancreatic cystic neoplasms, and previous data have suggested that NLR is predictive of invasive disease in patients with mucinous pancreatic cysts, including IPMN.¹⁴⁻¹⁷

In this study, we sought to determine whether NLR was predictive of grade of dysplasia and invasive carcinoma in our cohort of patients who have undergone resection for IPMN. Additionally, we investigated whether NLR can preoperatively predict high-risk versus low-risk lesions, and therefore, possibly help identify which patients should undergo surgical resection. We also explored the use of NLR to predict pathologic variables in IPMN-associated invasive carcinoma.

Methods

Patient Cohort

A prospectively maintained database was queried for patients who underwent resection of IPMN between January 2000 and January 2017 at Memorial Sloan Kettering Cancer Center (MSKCC). All patients included in the analysis had IPMN on final pathology and had a complete blood count (CBC) with differential within 30 days of operation. Exclusion criteria included diagnosis or treatment of non-pancreas associated cancer (excluding nonmelanoma skin cancers) within six months of operation for IPMN, documented infection or jaundice (bilirubin ≥ 1.0) within one month of surgery, immunosuppression or use of immunomodulatory medications. Approval for this study was obtained from MSKCC's Institutional Review Board.

Demographic, clinical, laboratory, radiologic and pathologic factors were collected for all patients in the cohort from the database and the electronic medical record. Preoperative imaging was reviewed and cyst characteristics including main pancreatic duct (MPD) size, cyst size and location were also recorded. IPMN were classified as main- or mixed-duct IPMN (MD-IPMN) and branch-duct IPMN (BD-IPMN) based on MPD dilatation. Patients with MPD ≤ 0.5 cm were designated to have BD-IPMN, while patients with MPD >0.5 cm were considered to have MD-IPMN. Symptoms were defined as any abdominal pain or upper gastrointestinal disturbance, whereas pancreatitis and weight loss were documented separately. Preoperative diagnostic procedures within 30 days of operation were recorded, and included endoscopic ultrasound (EUS) $\pm$ fine needle aspiration (FNA), endoscopic retrograde cholangiopancreatography (ERCP), percutaneous biopsy or esophagogastroduodenoscopy (EGD). All pathologic data had been previously reviewed by a GI pathologist, and the highest grade of dysplasia or carcinoma was recorded. Patients with low- or intermediate-grade dysplasia on final pathology were classified as having "low-risk" lesions, whereas patients with high-grade dysplasia or invasive carcinoma were considered to have "high-risk" lesions. Data recorded for patients with IPMN-associated invasive carcinoma included tumor size, carcinoma subtype, nodal status, and lymphovascular and perineural invasion. Microinvasion was defined as an invasive component less than 1cm.

Neutrophil-to-Lymphocyte Ratio

Laboratory data was retrospectively reviewed from the electronic medical record for preoperative CBC with differential blood cell count. If a patient had multiple CBC in the 30-day preoperative period, then the CBC immediately prior to the date of operation was used. NLR was calculated by dividing absolute neutrophil count ($K/\mu L$) by absolute lymphocyte count ($K/\mu L$).

Statistical analysis

Continuous data were expressed as median and interquartile range (IQR) and categorical variables were expressed as frequency and percentage. Continuous variables were analyzed using Wilcoxon rank sum or Kruskal Wallis tests, whereas categorical variables were

analyzed using Fisher's exact test. SAS version 9.4 SAS institute Inc., Cary, NC was used for all analysis. All tests were two-sided and $p < 0.05$ was considered significant.

Results

Patient cohort

Within the study period, 446 patients underwent resection for IPMN and 348 patients (78%) met the inclusion criteria. There were 98 patients excluded from analysis; 47 had a diagnosis or treatment of a non-pancreas associated cancer within six months of operation, 20 patients were either immunosuppressed or taking immunomodulatory medications, 19 patients had jaundice, 11 had a documented infection or pancreatitis within one month of operation, and one patient did not have a CBC within 30 days of surgery (Figure 1). MD-IPMN was present in 166 patients (48%) and 182 patients (52%) had BD-IPMN. Low-grade dysplasia was present in 60 patients (17%), 137 patients (39%) had intermediate-grade dysplasia, 76 (22%) had high-grade dysplasia and 75 (22%) had invasive carcinoma. Combined, 197 (57%) patients had low-risk disease and 151 (43%) patients had high-risk disease. Baseline demographic and clinical characteristics of the cohort, as well as a comparison between patients with invasive carcinoma and dysplasia, are shown in Table 1.

Invasive carcinoma was identified in 75 patients. Colloid carcinoma was present in 37 of these patients (49%), 34 (45%) had tubular adenocarcinoma, and 4 (5%) patients had a mixed subtype. Microinvasion was present in 18 patients (24%) compared to 57 (76%) who had an invasive component ≥ 1 cm. The majority of patients with invasive carcinoma had N0 disease (69%) and did not have lymphovascular or perineural invasion on final pathology (Table 2).

NLR as a predictive marker in IPMN

The median time between preoperative CBC and operation was 8 days (IQR 5–13). The distribution of NLR values based on grade of dysplasia are shown in Figure 2. The median NLR in patients with low-grade dysplasia was 2.60 (IQR 2.03–3.59), 2.86 (IQR 2.23–3.53) in those with intermediate-grade dysplasia, 2.43 (IQR 1.93–3.39) in those with high-grade dysplasia and 3.00 (IQR 2.26–4.13) in patients with invasive carcinoma. Higher NLR was associated with invasive IPMN as compared to non-invasive IPMN (3.00 vs 2.68, $p = 0.039$) (Table 3). Comparison between those with high-grade dysplasia and those with less than high-grade dysplasia (low and intermediate-grade dysplasia) showed no difference (2.80 vs 2.43, $p = 0.10$). Additionally, there was no significant difference in NLR in patients who had high-risk (high-grade dysplasia and invasive IPMN) as compared to low-risk (low and intermediate-grade dysplasia) lesions (2.80 vs 2.71, $p > 0.95$).

There were 59 (17%) patients in the cohort who underwent a preoperative procedure within 30 days of their operation. The majority of these patients (48/59, 81%) had a diagnostic EUS +/- FNA. The median NLR between patients who had undergone a preoperative procedure was not significantly different from those patients who did not (2.69 vs 2.78, $p = 0.514$).

In the subset of patients with IPMN-associated invasive carcinoma, NLR was not predictive of tubular versus colloid subtype of carcinoma (2.97 vs 3.19, $p > 0.95$). Furthermore, NLR

was not predictive of pathologic variables including nodal status, microinvasion, lymphovascular invasion or perineural invasion (Table 2).

Discussion

IPMN are premalignant cystic lesions of the pancreas that contain a spectrum of dysplasia. The Fukuoka guidelines stratify IPMN as high-risk, worrisome or low-risk based on radiographic characteristics to suggest which patients should be recommended for surgical resection versus surveillance.^{1,2} However, there is a critical need for a more discriminatory test to predict preoperatively which patients' cysts harbor high-grade dysplasia and invasive carcinoma. There exists a need for novel biomarkers, which combined with clinical and radiographic features, could improve stratification of patients for treatment. NLR is measure of systemic inflammation that is routinely available preoperatively and has been associated with poor outcomes in PDAC. Therefore, we sought to determine if NLR is predictive of high-risk disease in IPMN in our patient cohort.

Our study found that patients with IPMN-associated invasive carcinoma have a significantly higher NLR as compared to those with non-invasive disease. This is consistent with previously published data by Gemenetzis et al, which reported that $NLR > 4$ was predictive of invasive carcinoma as compared to dysplasia in 272 patients who underwent resection for IPMN.¹⁵ Similarly, Arima et al. showed that NLR was significantly higher in patients with IPMN-carcinoma as compared to non-invasive IPMN and healthy controls.¹⁴ Two additional studies demonstrated that NLR was predictive of invasive carcinoma on univariate analysis in all mucinous pancreatic cystic neoplasms.^{16,17}

Because NLR was elevated in patients with invasive disease, we further evaluated NLR for its association with pathologic factors that separate the more indolent colloid carcinoma from the more aggressive tubular subtype. Our results did not show that NLR was able to differentiate between the colloid and tubular subtypes, nor was it associated with any other pathologic variables. Therefore, in IPMN-associated invasive carcinoma, we do not feel that NLR is helpful in preoperatively predicting the presence of pathologic features associated with a poor prognosis.

Consistent with previous data,¹⁵ we demonstrated that NLR did not differentiate between patients with high-grade dysplasia and those with less than high-grade dysplasia or between high-risk versus low-risk lesions. Ideally, all patients with both high-grade dysplasia and invasive carcinoma would be identified preoperatively and recommended for resection. Therefore, as a biomarker in IPMN, NLR appears to be of limited clinical value and should not be used independently to select patients for surgical resection.

One of the strengths of this study was the strict exclusion criteria by which we selected patients. We excluded all patients known to have a cause of inflammation that could confound an elevated NLR in the setting of a neoplastic process, including jaundice and pancreatitis. Although other studies have obtained the same results while including patients with jaundice, our results confirm that an elevated NLR is not solely secondary to inflammation from another cause. Furthermore, the presence of jaundice is highly predictive

of invasive disease in IPMN, and such patients would be recommended for a resection independently of their NLR. Patients who had undergone a diagnostic procedure within 30 days of surgery were included in this study. Although there is a theoretical immune response associated with preoperative instrumentation, there was no difference in NLR between the two groups and therefore, we do not believe the inclusion of these patients had an influence on the results of this study.

Limitations of this study include its retrospective nature and the fact that all patients included had undergone resection. Additionally, the subgroups analyzed were small in size, and thus we recognized the power limitations of the comparisons between these groups. Furthermore, NLR has been shown to be elevated with age¹⁸ and other comorbidities such as severe CAD¹⁹, and these variables were not controlled for in this study. We did not look to see if using NLR combined with other cyst features increased the sensitivity and specificity of existing models, as we did not find NLR to independently differentiate between high and low-risk lesions.

In conclusion, NLR was significantly higher in patients with IPMN-associated invasive carcinoma as compared to those with non-invasive disease in our cohort. NLR was not helpful in preoperative identification of patients with high-grade dysplasia, or in differentiating high-risk versus low-risk lesions. Therefore, we believe at this time, that this marker alone is of limited value in the clinical management of patients with IPMN. Future studies could include evaluation of NLR in patients undergoing radiographic surveillance for IPMN to determine if a change in NLR is reflective of radiographic change, and hence, possible malignant transformation. Furthermore, NLR could be combined with other biomarkers or radiographic features for improved preoperative prediction of grade of dysplasia in IPMN.

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Synopsis

Neutrophil-to-lymphocyte ratio (NLR) is predictive of invasive carcinoma as compared to dysplasia in pancreatic intraductal papillary mucinous neoplasms (IPMN), but does not differentiate between between grades of dysplasia or high- versus low-risk lesions.

Figure 1.
Flow chart of patient cohort included in study.

Figure 2.

Box plot of NLR values by grade of dysplasia. The components are as follows: diamond = mean, horizontal bar = median, upper bar of box = 75th percentile, lower bar of box = 25th percentile, the bottom bar and top bar represent the minimum and maximum values that are not outliers, respectively; the small circles represent outliers.

Table 1.

Demographic and clinical characteristics of all patients as well as those with dysplasia and invasive carcinoma.

	All patients (n=348)	No Invasion (n=273)	Invasion (n=75)	p-value
Age, median (IQR)	68.0 (60.0–75.0)	68.0 (60.0–75.0)	71.0 (59.0–77.0)	0.291
Gender, n (%)				
Male	175 (50)	131 (48)	44 (59)	0.118
Female	173 (50)	142 (52)	31 (41)	
BMI, median (IQR)	26.6 (23.6–30.0)	26.8 (23.8–30.4)	26.1 (23.3–29.2)	0.119
Symptoms, n (%)	190 (55)	136 (50)	54 (72)	<0.001
Weight loss, n (%)	76 (22)	37 (14)	39 (52)	<0.001
Diabetes, n (%)	81 (23)	53 (19)	28 (37)	0.002
Pancreatitis, n (%)	57 (16)	40 (15)	17 (23)	0.113
Preoperative procedure, n (%)	59 (17)	34 (13)	25 (33)	<0.001
Radiologic Duct Type, n (%)				
Main/mixed	166 (48)	107 (39)	59 (79)	<0.001
Branch	182 (52)	166 (61)	16 (21)	
Radiologic Cyst Size, median (IQR)	3.0 (2.1–4.0)	2.9 (2.1–3.7)	4.0 (2.5–5.6)	<0.001
Cyst Location, n (%)				
Head	206 (59)	155 (57)	51 (68)	0.062
Body	87 (25)	74 (27)	13 (17)	
Tail	49 (14)	41 (15)	8 (11)	
No discrete mass	6 (2)	3 (1)	3 (4)	
Operation, n (%)				
Total pancreatectomy	12 (3)	6 (2)	6 (8)	0.002
Pancreaticoduodenectomy	208 (60)	156 (57)	52 (69)	
Distal pancreatectomy	102 (29)	85 (31)	17 (23)	
Central pancreatectomy	18 (5)	18 (7)	0 (0)	
Enucleation	8 (2)	8 (3)	0 (0)	

Table 2.

NLR in patients with IPMN-associated invasive carcinoma.

	Number (%)	NLR, median (IQR)	p-value
Carcinoma Subtype			
Tubular	34 (45)	2.97 (2.36–4.47)	0.950
Colloid	37 (49)	3.19 (2.31–4.13)	
Lymph Node Status			
N0	52 (69)	3.27 (2.36–4.13)	0.343
N1	23 (31)	2.82 (2.19–4.40)	
Lymphovascular Invasion			
Yes	16 (21)	2.97 (2.47–4.51)	0.651
No	59 (79)	3.07 (2.25–4.13)	
Perineural Invasion			
Yes	23 (31)	3.14 (2.19–4.40)	0.558
No	52 (69)	2.93 (2.29–3.94)	
Microinvasion			
Yes	18 (24)	2.93 (2.26–4.13)	0.738
No	57 (76)	3.07 (2.31–4.13)	

Table 3.

NLR in patients with grades of dysplasia and invasive carcinoma.

	All grades of dysplasia (n=273)			Carcinoma (n=75)	p-value
NLR, median (IQR)	2.68 (2.08–3.55)			3.00 (2.26–4.13)	0.039
	Low-grade Dysplasia (n=60)	Intermediate-grade Dysplasia (n=137)	High-grade Dysplasia (n=76)	Invasive Carcinoma (n=75)	p-value
NLR, median (IQR)	2.60 (2.03–3.59)	2.86 (2.23–3.53)	2.43 (1.93–3.39)	3.00 (2.26–4.13)	0.068
	Low-grade Dysplasia (n=60)	Intermediate-grade Dysplasia (n=137)	High-grade Dysplasia (n=76)		p-value
NLR, median (IQR)	2.60 (2.03–3.59)	2.86 (2.23–3.53)	2.43 (1.93–3.39)		0.225
	Low- and Intermediate-grade Dysplasia (n=197)		High-grade Dysplasia (n=76)		p-value
NLR, median (IQR)	2.80 (2.17–3.56)		2.43 (1.93–3.39)		0.100
	Low Risk (n=197)		High Risk (n=151)		p-value
NLR, median (IQR)	2.80 (2.17–3.56)		2.71 (2.07–3.82)		>0.95