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Preoperative platelet-to-lymphocyte ratio improves the performance of the international consensus guidelines in predicting malignant pancreatic cystic neoplasms

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ABSTRACT

Introduction: To determine if neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were predictive of malignancy in pancreatic cystic neoplasms (PCN) and if these improved the performance of the international consensus guidelines (ICG) in the initial triage of these patients.
Methods: 318 patients with surgically-treated suspected PCN were retrospectively reviewed. Malignant neoplasms were defined as neoplasms harbouring invasive carcinoma. The optimal cut-off for NLR and PLR were determined by plotting the receiver operating characteristics (ROC) curves of NLR/PLR in predicting malignant PCN and utilizing the Youden index.
Results: The optimal NLR and PLR cut-offs were determined to be 3.33 and 205, respectively. Univariate analyses demonstrated that symptomatic PCNs, age, obstructive jaundice, presence of solid component, dilatation of main pancreatic duct ≥10 mm, high NLR and high PLR were predictive of a malignant PCN. Multivariate analyses demonstrated that obstructive jaundice, presence of solid component, MPD ≥10 mm and high PLR but not NLR were independent predictors of a malignant PCN. A high PLR significantly predicted invasive carcinoma in patients classified within the ICG^{HR} group. Comparison between the ROC curves of the ICG versus ICG plus high PLR in predicting malignant PCN demonstrated a significant improvement in the accuracy of the ICG when PLR was included [AUC 0.784 (95% CI: 0.740–0.829) vs AUC 0.822 (95% CI: 0.772–0.872) (p = 0.0032)].
Conclusions: High PLR is an independent predictor of malignancy in PCN. The addition of PLR as a criterion to the ICG improved the accuracy of these guidelines in detecting invasive neoplasms.

1. Introduction

International consensus guidelines (ICG) were first proposed in 2006 in Sendai [1] and subsequently revised in 2012 in Fukuoka [2] for the management of mucinous pancreatic cystic neoplasms (PCNs) such as mucinous cystic neoplasms (MCNs) and IPMN (IPMN) [3]. Today, these guidelines have been widely adopted by clinicians to guide management of mucinous PCNs [3,4]. However at present, even with advancements in imaging and improved knowledge of the morphologic characteristics of PCN [5–8]; preoperative characterization and classification of PCNs is frequently difficult if not impossible especially via cross-sectional imaging studies alone [8,9]. Hence, in clinical practice the ICG is frequently applied to all cystic lesions of the pancreas especially during the initial triage of these lesions [10–12]. The utility of the ICG for the management of pathologically-proven IPMNs have been validated by numerous studies [13,14]. However, its use when applied to all

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suspected PCNs have not been as well-studied [10,12]. Two recent studies [10,11] have demonstrated that the 2012 ICG for mucinous neoplasms was useful in the initial triage of all PCNs.

We have recently studied the value of neutrophil-lymphocyte-ratio (NLR) and platelet-lymphocyte-ratio (PLR) in predicting malignancy in IPMN and MCN and demonstrated that PLR was an independent predictor of invasive carcinoma [15]. Furthermore, we found that addition of PLR as a criterion to the ICG improved the predictive value of these guidelines in detecting invasive carcinoma. Based on the findings from these previous studies [10,11,15], we hypothesized that NLR and PLR may predict malignancy in all suspected PCNs. In this study, we aimed to determine if NLR and PLR were predictive of malignancy in all suspected PCN and if these markers could improve the performance of the ICG in the initial triage of these patients.

2. Methods

From 1999 to 2015, 318 patients who underwent surgery for a pathologically-proven PCN at a single institution were retrospectively reviewed. This study was approved by our institution review board. The clinicopathologic features of 265 of these patients have been reported in a previous study [11]. Briefly, all data were obtained from patients' clinical, radiology and pathology reports. Data of preoperative blood counts were retrospectively retrieved from an electronic database (Sunrise Clinical Manager). The preoperative blood counts used for analysis in this study were taken as close to the date of surgery as possible. This was taken at a median 5 (range, 1–22) days prior to surgery.

2.1. Definitions

The definitions adopted in this study have been described previously [11,13]. Briefly, the diagnosis of PCNs was made based on current histological criteria after review of the pathological and radiological findings. A PCN was considered symptomatic if it was identified on imaging performed for the evaluation of upper abdominal symptoms such as upper abdominal pain, jaundice, pancreatitis or dyspepsia. All cross-sectional imaging morphologic features were identified from the computer tomography (CT) or magnetic resonance imaging (MRI) reports. The main imaging features identified was those included in the ICG including cyst size, presence of solid component and dilatation of the main pancreatic duct.

In this study, according to the ICG [2,11,15], a PCN with high risk features (ICG^{HR}) include presence of obstructive jaundice in proximal lesions, presence of solid component or MPD dilation $\geq$ 10 mm. PCN with 'worrisome' features (ICG^{WR}) include cyst size $\geq$ 3 cm, pancreatitis, thickened enhancing cyst walls, PD 5 to <10 mm, abrupt change in the duct caliber with distal atrophy of the pancreas or the presence of lymphadenopathy. Cysts which did not display any of the above features were deemed 'low risk' (ICG^{LR}) [11,15].

The malignant potential of PCNs was classified on the basis of the most aggressive histological epithelial changes according to the World Health Organization (WHO) classification system [2,16]. In this study, only PCN with invasive carcinoma were defined as malignant as proposed by the current guidelines [2]. These included all ductal adenocarcinomas (DAC) and IPMN or MCN with invasive features. All other potentially malignant or benign cystic neoplasms such as IPMN or MCN with high grade dysplasia, cystic pancreatic neuroendocrine neoplasms (PNEN), solid pseudopapillary neoplasms or serous cystic neoplasms were defined as non-invasive. None of the cystic PNENs or solid pseudopapillary neoplasms displayed lymph node involvement on distant metastases.

2.2. Statistical analyses

The statistical analysis in this study was performed using the program Statistical Package for Social Sciences for Windows, version 21.0 (SPSS Inc, Chicago, IL) and SAS, version 9.3 (SAS Ins, Cary, NC). Continuous variables were presented as median (range) and categorical variables were presented as frequency (%). The Mann-Whitney-U test and the Chi-square or Fisher's exact test were used to analyse continuous variables and categorical variables, respectively. Multivariate analysis was performed using logistic regression analyses. Two-tailed p-values were reported and a p-value <0.05 was considered statistically significant. Blood NLR was calculated using the formula absolute neutrophil count (number of neutrophils/μL) divided by absolute lymphocyte count (number of lymphocytes/μL) and blood PLR was calculated as absolute platelet count (number of platelets/μL) divided by absolute lymphocyte count (number of lymphocytes/μL) [15]. The optimal cut-off values for NLR and PLR were determined by plotting the receiver operating characteristics (ROC) curves of NLR/PLR in predicting malignant PCN. The Youden index was than utilized to determine the best cut-off [17].

3. Results

The final pathologic diagnosis of the 318 surgically-treated PCNs stratified by the ICG is summarized in Table 1. Based on the ROC curve, the optimal NLR and PLR cut-offs were determined to be 3.33 and 205, respectively. The baseline patient demographic and clinicopathologic features stratified by NLR and PLR are summarized in Table 2. PCNs with a high NLR were significantly more likely to be

Table 1
Pathology of the 318 pancreatic cystic neoplasms classified by the International Consensus Guidelines.

Pathology	N
High risk	**152**
IPMN	49
MCN	19
SCN	15
SPPN	24
PNEN	12
Ductal adenocarcinoma	28
Pseudocyst	0
Other malignancies	3
Other benign cysts	2
Worrisome risk	**100**
IPMN	24
MCN	19
SCN	30
SPPN	2
PNEN	5
Ductal adenocarcinoma	3
Pseudocyst	9
Other malignancies	0
Other benign cysts	8
Low risk	**66**
IPMN	13
MCN	2
SCN	32
SPPN	1
PNEN	4
Ductal adenocarcinoma	0
Pseudocyst	1
Other malignancies	0
Other benign cysts	13

IPMN, intraductal papillary mucinous neoplasms; MCN, mucinous cystic neoplasms; PNEN, pancreatic neuroendocrine neoplasms; SCN, serous cystic neoplasms; solid pseudopapillary neoplasms.
Bold is for P values < 0.05.