ORIGINAL ARTICLE

The diagnostic and prognostic values of inflammatory markers in intraductal papillary mucinous neoplasm

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Abstract

Background: Intraductal papillary mucinous neoplasm (IPMN) is an broad-spectrum disease from benign to malignant. Inflammatory markers are known as prognostic predictors in various diseases. The purpose of this study was to determine the predictive value of inflammatory markers for prognosis in IPMN.

Methods: From April 1995 to December 2016, patients who underwent pancreatectomy with pathologically confirmed IPMN at four tertiary centers were enrolled. Patients with a history of pancreatitis or cholangitis, and other malignancies were excluded. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and advanced lung cancer inflammation index (ALI) were calculated.

Results: Of all, ninety-eight patients (26.8%) were diagnosed as invasive IPMN. The NLR and PLR were significantly elevated in invasive IPMN than in non-invasive disease (2.0 vs 1.8, $p = 0.004$; 117.1 vs 107.4, $p = 0.009$, respectively). ALI was significantly higher in non-invasive IPMN than in invasive disease (58.1 vs 45.9, $p < 0.001$). In multivariate analysis, only NLR showed significant association among the inflammatory markers studied ($p = 0.044$). In invasive IPMN, the five-year recurrence-free survival rate for NLR less than 3.5 was superior to the rest (59.1 vs 42.2, $p = 0.023$).

Conclusion: NLR may help to rightly select IPMN patients who will require surgery and may serve as a useful prognostic factor.

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Introduction

Inflammatory markers, which reflect immune status, are known as prognostic predictors in various diseases.[1–3] Some of the inflammatory markers that have diagnostic and/or prognostic value include neutrophil-lymphocyte ratio (NLR),[4] platelet-lymphocyte ratio (PLR),[5] Glasgow prognostic score (GPS),[6] combination of C-reactive protein (CRP) and albumin, and advanced lung cancer inflammation index (ALI).[7] ALI was first introduced as a prognostic factor in lung cancer, and then it was also found to be useful in prognosticating esophageal cancer. It is calculated with body mass index (BMI), albumin, and NLR, and it represents inflammatory and nutritional status. CRP assay is not an essential laboratory test for pre-operative evaluation, but white blood cell (WBC) count, neutrophil count, platelet count, and albumin are routinely checked during pre-operative evaluation of patients. Prognostic parameters that may be predicted by inflammatory markers include long-term survival.

Intraductal papillary mucinous neoplasm (IPMN) has a wide disease spectrum, from benign to malignant, and it is a precursor

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lesion for pancreatic cancer.[8] Therefore, it is important to decide whether a patient with IPMN will benefit from careful, regular surveillance or from surgical resection. High-risk stigmata and worrisome features, as defined by international consensus guidelines, are the most common references in the treatment of IPMN.[9] There are also other guidelines that suggest treatment modalities for IPMN.[10,11] Several nomograms that are made up of easily accessible information have also been suggested to help in the establishment of treatment plans.[12,13] However, the sensitivity of these guidelines for detecting early invasive carcinoma in IPMN lesions is limited, and several imaging modalities are needed. Therefore, there is a critical need for predictive markers that can assist in patient selection for surgical resection of IPMNs.

IPMN is accompanied by inflammation. Obstruction of the pancreatic duct by mucin plug results in chronic pancreatitis. Accordingly, there have been several reports about the relationship between IPMN and inflammatory markers.[14,15]

Therefore, the purpose of this study was to identify the predictive value of inflammatory markers for invasiveness in IPMN and to find out the relationship between inflammatory markers and long-term outcomes.

Methods

From 1995 to 2016, patients with pathologically confirmed IPMN after surgery were enrolled from the following four tertiary referral hospitals in South Korea: Dongguk University Ilsan Hospital (DUIH), Boramae Medical Center (BMC), Samsung Medical Center (SMC) and Ilsan Paik Hospital (IPH). Among these patients, those with a history of pancreatitis or cholangitis and those with histories of other cancers were excluded, as these conditions may affect inflammation. This study was approved by the institutional review board of each participating center (DUIH: 2018-01-002, BMC: 2018-42-051, SMC: 2017-07-016-005 and IPH: 2017-12-008).

Laboratory data, including tumor markers, were used for pre-operative evaluation, and based on these data, inflammatory markers were calculated. NLR was calculated as the total count of neutrophils divided by total count of lymphocytes, and PLR as total count of platelets divided by total count of lymphocytes. ALI was calculated as follows: BMI * albumin/NLR.[7] In the case of endoscopic ultrasonography (EUS) biopsy or endoscopic procedure, the pre-procedure data was used and the rest of the data was used immediately before the procedure.

The type of IPMN and presence of solid portion in the tumor were defined by pre-operative imaging, using computed tomography (CT), magnetic resonance imaging (MRI) or endoscopic EUS. Because the study registration period was long and the quality of the imaging studies were different among the four hospitals, an enhancing mural nodule was not described as such but instead defined as a solid portion. IPMN was classified as non-invasive IPMN (from low grade dysplasia to high grade dysplasia) or invasive IPMN. To find out risk factors for invasiveness of IPMN, the patients were grouped into non-invasive and invasive IPMN groups.

Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Results were presented as median and interquartile ranges. The receiver operating characteristic (ROC) curve was used to find the inflammatory marker cut off value predicting invasive IPMN, and it was compared with the cut off value that made the false positive rate the lowest.

Nominal variables were compared using chi-squared test and t-test, while continuous variables were compared with Wilcoxon signed rank test. Logistic regression analysis was performed to determine risk factors for invasiveness, and survival analysis was performed with Kaplan–Meier analysis and log rank test. P values < 0.05 were considered statistically significant.

Results

Demographics

The total number of patients was 468 over the study period. Among these patients, 2 did not have lymphocyte count data, and 103 patients with history of pancreatitis, cholangitis or other malignancy, and no data of carbohydrate antigen 19–9 (CA 19–9) were excluded. Finally, 365 patents were analyzed in this study (Fig. 1). Median age of the patients was 63 years, and 66.3% of them were males. Median values of BMI, bilirubin, and CA 19–9 were 23.8, 0.7, and 12.7 respectively. Median values of NLR, PLR, and ALI were 1.8, 109.5, and 56.3 respectively. The most common type of IPMN was branch duct type, which was present in 50.7% of patients, while 24.4% had solid tumor portions. Median size of lesions was 3.1 cm. Final pathological diagnosis of invasive IPMN was made in 98 (26.8%) patients (Table 1).

Risk factors for invasive IPMN

In the invasive IPMN group, the levels of bilirubin and CA 19–9 were significantly higher than in the non-invasive IPMN group (0.9 vs 0.7, $p = 0.031$; 15.2 vs 12.5, $p < 0.001$, respectively). Main duct type IPMN and solid portions were significantly more common in the invasive IPMN group (31.6% vs 16.9%,

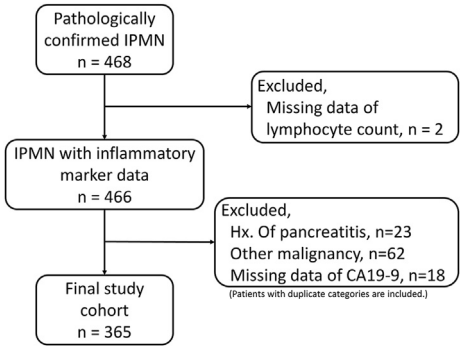

Figure 1 Study cohort selection flowchart

Table 1 Demographics

Variables	n = 365
Age (years, median, IQR)	63 (57–69)
Sex (male, %)	242 (66.3)
BMI (kg/m^2, median, IQR)	23.8 (22.1–25.5)
Bilirubin (mg/dl)	0.7 (0.5–1.2)
CA19-9 (U/ml)	12.7 (6.4–24.7)
NLR	1.8 (1.3–2.5)
PLR	109.5 (85.7–152.4)
ALI	56.3 (36.8–80.6)
Ductal type (%)	
Branch	185 (50.7)
Main	76 (20.8)
Mixed	104 (28.5)
Presence of solid portion (%)	89 (24.4)
Cyst size (cm)	3.1 (2.4–4.2)
Pancreatic duct size (mm)	4.7 (3.0–7.0)
Method of operation (%)	
Open	330 (90.4)
Laparoscopic	35 (9.6)
Type of operation (%)	
(PP)PD	120 (32.9)
(SP)DP	120 (32.9)
Central	13 (3.6)
Others	48 (31.1)
Histologic grade (%)	
Low	120 (32.9)
Intermediate	119 (32.6)
High	28 (7.7)
Invasive	98 (26.8)

IQR, interquartile range; BMI, body mass index; CA19-9, carbohydrate antigen 19–9; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; ALI, advanced lung cancer inflammation index; (PP)PD (pylorus preserving) pancreaticoduodenectomy; (SP)DP (spleen preserving) distal pancreatectomy.

$p < 0.001$; 49.0% vs 15.4%, $p < 0.001$, respectively). Difference in BMI of patients in the two groups and difference in the size of IPMN (as measured with pre-operative imaging) were only marginal. NLR and PLR were significantly elevated in patients with invasive IPMN (2.0 vs 1.8, $p = 0.004$; 117.1 vs 107.4, $p = 0.009$ respectively). ALI was significantly higher in patients with non-invasive IPMN (58.1 vs 45.9, $p < 0.001$) (Table 2). In multivariate analysis, the levels of bilirubin and CA 19–9, and presence of solid portion were risk factors for invasive IPMN. In multivariate analysis of inflammatory markers, only NLR showed significant ($p = 0.044$) association with invasiveness. ALI was calculated with BMI and NLR; therefore, multivariate analysis of ALI was performed separately, and it was not found to

Table 2 Risk factors of invasiveness in IPMN

Variables (n = 365)	Invasive (n = 98)	Non-invasive (n = 267)	*p*-value
Age (years)	64 (58–70)	64 (57–70)	0.622
Sex, male (%)	63 (64.3%)	179 (67.0%)	0.628
BMI (kg/m^2)	23.7 (21.5–25.1)	24.0 (22.2–25.5)	0.056
Bilirubin (mg/dl)	0.9 (0.5–3.1)	0.7 (0.5–1.0)	0.031
CA 19–9 (U/ml)	15.2 (7.8–150.0)	12.5 (6.3–19.1)	<0.001
NLR	2.0 (1.4–2.9)	1.8 (1.2–2.3)	0.004
PLR	117.1 (97.3–164.9)	107.4 (81.0–148.8)	0.009
ALI	45.9 (29.7–68.8)	58.1 (39.4–86.8)	<0.001
Ductal type			<0.001
Branch	30 (30.6%)	155 (58.1%)	
Main	31 (31.6%)	45 (16.9%)	
Mixed	37 (37.8%)	67 (25.1%)	
Presence of solid portion	48 (49.0%)	41 (15.4%)	<0.001
Size (cm)	3.4 (2.5–5.0)	3.1 (2.3–4.0)	0.059
P-duct size, mm	5.0 (3.0–7.8)	4.5 (3.0–6.6)	0.946

BMI, body mass index; CA19-9, carbohydrate antigen 19–9; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; ALI, advanced lung cancer inflammation index.

be significant (Table 3). The subgroup analysis was performed, stratified by IPMN subtypes. NLR values of non-invasive IPMN and invasive IPMN were not different in the main duct type (2.242 vs 2.589, p = 0.329) however, there was a difference between those of the branch duct IPMN (1.893 vs 2.537, p = 0.014).

Cut-off value for predicting invasive IPMN

The cut-off value of NLR for predicting invasive IPMN was 1.9 with ROC curve, and area under curve (AUC) was 0.62. The division value of NLR was determined with reducing the false-positive rate; in other words, reducing unnecessary resection of the pancreas. Therefore, several sub-analyses were performed additionally. With a NLR of 3.5, the false-positive rate was low. Therefore, we divided patients into two groups, those with a NLR greater than or equal to 3.5 and with a NLR less than 3.5. The number of patients with a NLR greater than 3.5 was 37 (10.1%).

NLR as a prognostic factor

The median follow-up duration was 43 months. To evaluate the prognostic value of NLR, patients were divided into two groups based on NLR cut-off of 3.5. In the non-invasive IPMN group, there was no significant difference in recurrence-free survival rate. However, in invasive IPMN, there was significant difference in recurrence-free survival rate between groups with NLR greater than or equal to 3.5 and those with NLR less than 3.5. The five-year recurrence-free survival rates with NLR greater than or equal to 3.5 and with NLR less than 3.5 were 42.2% and 59.1% respectively ($p = 0.023$) (Fig. 2).

Table 3 Multivariate analysis

Variables	HR [95% CI]	P-value
Bilirubin ≥2 mg/dl	5.347 [2.047–13.964]	0.001
CA 19–9 ≥37U/ml	4.239 [1.996–9.004]	<0.001
Size, cm	1.045 [0.920–1.187]	0.502
Type (Branch)	Ref.	0.056
Main	2.175 [0.904–5.231]	0.083
Mixed	2.728 [1.274–5.839]	0.027
Presence of solid portion	5.865 [2.999–11.471]	<0.001
BMI <25 kg/m^2	1.199 [0.574–2.5004]	0.630
NLR ≥3.5	3.218 [1.029–10.057]	0.044
PLR ≥170	2.004 [0.677–5.936]	0.210
ALI <30	1.554 [0.598–4.041]	0.366

BMI, body mass index; CA19-9, carbohydrate antigen 19–9; NLR, neutrophil lymphocyte ratio; PLR, platelet lymphocyte ratio; ALI, advanced lung cancer inflammation index.

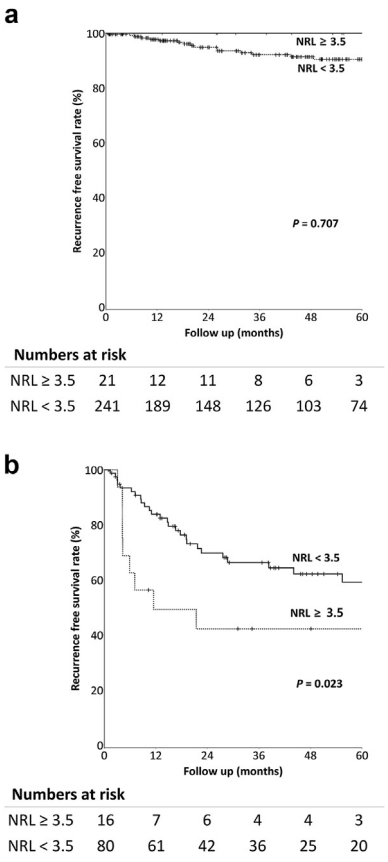

Figure 2 The 5-year recurrence-free survival rate according to the NLR (a) in patients with non-invasive IPMN and (b) in those with invasive IPMN

Discussion

In this retrospective multicenter study, predictive factors for the invasiveness of IPMN were elevated bilirubin, elevated CA 19–9, presence of solid tumor portion, main or mixed type IPMN, and elevated NLR. Elevated NLR was also associated with high recurrence rate in the invasive IPMN group. These findings suggest that inflammatory markers have a diagnostic and prognostic value in the management of IPMN.

NLR is linked to the long-term outcome of various cancer patients. In a study on pancreatic ductal adenocarcinoma, NLR (cut off value: 2.0) was an independent prognostic factor for overall survival (hazard ratio = 1.51; 95% confidence interval = 1.15–1.99; $p = 0.003$) in multivariate analysis.[16] In a meta-analysis of NLR and the survival of pancreatic cancer patients,[4] high pre-operative NLR indicated a worse prognosis than low NLR. NLR cut-off values ranged from 2 to 5 in these studies, and a specific cut-off value has not been established.[1–3]

Inflammatory markers are not only associated with survival rate in patients with malignancies, but they are also effective for predicting malignant transformation in patients with premalignant lesions. There are some studies on the relationship between NLR and invasiveness of IPMN.[14,15,17] Again, the cut-off values of NLR were different among studies, being 4, 2.074 and 2.551, respectively, and a specific cut-off value for the prediction of invasiveness of IPMN has not been established. The association of NLR with the progress of malignancy can be explained by two mechanisms. First is impairment of the patient's immune system as a result of systemic inflammation due to malignancy. Increased neutrophils may occur due to paraneoplastic activity of the primary lesion,[18] and decreased lymphocytes is explained by suppression of the immune system.[19] Systemic inflammation is thought to be secondary to tumor hypoxia or necrosis.[20] These findings and theories reflect that malignancy causes systemic inflammation. The second possible mechanism is causative factor. This theory suggests that loss of immune surveillance is the cause of progression of premalignant lesions to malignancy and not its result.[15,21] Considering that NLR is useful in evaluating premalignant lesions as well as malignant lesions, the causative theory is more convincing than the result theory.

In this study, the cut-off value of NLR for predicting invasive IPMN was 1.9 with the receiver ROC curve, and area under curve (AUC) was 0.62. Screening was not effective when using these values. The aim of this study was to determine how helpful NLR is in determining whether an IPMN patient should undergo surgery. The division value of NLR was determined with the intent of reducing the false-positive rate; in other words, reducing unnecessary pancreatic resection. Therefore, several sub-analyses were performed additionally. In patients with a

NLR of 3.5, the false-positive rate was low. Therefore, we divided patients into two groups, those with a NLR greater than or equal to 3.5 and those with a NLR less than 3.5.

There is also a report on the clinical utility of inflammatory markers other than NLR. In ampullary cancer, patients with PLR greater than 160 had poorer overall survival rate than patients with lower PLR (16.6 months vs 78.7 months median survival respectively; $p < 0.001$).[5] ALI, calculated from a combination of inflammatory and nutritional markers, is also utilized for predicting prognosis. ALI was calculated as BMI * albumin/NLR. In esophageal cancer, patients with ALI below 18 had a significantly poorer five-year cancer-specific survival rate compared to those with ALI over 18 (21.7% vs. 43.4%, $p < 0.001$).[7]

The detection of pancreatic cystic neoplasm, including IPMN, is increasing due to the use of screening tests.[22,23] The size of pancreatic cysts that are detectable is also getting smaller.[24] Therefore, it is very important to correctly choose the patients that need surgery. Currently, the most widely used guideline for selecting IPMN patients for surgery is the international consensus guideline, which provides a flow chart according to radiologic findings and other laboratory findings.[9,25] However, this has many limitations. Other guidelines like the European guideline and American Gastroenterological Association (AGA) guideline also are limited.[10,11] Moreover, diagnostic accuracy varies among these clinical guidelines.

When determining the need for surgical resection in IPMN patients, consideration should be given to disease factors such as natural history, malignant potential, and symptoms of IPMN, and to host factors such as age, co-morbidity, and operation risk. Considering these factors, there are nomograms that convert multiple risk factors into scores[12,13] and nomograms that utilize NLR.[15] In this nomogram, NLR greater than 4 is considered high risk of invasive IPMN.

In combination with other factors, such as the nomogram above, the usefulness of inflammatory markers increases, but the clinical utility is not high when used alone. As shown in Table 3, the most potent risk factors included elevated bilirubin levels, elevated CA 19-9 levels, presence of a solid tumor fraction, and primary or mixed type IPMN. In other words, the inflammatory marker LNR is not an absolute criterion for determining surgery, but it can serve as an important factor when deciding on a treatment strategy. For example, if the patient's NLR is high while all other independent prognostic factors are normal, further tests can be done, or a shorter follow-up period can be scheduled.

There are some limitations to this study. The study was a retrospective study; therefore, some patients were excluded due to missing data. Also, despite the thorough review of imaging data, enhancing mural nodule could not be defined and was instead defined as a solid component. There was a difference between NLR with minimum false-positive rate and the malignant prediction cut-off value when determining reference value for NLR. Despite these limitations, this study was a large cohort multicenter study, and it has suggested the usefulness of inflammatory markers in the management of IPMN.

In conclusion, NLR as an inflammatory marker can be considered as a factor in deciding which patients need surgery and may serve as a useful prognostic factor in the management of invasive IPMN.

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Conflict of interest

None declared.

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