



## ORIGINAL ARTICLE

# A new combined criterion to better predict malignant lesions in patients with pancreatic cystic neoplasms

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### ABSTRACT

**Objective:** Cystic lesions of the pancreas have been increasingly recognized. Some lesions exhibit benign behavior, while others have unequivocal malignant potential. Thus, accurate identification of malignancy in patients diagnosed with pancreatic cystic neoplasms (PCNs) remains a major challenge. The aim of this study was to define a combined criterion to better predict malignant lesions in patients with PCNs.

**Methods:** We retrospectively analyzed 165 patients who underwent resection of PCNs from October 2011 to May 2017. The relationship among malignancy and serum carbohydrate antigen 19-9 (CA19-9), preoperative neutrophil-to-lymphocyte ratio (NLR), and the presence of enhanced solid component on imaging was analyzed.

**Results:** NLR before surgery in patients with malignant PCNs ( $2.81 \pm 2.14$ ) was significantly higher than that in patients diagnosed with pancreatic neuroendocrine tumor ( $1.90 \pm 0.69$ ,  $P=0.013$ ) or healthy volunteers ( $1.40 \pm 0.48$ ;  $P<0.001$ ). Serum CA19-9  $\geq 39$  U/mL, NLR  $>1.976$  and presence of enhanced solid component were independent predictors of PCN malignancy. A combined criterion meeting any two or more of the three elements including CA19-9  $\geq 39$  U/mL, NLR  $>1.976$ , and presence of enhanced solid component on computed tomography imaging is an indicator with a high positive predictive value of 80.5% and a high negative predictive value of 87.9%, and thus, represents a highly accurate test (86.1%).

**Conclusions:** The new combined criterion is an effective predictor of tumor malignancy in patients with PCNs.

### KEYWORDS

Malignant pancreatic cystic neoplasm; neutrophil-lymphocyte ratio; enhanced solid component; combined criterion; diagnosis

## Introduction

The detection rate of pancreatic cysts has increased dramatically owing to the universal use of cross-sectional imaging modalities<sup>1,2</sup>. Pancreatic cystic neoplasms (PCNs) account for approximately 10%–15% of all pancreatic cystic lesions<sup>1,3</sup> and approximately 1% of all pancreatic neoplasms<sup>3</sup>. PCNs include three distinct common tumor types: serous cystic neoplasm (SCN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN)<sup>4,5</sup>. IPMN and MCN are believed to potentially lead to pancreatic ductal adenocarcinoma, whereas SCN is almost always benign<sup>4,6,7</sup>.

Some PCNs undergo malignant transformation, and detection thus provides an opportunity to surgically cure or

prevent pancreatic adenocarcinoma<sup>8</sup>. In current clinical practice, evaluation of the benign or malignant status of PCNs remains a major challenge. Surgery is recommended for all suitable patients with suspected PCNs<sup>9,10</sup>. However, it is important to consider that pancreatic surgery is risky, and the possibility of major postsurgical complications (as well as of long-term impairment of pancreatic function) is non-negligible<sup>11,12</sup>. The risk of over-treatment (unnecessary pancreatectomy) should be balanced carefully with the risk of under-treatment (missing the opportunity to cure a potentially curable malignant or premalignant lesion)<sup>4</sup>. The differentiation of a potentially malignant cystic neoplasm from other benign neoplasms prior to surgery plays an important role in treatment planning<sup>13,14</sup>. Use of a combined diagnostic method is recommended not only for preoperative diagnosis, to reduce the performance of unnecessary surgery in patients with observable progress, but also to prevent surgical delay when appropriate<sup>9</sup>.

Unfortunately, based on current guidelines, diagnosis and management of PCNs is a clinical challenge<sup>15</sup>. Preoperative diagnosis of pancreatic cysts is largely reliant on radiographic

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and clinical features and lacks both consistency and sensitivity<sup>16</sup>, particularly for non-symptomatic cystic neoplasms of the pancreas. In many cases, PCNs have characteristic morphological imaging features that can inform diagnosis<sup>17</sup>. However, it is often difficult to accurately differentiate these lesions due to morphological overlaps in imaging between benign and malignant forms<sup>18</sup>. For example, up to one-fifth of pancreatic cystic lesions resected for malignancy, even in high-volume medical research centers, were confirmed to be benign on final pathology<sup>19</sup>. Misdiagnosis often leads to unnecessary surgeries with associated complications<sup>4,17</sup>. As accurate differentiation among types of pancreatic cysts remains impossible with abdominal imaging, considerable effort has been made toward development of improved combinational diagnostic methods.

A variety of diagnostic imaging modalities are routinely used, such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), contrast-enhanced ultrasound (CEUS), and endoscopic ultrasonography (EUS) with cystic fluid aspiration<sup>16</sup>. Recently, studies have reported similar diagnostic accuracy among CT, MRI, and CEUS in the characterization of pancreatic cystic masses<sup>20–23</sup>. Radiologic features, including the size, density, and location of the lesion; wall characteristics such as septations; nodules; and calcification, have been suggested as potential categorization criteria for the lesions<sup>24</sup>. However, the ideal test has not yet been identified<sup>20,25</sup>.

The serum tumor markers carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) have both been shown to be relatively adequate diagnostic and prognostic predictors for malignant PCNs<sup>26</sup>. However, CA19-9 appears to be a better predictor of malignancy. These markers assist in the identification of potentially malignant PCNs that require resection. Host inflammatory responses to types of cancers have been indicated to be correlated with tumor progression<sup>27,28</sup>. Neutrophil-to-lymphocyte ratio (NLR) is a simple and convenient index of systemic inflammation. Elevated pretreatment NLR was identified as an independent prognostic factor correlated with poor prognosis in patients with several types of malignancy<sup>29,30</sup>. Studies have reported that elevated NLR correlates with poor prognosis in patients with pancreatic cancer undergoing curative resection and bypass surgery<sup>31,32</sup>. However, the relationship between NLR and the pathological characteristics of PCNs has not been sufficiently elucidated. The purpose of this study was to examine whether a combination of NLR with other factors could better predict malignancy of PCNs.

## Patients and methods

### Patients and control subjects

This retrospective study included 165 patients who underwent surgery for PCNs between October 2011 and May 2017 at Tianjin Medical University Cancer Institute and Hospital (TMUCIH). Data from 49 patients with pancreatic ductal adenocarcinoma (PDAC), 44 patients with pancreatic neuroendocrine tumors (PNETs), and 15 patients diagnosed with IgG4-related sclerosing pancreatitis who were previously treated at TMUCIH were also included. In addition, 330 healthy, cancer-free men and women were randomly sampled to be used as healthy controls from those who visited TMUCIH for physical check-ups. All participants enrolled in the study were of Chinese Han ethnicity. The healthy controls were frequency (age and sex) matched to the patients with PCNs. Informed consent was obtained from all patients who participated, and the study was approved by the ethics committee of TMUCIH.

### Clinical characteristics

Clinical characteristics such as age, sex, and presence of symptoms were reviewed from the hospital electronic medical records.

### Blood examination

No patients included in this study exhibited infectious disease. Routine blood examinations were performed, including hepatic and renal function tests. Blood was collected 2–4 days before surgery, and NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count in these samples. Serum tumor markers such as CA19-9, CEA, and carbohydrate antigen 242 (CA242) were measured within the week before surgery.

### Imaging

Abdominal CT scanning was performed in all patients prior to surgery. Images were acquired in unenhanced as well as contrast-enhanced arterial and portal venous phases. The images were reviewed on the hospital picture archiving and communication system. The longest diameter of the largest lesion was measured for patients with multiple cystic lesions on imaging examination.

### Pathological presentation

All pathologic specimens were blindly reviewed by two

pathologists. Tumors were classified as benign or malignant according to the American Joint Committee on Cancer (AJCC), 7th edition.

## Development of the combined criterion

The receiver operating characteristic (ROC) curve and area under the ROC curve were applied to determine the best cut-off values for baseline NLR. We defined the presence of any two or more of the three predictive factors, including abnormal serum CA19-9 level,  $\text{NLR} > \text{cut-off value}$ , and enhanced solid component on CT imaging, as meeting the criterion for malignancy.

## Statistical analysis

For continuous variables, descriptive statistics were used and were reported as mean  $\pm$  standard deviation (SD) or as median with range. Categorical variables were described using frequency distributions. An independent sample *t*-test was calculated to detect differences in the means of continuous variables. Chi-square and Spearman rank correlation coefficient testing were used for qualitative variables, and one-way analysis of variance (ANOVA) was applied to detect differences among several groups. All variables with statistically significant malignant predictive value in univariate analysis were selected for further investigation in the multivariate analyses. All statistical analysis was performed using the SPSS software (version 18.0; SPSS Inc., Armonk, NY, USA). *P* values were two-tailed and regarded as significant when less than 0.05.

## Results

### Characteristics of study subjects

**Table 1** shows the clinical characteristics of 165 patients with PCNs. Among these patients, 65 were men and 100 were women, with a mean age of 56.59 years (range, 20–81). Regarding tumor types, 29 patients had pancreatic IPMN, 67 had SCN, and 69 had MCN. While 124 cysts were identified as benign, 41 were malignant. Sixty-nine patients were asymptomatic, and 96 patients experienced one or more symptoms including abdominal pain/discomfort, vomiting, jaundice, weight loss, or abdominal mass. The mean diameter of PCNs was  $4.60 \pm 2.65$  cm (range, 1.2–16 cm). Regarding location, 51.5% (85) of PCNs were located in the head or neck of the pancreas, and 48.5% (80) were located in the body or tail. The mean NLR in all patients with PCN was

$2.10 \pm 1.34$ . Serum CA19-9, CEA, and CA242 were measured in all patients. The ratios of normal to abnormal were 127/38, 112/53, and 144/21 for CA19-9, CEA, and CA242, respectively. An enhanced solid component inside the cyst was observed in 77 patients (46.7%) on CT imaging.

### Correlation between clinical characteristics and PCN malignancy

According to pathology results, the patients were divided into benign and malignant groups. Sex could not be considered a predictor of malignancy in the patients with PCNs. Tumor location between body or tail of the pancreas and older age were significantly associated with malignancy ( $P=0.005$ ,  $P=0.002$ , respectively) (**Table 1**). Symptoms at admission were recorded more often in the malignant group (31/41; 75.6%) ( $P=0.009$ ). Preoperative serum CA19-9, CA242, and CEA levels were closely associated with PCN malignancy ( $P<0.001$ ,  $P<0.001$ , and  $P=0.010$ , respectively) (**Table 1**).

Representative pathology and images of both benign and malignant lesions are shown in **Figure 1**. Patients with malignant PCNs had a higher probability of exhibiting enhanced solid components on CT images ( $P<0.001$ ) (**Table 1**). It is unsurprising that the presence of an enhanced solid component is strongly associated with malignant PCNs.

To determine whether NLR prior to surgery was predictive of malignant potential, we compared the preoperative NLR in 124 patients with benign PCNs with that in 41 patients with malignant PCNs. The NLR of patients with benign PCNs ( $1.87 \pm 0.84$ ) was significantly lower than that of patients with malignant PCNs ( $2.81 \pm 2.14$ ,  $P=0.009$ ). Furthermore, we compared peripheral blood NLR in patients with benign PCNs, malignant PCNs, PNET, PDAC, and IgG4-related sclerosing pancreatitis, with that in healthy controls (**Figure 2**). The NLR in patients with malignant PCNs was similar to that in patients with PDAC ( $P=0.640$ ), and was significantly higher than that in patients diagnosed with PNET ( $1.90 \pm 0.69$ ,  $P=0.013$ ) or in healthy donors ( $1.40 \pm 0.48$ ;  $P<0.001$ ). NLR in patients with malignant PCNs and PDAC was higher than that in healthy volunteers, indicating that the increase in NLR might be caused by tumor microenvironment.

### Independent factors predicting malignancy in PCNs

The optimal cut-off value of NLR for predicting malignant PCNs was 1.976 (AUC=0.673, **Figure 3**). Patients were divided into a low NLR group ( $\text{NLR} \leq 1.976$ ;  $n=96$ ) and a high

**Table 1** Background characteristics of patients with PCNs

Clinicopathological factors	Benign group (n=124)	Malignant group (n=41)	$\chi^2$	P
Age, years	55.00±12.23	61.41±8.95	3.092	0.002
NLR	1.87±0.84	2.81±2.14	2.738	0.009
Sex (male/female)	44/80	21/20	3.196	0.074
Age, years				
≤56	58	13	2.853	0.091
>56	66	28		
CA19-9 (U/mL)				
<39	112	15	50.194	<0.001
≥39	12	26		
CEA (ug/L)				
<5	113	31	6.681	0.010
≥5	11	10		
CA242 (U/mL)				
<12	95	17	17.460	<0.001
≥12	29	24		
Enhanced solid component				
Absence	88	10	27.717	<0.001
Presence	36	31		
Cyst diameter (mm)				
<30	53	15	0.482	0.487
≥30	71	26		
Symptom				
Absence	59	10	6.811	0.009
Presence	65	31		
Tumor location				
Head/neck	56	29	8.066	0.005
Body/tail	68	12		

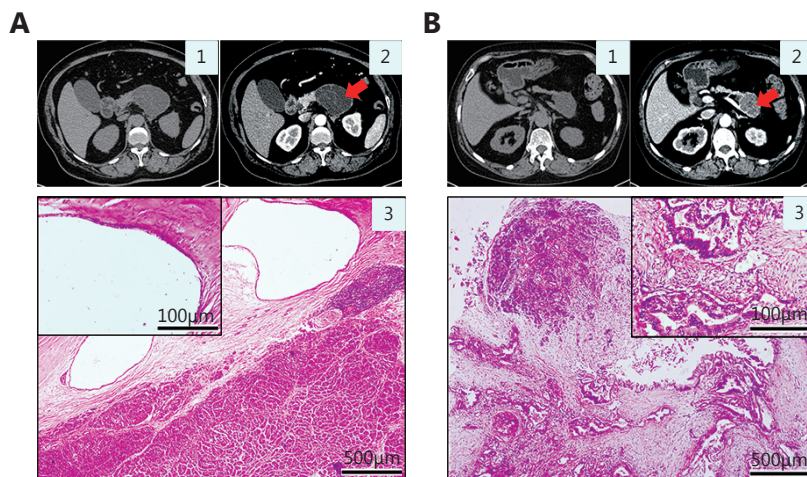
<sup>a</sup>Student's *t*-test for age and NLR distributions between benign and the malignant group; and two-sided  $\chi^2$  test for other selected variables.

NLR group (NLR >1.976; *n*=69). To evaluate the utility of NLR prior to surgery in identifying patients with malignancy, logistic regression analysis was performed with clinical parameters including NLR (**Table 2**). Univariate analysis showed that high NLR (>1.976), older age (>56 years), high CA19-9 (≥39 U/mL), high CEA (≥5 ng/dL), high CA242 (≥12 U/mL), presence of enhanced solid component, and tumor location in the body or tail of pancreas were all significantly associated with malignancy. Multivariate analysis revealed that high CA19-9 (≥39 U/mL), presence of enhanced solid component, and high NLR were independent predictors of

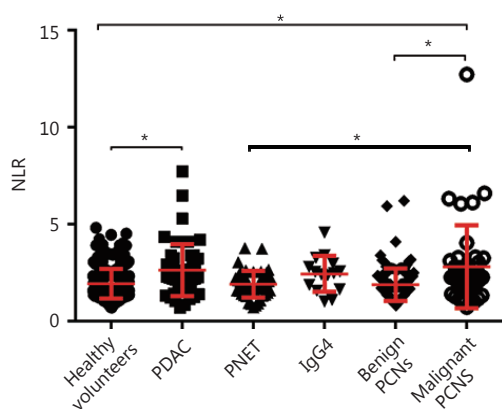
PCN malignancy.

### Clinical utility of NLR and the new combined criterion

Next, we aimed to identify whether NLR could be a supportive index to predict malignancy of PCNs when combined with other conventional indicators. The distribution of NLR value, serum CA19-9 level, presence of enhanced solid component, and the presence of PCN malignancy is shown in **Figure 4**. The sensitivity, specificity,

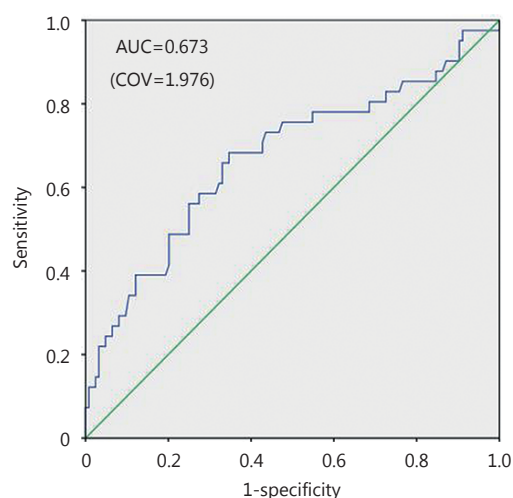


**Figure 1** (A) A 69-year-old asymptomatic woman with pancreatic body-tail cyst incidentally found by routine examination. (1) Computed tomography (CT) scan shows 8 cm cyst at body-tail of pancreas. (2) Axial contrast-enhanced CT image in portal venous phase demonstrates a large nonenhancing mass in pancreas (arrow). (3) Serous cystic neoplasm (SCN) confirmed by pathology (IHC staining, 20 x). (B) A 48-year-old woman with upper abdominal pain. (1) Computed tomography (CT) scan shows 7 cm cyst at body-tail of pancreas. (2) Axial contrast-enhanced CT image in portal venous phase demonstrates a large enhancing mass in pancreas (arrow). (3) Invasive mucinous cystic neoplasm (MCN) confirmed by pathology (IHC staining, 20 x).



**Figure 2** Distribution of NLR in 603 patients with various types of pancreatic disease is shown. NLR values are compared among these groups. Healthy volunteers ( $n=330$ ), PDAC: pancreatic ductal adenocarcinoma ( $n=49$ ), PNET: pancreatic neuroendocrine tumor ( $n=44$ ), IgG4: IgG4-related sclerosing pancreatitis ( $n=15$ ), benign PCNs in the study ( $n=124$ ), malignant PCNs in the study ( $n=41$ ). \* $P<0.05$ , \*\* $P<0.01$ .

positive predictive value (PPV), and negative predictive value (NPV) for predicting PCN malignancy were evaluated with the combined criterion of  $NLR>1.976$ , abnormal serum CA19-9 level, and presence of enhanced solid component. The sensitivity, specificity, PPV, NPV, and accuracy of the new diagnostic criterion for predicting PCN malignancy are shown in **Table 3**, in comparison with each conventional

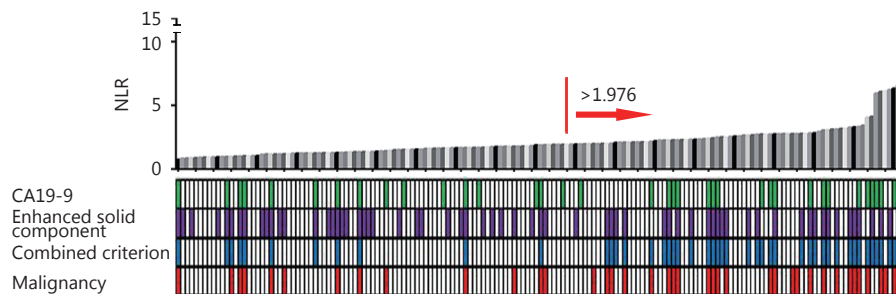


**Figure 3** Optimal NLR value for predicting malignant PCNs. Receiver operating characteristic (ROC) curve analysis for determining NLR cut-off value predictive of malignant PCNs is shown. Curved line shows ROC curve. AUC: area under the curve, COV: cut-off value.

indicator of PCN malignancy. Furthermore, the sensitivity, specificity, PPV, and NPV predicted by the new criterion were 68.8%, 93.2%, 80.5%, and 87.9%, respectively. The new criterion demonstrated both a high PPV of 80.5% and a high NPV of 87.9%. Thus, a higher accuracy (86.1%) in identifying malignancy could be obtained with the new

**Table 2** Univariate and multivariate analysis for predicting malignancy in PCNs

Factors	Univariate analysis			Multivariate analysis		
	Odds ratio	95 % CI	P	Odds ratio	95 % CI	P
Age (> 56 years)	1.893	0.897–3.993	0.094			
Sex (male/female)	0.524	0.256–1.070	0.076			
NLR >1.976	4.360	2.046–9.293	<0.001	4.892	1.735–13.792	0.003
CA19-9 $\geq 39$ U/mL	16.178	6.772–38.645	<0.001	13.527	3.673–49.822	<0.001
CEA $\geq 5$ ng/dL	3.314	1.289–8.518	0.013	1.048	0.247–4.441	0.950
CA242 $\geq 12$ U/MI	4.625	2.190–9.767	<0.001	1.176	0.343–4.026	0.796
Enhanced solid component	7.578	3.366–17.059	<0.001	6.629	2.323–18.917	<0.001
Cyst diameter >30 mm	1.294	0.625–2.680	0.488			
Symptom	2.814	1.270–6.232	0.011	2.139	0.691–6.626	0.187
Tumor location	0.341	0.159–0.729	0.006	0.657	0.225–1.916	0.442

**Figure 4** High NLR level is associated with the presence of malignant PCNs. Distributions of NLR level and serum CA19-9 level, presence of enhanced solid component, and presence of malignant lesions in patients with PCNs ( $n=165$ ) are shown. Each bar chart shows the patient's NLR value, and lower heat map shows if patient meets the criterion. Red arrow shows the high NLR group (>1.976).**Table 3** The sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV) and accuracy for predicting PCNs malignancy of NLR, CA19-9, presence of enhanced solid component and combined criterion are all shown

Factors	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
NLR>1.976	40.6	86.5	68.3	66.9	67.3
CA19-9 $\geq 39$ U/mL	68.4	88.2	63.4	90.3	83.6
Presence of enhanced solid component	46.3	89.8	75.6	71.0	72.1
CA19-9 and enhanced solid component	83.3	85.1	48.8	96.8	84.8
Combined criterion	68.8	93.2	80.5	87.9	86.1

<sup>a</sup>Meeting both of the elements including serum CA19-9  $\geq 39$  U/mL and the presence of enhanced solid component in CT imaging.

diagnostic criterion.

## Discussion

PCNs are now more frequently discovered with the increased use of abdominal CT imaging<sup>33</sup>. Some of these neoplasms undergo malignant transformation<sup>8,34</sup>. Therefore, considering the current efficacy of pancreatic resection, it is

not surprising that the number of operations for PCNs has increased. Pancreatic resection can remove symptomatic, malignant, or potentially malignant lesions. However, some cystic lesions are benign or slow growing, and their potential for malignant transformation remains unclear<sup>33</sup>. Recent studies have shown that only one-fifth of the resected asymptomatic pancreatic cysts are malignant<sup>35</sup>. Surgeons require a rapid and accurate assessment of the risk benefit

ratio of observation versus resection of these neoplasms in individual patients.

Serous cystadenomas, which are often located in the body or tail of the pancreas, occur most commonly in middle-aged women. In contrast, IPMN occurs more frequently in the pancreatic head in elderly male patients, and mucinous cystadenomas occur mostly in elderly females<sup>34,36</sup>. In our results, sex could not be considered a predictor of malignant PCN. Patients with benign MCN have a median age of 50 years, whereas patients with mucinous cyst adenocarcinoma have a median age of 65 years<sup>3</sup>. Other studies reported that patients with malignant cysts were older than patients with benign cysts, with statistical significance<sup>16,37</sup>. This observation is consistent with our findings that age is correlated with malignant cystic pancreatic neoplasms.

Medical consensus suggests 3 cm as the cut-off value for resection of asymptomatic lesions<sup>8</sup>. On the other hand, large numbers of studies have reported that cyst size had little correlation with pathological malignant traits<sup>35</sup>. Sarr et al.<sup>38</sup> reported no difference in the mean size between benign mucinous cystadenoma and mucinous cystadenocarcinoma. Lee et al.<sup>39</sup> found that 19% (31/166) of cystic pancreatic tumors <3 cm proved to be malignant. In the present study, lesion size was also not predictive of malignant cysts. However, we found that tumor location was a predictive factor of malignant PCNs. Lesions located in the body or tail of the pancreas were more likely to be malignant.

Owing to the morphological overlap in imaging, and poor inter-observer consensus in relation to the standards between benign and malignant PCNs, CT images allow correct characterization of only 25%–60% of cystic pancreatic masses<sup>40</sup>. Numerous researchers have reported that the presence of solid component inside the cyst on imaging is a significant predictor of malignancy<sup>40</sup>. In the present study also, the most significant radiological finding correlated with malignancy was the presence of enhanced solid component. Moreover, the presence of enhanced solid component was found to be an independent predictor in multivariate analysis.

In clinical practice, CA19-9 and CEA are two of the important biomarkers for patients with pancreatic malignant diseases<sup>41</sup>. Serum CA19-9 level is elevated in more than three quarters of patients with pancreatic ductal adenocarcinoma<sup>42</sup>. These biomarkers were found to be correlated with the presence of malignancy. An increased level of CA19-9 was found to be specifically correlated with malignant PCNs. Thus, CA19-9 is considered to be a vital test for all patients, a finding consistent with the results of other series<sup>8</sup>. However, although the specificity of serum CA19-9 is high, its

sensitivity has been shown to be very low<sup>42</sup>. Some researchers have suggested that endoscopic ultrasound with fine-needle aspiration (EUS-FNA) and cystic fluid analysis hold promise in identifying lesions with malignant potential<sup>43</sup>. EUS is not always accessible, however, particularly in rural areas where the equipment for distinguishing malignant lesions from benign PCNs is not available<sup>44</sup>. Limitations to the access of EUS indicate that clinicians must rely on other noninvasive techniques to assess the risk of PCN.

Various investigations of NLR have been performed in various types of cancer, considering its role in the prediction of cancer development<sup>29,45</sup>. A strong connection between neutrophil infiltration and malignant progression has been described by inflammatory mediators released by peripheral blood cells, which play a vital role in the intersection between neoplastic and inflammatory cells<sup>46</sup>. Recently, it was reported that tumorigenesis in the pancreas correlates with distinct intra- and peri-tumoral inflammation<sup>47</sup>. Thus, despite its non-specificity, increased NLR might be indicative of increased inflammatory activation in PCN-derived malignancies. The present study demonstrated that NLR is significantly higher in patients diagnosed with malignant PCNs than in those with benign lesions. As there was a remarkable difference in NLR value between healthy volunteers and patients with malignant PCNs, NLR might be important for monitoring malignant progression of PCNs. Intriguingly, in our study, we found that the cut-off value of  $NLR > 1.976$  was an independent predictor for the malignant potential of PCNs. Other studies selected different cut-off values of NLR<sup>48,49</sup>, but these findings all indicate that high NLR is a supportive predictor of malignancy in PCNs.

The conventional guidelines for the diagnosis of malignancy of PCNs were unsatisfactory and complex, owing to the variety of predictors and their ambiguity. Preoperative prediction of malignancy often depends on the surgeon's experience or other important factors that are difficult to clearly ascertain and have low PPV and NPV<sup>50</sup>. The new combined criterion is a quantitative standard that is more accurate, practical, and convenient for all surgeons. Therefore, we recommend the diagnosis of malignancy of PCNs on the basis of CA19-9, NLR, and CT imaging.

In conclusion, we defined a new combined criterion to predict malignancy in patients with PCNs. The combined accuracy for predicting malignant PCNs was superior to that of any one of the abovementioned three standards. This criterion is superior to current practice in the identification of patients with malignant lesions in PCNs. It is important to distinguish benign from malignant lesions to select

individuals who would benefit from early surgery.

## Conflict of interest statement

No potential conflicts of interest are disclosed.

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