Carbohydrate Antigen 125 Supplements Carbohydrate Antigen 19-9 for the Prediction of Invasive Intraductal Papillary Mucinous Neoplasms of the Pancreas

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Abstract

Background

Intraductal papillary mucinous neoplasm (IPMN) is a disease with malignant potential. IPMNs of the pancreas are mainly managed according to radiographic indications, which lack accuracy in defining grades of IPMNs. Therefore, other indications such as serological biomarkers should be employed to predict the invasiveness of IPMNs.

Methods

We investigated preoperative serum levels of CA19-9, CA125 and CEA of 381 surgical patients with a definite pathological diagnosis of IPMN from July 2010 to December 2019 at Shanghai Cancer Center. We calculated the Youden indices of each point of receiver operating characteristic (ROC) curves to find the most appropriate cut-off values of CA19-9, CA125 and CEA in recognizing malignant IPMNs. Serological biomarker differences were correlated with grades and biological behaviours of IPMNs. Diagnostic indices of these serum biomarkers were calculated.

Results

Malignant group had higher serum levels of CA19-9, CA125 and CEA. According to ROC curves, the most appropriate cut-off value of CA125 were readjusted to 13.5 U/ml while the cut-off values of CA19-9 and CEA remained 37 U/ml and 5.3 ng/l as them mostly be employed. Besides, CA19-9 elevation was significantly associated with vascular invasion and perineural infiltration. We found CA125 may predict invasive IPMN in CA19-9 negative subgroup according to ROC curve.

Conclusions

Serological biomarkers are useful and sensitive indications for recognizing invasive IPMNs. CA19-9 has the upmost diagnostic indices among all regularly used serum biomarkers in differentiating malignant and benign IPMNs. CA19-9 should be combined with CA125 to form a more favourable biomarker panel for IPMNs malignancy prediction.

Background

Intraductal papillary mucinous neoplasms (IPMNs) are characterized by mucin production, pancreatic ductal dilation and intraductal growth. Patients with IPMN are generally old, and abdominal pain, diarrhoea and weight loss are the major symptoms of IPMN[1]. IPMN is considered a premalignant condition and has the potential to transform into invasive cancer; in particular, malignant IPMNs are characterized as aggressive tumours. Therefore, surgical intervention is warranted for patients with these early-stage cancerous lesions. However, for patients with IPMNs without malignant potentiality, lifelong follow-up is recommended rather than surgical intervention[2]. The accurate prediction of IPMN malignancy is important for clinical management because surgery of the pancreas is complicated and

associated with a high possibility of complications, especially for lesions located in the head of the pancreas.

Currently, various kinds of examinations are used to distinguish the morphology of IPMNs of the pancreas, including cross-sectional computerized tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasonography (EUS). Certain morphological subtype of IPMN, i.e. main pancreatic duct IPMN is recommended to undergo surgery according to consensus guidelines published by the International Association of Pancreatology (IAP)[3].

Over the past decades, IPMNs have had an increasing incidence and constitute the largest proportion of pancreatic cystic lesions[2,4]. Incidentally diagnosed IPMNs account for many pancreatic surgeries, but controversy remains since the proportion of malignant IPMNs according to postoperative histology in all resected IPMNs is decreasing[5]. The efficacy of radiological examination is unsatisfactory; therefore, to accurately perform surgical resection on invasive IPMNs while avoiding unnecessary surgery, there is a clinical need to find sensitive and specific preoperative indications to assess the necessity of surgery[6].

The major serological biomarker of IPMN is carbohydrate antigen 19-9 (CA19-9). IPMNs with elevated CA19-9 have more potential to be malignant. However, false negativity and positivity have been the limitations of CA19-9 as a diagnostic biomarker. The combination of multiple biomarkers can overcome the limitation of a single biomarker. Apart from CA19-9, in the preoperative identification of pancreatic disease, there are two measured biomarkers that are most commonly used, carbohydrate antigen 125 (CA125) and carcinoembryonic antigen (CEA). CA125 and CEA have already shown their potential to predict CA19-9-negative pancreatic cancer[7,8]. Compared to radiological methods, serological biomarker tests are more sensitive, affordable and cost-effective and deserve more investigation.

In this study, we investigated whether CA125 and CEA could be combined with CA19-9 to distinguish high-grade IPMN from indolent dysplasia. In addition, we examined CA19-9-negative patients and analysed the difference in serological biomarkers between benign and malignant IPMNs in this subgroup. To the best of our knowledge, this is the first article to evaluate the combination of multiple biomarkers, CA19-9, CA125 and CEA, in predicting invasive IPMN.

Materials And Methods

Design and patients

A retrospective study consisting of 381 patients with a definite pathological diagnosis of IPMN from July 2010 to December 2019 was conducted at Shanghai Cancer Center, Fudan University, China. All patients underwent surgical resection. The pathology diagnoses were all based on post-operative pathology reports. The exclusion criteria were as follows: (1) patients with more than one serum biomarker records were missing; (2) patients with secondary malignancies or multiple primary malignancies; (3) patients with serum bilirubin greater than 34.2 μmol/L; (4) patients diagnosed with pathology other than IPMN.

Baseline clinical data, including sex and age, were collected according to the patients' medical history. CA19-9, CEA and CA125 serum levels were collected preoperatively according to serum tests. Postoperative pathological reports, including tumour grade, tumour behaviour, and tumour location, were acquired from Fudan University Shanghai Cancer Center. Tumour grade was assessed according to the fifth edition of the WHO Classification of Tumours[9] and was reviewed by expert pathologists. IPMNs were classified into four pathological grades: invasive carcinoma, high-grade dysplasia, moderate-grade dysplasia and low-grade dysplasia.

The major objective of this research is to assess the clinical significance of different serum biomarkers for predicting IPMNs with malignant potential and to find an ideal serum biomarker panel to guide future clinical practice. Therefore, carcinoma and high-grade dysplasia were integrated into the malignant subgroup, and moderate-grade and low-grade dysplasia were integrated into the benign subgroup. The following analysis of IPMN malignancy was performed on the basis of this classification.

Additional objectives include finding more appropriate cut-off values and investigating the associations between serum biomarker levels and sex, age, tumour location, vascular invasion and perineural infiltration. This study was approved by the Ethics Board of Shanghai Cancer Center, Fudan University, and all patients involved in this study provided informed consent for the use of their personal data for research purposes.

Statistical analysis

The comparison of serum biomarker values of each subgroup was based on the mean value. The distribution of each tumour marker is shown in a scatter plot, and Student's t test was used to analyse the difference between subgroups. Pearson's $\chi 2$ test and Fisher's exact test were used to analyse the correlations between serum biomarker levels and major baseline characteristics. All statistics were analysed by SPSS 26.0 software (SPSS, Inc., Chicago, IL). A p value < 0.05 was considered statistically significant, and all p values were two sided.

Results

Patient baseline characteristics

There were 381 patients with a pathological diagnosis of IPMN, including 215 male patients and 166 female patients. Their ages ranged from 31 to 84 (median age, 62.4) years old. Of all these IPMN patients, 228 had lesions located at the head of the pancreas (59.8%), 119 had lesions located at the pancreatic body or tail (31.2%), and the rest of the patients did not have a definite location of the lesion.

With regard to histological grade, 118 patients had invasive carcinoma (31.0%), 17 patients had high-grade dysplasia (4.5%), and the remaining patients had low- or moderate-grade dysplasia (64.6%). According to pathological reports, 5 patients had vascular invasion (2.6%), and 11 patients had perineural infiltration (5.8%).

Regarding serum biomarkers, 379 patients had CA19-9 levels measured preoperatively, and 95 patients had elevated CA19-9 levels (25.1%, cut-off value = 37 U/ml). A total of 378 patients had preoperative records of CA125 levels, and 8 of them had elevated CA125 levels (2.12%, cut-off value = 35 U/ml). A total of 381 patients had preoperatively documented CEA levels, and 48 patients had elevated CEA levels (12.6%, cut-off value = 5.3 ng/l).

Value of CA19-9, CA125 and CEA in predicting invasive IPMN

The malignant and benign IPMN subgroups differed in serum biomarker levels. Invasive IPMNs had higher average CA19-9 levels (149.4 vs 20.4U/ml, $p < 0.0001$), higher average CA125 levels (17.5 vs 11.8U/ml, $p < 0.0001$), and higher average CEA levels (5.27 vs 2.72ng/l, $p < 0.0001$) (Figure 1).

Compared to patients with normal CA19-9 levels, patients with elevated CA19-9 levels were more likely to have invasive carcinoma or high-grade dysplasia ($p < 0.001$, Table 1). Elevated CA19-9 was also associated with vascular invasion (HR = 18.06, $p < 0.001$) and perineural infiltration (HR = 3.79, $p = 0.042$). The specificity and sensitivity of CA19-9 were 89.8% and 51.9%, respectively. Although its specificity was acceptable, its sensitivity was less than satisfactory.

Table 1
Characteristics of IPMN patients stratified by CA19-9

variables	CA19-9≤36.9U/ml	CA19-9>36.9U/ml	P value
Age, n(%)			0.513
<60	94(33.1%)	28(29.5%)	
≥60	190(66.9%)	67(70.5%)	
Sex, (n%)			0.159
Male	167(58.8%)	48(50.5%)	
Female	117(41.2%)	47(49.5%)	
Location, (n%)			0.470
Head	169(64.8%)	58(69.0%)	
Body and tail	92(35.2%)	26(31.0%)	
Tumour grade, (n%)			0.001
Low and Moderate	219(77.1%)	25(26.3%)	
High and Carcinoma	65(22.9%)	70(73.7%)	
Vascular invasion, (n%)			0.006
No	149(99.3%)	33(89.2%)	
Yes	1(0.7%)	4(10.8%)	
Perineural infiltration, (n%)			0.042
No	145(96.0%)	32(86.5%)	
Yes	6(4.0%)	5(13.5%)	

Table 2. Characteristics of IPMN patients stratified by CA125

variables	CA125≤13.5 U/ml	CA125>13.5 U/ml	P Value
Age, n(%),y			1.000
< 60	81(32.3%)	41(32.3%)	
≥ 60	170(67.7%)	86(67.7%)	
Sex, (n%)			0.037
Male	152(60.6%)	62(48.8%)	
Female	99(39.4%)	65(51.2%)	
Location, (n%)			0.401
Head	146(64.0%)	80(69.0%)	
Body and tail	82(36.0%)	36(31.0%)	
Tumour grade, (n%)			<0.001
Low and Moderate	178(70.9%)	66(52.0%)	
High and Carcinoma	73(29.1%)	61(48.0%)	
Vascular invasion, (n%)			0.334
No	124(98.4%)	59(95.2%)	
Yes	2(1.6%)	3(4.8%)	
Perineural infiltration, (n%)			0.731
No	121(95.2%)	58(93.5%)	
Yes	6(4.7%)	4(6.5%)	
Table2. Characteristics of IPMN patients stratified by CA125			

Preoperative serum CA125 and CEA levels also showed efficacy in predicting the risk of IPMN when applied with clinical cut-off values (35 U/ml for CA125 and 5.3 ng/l for CEA). The specificities of CA125 and CEA were 99.6% and 93.5%, respectively. However, the sensitivities of CA125 and CEA were 5.2% and 23.9%, respectively, suggesting that they had limited efficacy, and their cut-off values should be readjusted to recognize malignant IPMNs more sensitively.

Therefore, receiver operating characteristic (ROC) curves of CA19-9, CA125 and CEA were generated, and the Youden indices of each point were calculated to determine the most appropriate cut-off values (Figure 2). The areas under the curve (AUCs) of the ROC curves of CA19-9, CA125 and CEA were 0.724, 0.609 and 0.629, respectively.

New Cut-off Values Calculated According To The Roc Curves

The values when the largest Youden index was reached for CA19-9, CA125 and CEA were 36.9 U/ml (sensitivity = 51.9%, specificity = 89.8%), 13.5 U/ml (sensitivity = 54.5%, specificity = 73.0%) and 5.3 ng/l (sensitivity = 25.2%, specificity = 94.2%), respectively. We used these values as new cut-off values.

The baseline clinical data and pathological features were analysed according to the new cut-off values (Table 2, Table 3). Of all regularly used serum biomarkers, CA19-9 was the best in identifying invasive IPMN. CA125 and CEA also showed efficacy in distinguishing between malignant and benign IPMNs with the new cut-off values ($p < 0.001$). In addition, CA125 was more likely to be elevated in female patients than in male patients (39.6% vs 29.0%, $p = 0.037$).

Table 3. Characteristics of IPMN patients stratified by CEA

variables	CEA ≤ 5.3 ng/l	CEA□5.3 ng/l	P Value
Age, n(%),y			0.248
< 60	111(33.3%)	12(25.0%)	
≥ 60	222(66.7%)	36(75.0%)	
Sex, (n%)			0.978
Male	188(56.5%)	27(56.3%)	
Female	145(43.5%)	21(43.8%)	
Location, (n%)			0.238
Head	197(64.6%)	31(73.8%)	
Body and tail	108(35.4%)	11(26.2%)	
Tumour grade, (n%)			<0.001
Low and Moderate	231(69.4%)	16(33.3%)	
High and Carcinoma	102(30.6%)	32(66.7%)	
Vascular invasion, (n%)			0.176
No	162(98.2%)	22(91.7%)	
Yes	3(1.8%)	2(8.3%)	
Perineural infiltration, (n%)			0.050
No	159(95.8%)	20(83.3%)	
Yes	7(4.2%)	4(16.7%)	

Combination Of Ca19-9 With Ca125 Or Cea

To improve diagnostic indices and better recognize malignant IPMNs, attempts had been made to combine CA19-9 with CA125 or CEA. The combination of CA19-9 and CA125 (CA19-9 > 37 U/ml or CA125 > 35 U/ml) improved the diagnostic indices (Table 4). Other combination methods, however, failed to improve the diagnostic accuracy and did not show an overall superiority over usage of CA19-9 alone.

Table 4
Diagnostic indices for CA19-9, CA125, CEA and their combination

	CA19-9	CA125	CA125	CEA	CA19-9 and/or CA125 positive	CA19-9 and/or CA125 positive	CA19-9 and/or CEA positive
Cut-off value	37U/mL	35U/mL	13.5U/mL	5.3ng/l	37U/mL & 13.5U/mL	37U/mL & 35U/mL	37U/mL & 5.3ng/l
Sensitivity	51.9%	5.2%	45.5%	25.2%	69.4%	53.0%	60.0%
Specificity	89.8%	99.6%	73.0%	94.3%	68.2%	90.1%	84.9%
Positive predictive value	73.7%	87.5%	48.0%	70.8%	54.7%	74.7%	68.6%
Negative predictive value	77.1%	65.7%	70.9%	69.7%	79.8%	77.6%	79.4%
Accuracy	76.3%	66.1%	63.2%	69.8%	68.6%	76.9%	76.1%

The combination of CA19-9 and CA125 (CA19-9 > 37 U/ml and CEA > 35 U/ml) had the best positive predictive value of 74.7%, and the combination of CA19-9 and CA125 with the new cut-off values (CA19-9 > 37 U/ml or CA125 > 13.5 U/ml) had the best negative predictive value of 79.8%. Considering the hazard of malignant pancreatic lesions and the unsatisfactory sensitivity of CA19-9, the combination of CA19-9 and CA125 (CA19-9 > 37 U/ml or CA125 > 13.5 U/ml) had clinical benefit for identifying invasive IPMN without compromising other indices too much.

Efficacy of CA125 and CEA in identifying invasive IPMN in the CA19-9-negative subgroup

The sensitivity of CA19-9 in predicting malignant IPMNs was 51.9%, which means that nearly half of invasive IPMNs cannot be distinguished by CA19-9. Therefore, it is necessary to find biomarkers to assist in predicting invasive IPMN in CA19-9-negative patients.

Concerning CA19-9-negative IPMN patients, 35.4% of the malignant subgroup patients had elevated serum CA125 levels, whereas 24.5% of the benign subgroup patients had elevated serum CA125 levels (cut-off value = 13.5 U/ml, Figure 3). A total of 16.9% of the malignant subgroup patients had elevated serum CEA levels, and 5.4% of the benign subgroup patients had elevated serum CEA levels (cut-off value = 5.3 ng/l, Figure 3). Total serum CA125 levels and serum CEA levels were associated with the invasiveness of IPMNs. The average serum level of CA125 was 14.08 U/ml in the malignant subgroup and 11.27 U/ml in the benign subgroup ($p = 0.011$). The average level of CEA was 4.11 ng/l in the malignant subgroup and 2.63 ng/l in the benign subgroup without statistical significance ($p = 0.183$).

ROC curves were generated to show the efficacy of CEA and CA125 in recognizing invasive IPMNs in CA19-9-negative patients (Figure 4). The AUC of CA125 was 0.596 with a p value of 0.019. The AUC of CEA was 0.531 with a p value of 0.447. Therefore, CA125 was superior to CEA in predicting CA19-9-negative invasive IPMNs.

Discussion

In this retrospective study, we analysed serum biomarkers in 381 IPMN patients to evaluate the correlations between biomarkers and pathological characteristics and baseline characteristics, thus providing an optimum biomarker panel for predicting the malignant potentiality and invasive behaviours of IPMNs.

CA19-9, also known as sialyl Lewis a, is a well-known serologic biomarker of pancreatic diseases and indicator of aberrant glycosylation[10]. CA19-9 is widely applied in predicting the malignancy of various kinds of pancreatic oncologic lesions, such as pancreatic ductal adenocarcinoma[11] and pancreatic mucinous cystic neoplasms[12]. CA125, also known as MUC16, is involved in cell signalling through the phosphorylation of its C-terminal domain and has a potential prometastatic role in cancer cells[13]. CA125 is a membrane-spanning mucin and is mostly used to detect the incidence and assess the therapeutic response of epithelial ovarian cancer with the cut-off value of 35 U/ml[14]. Hence in tumorous lesions of other organs, the cut-off value of CA125 should be readjusted. CEA was first extracted from colon cancer and has been widely used in the diagnosis of gastrointestinal neoplasms[15,16].

Our study focused on CA19-9, CA125 and CEA and revealed that patients with malignant IPMNs had higher serum CA19-9, CA125 and CEA levels. CA19-9 is the best regularly tested serum biomarker when used to detect malignant IPMNs. Moreover, CA19-9 elevation was able to predict vascular invasion and perineural infiltration. Recently, it was reported that CA19-9 is not merely a biomarker but also a culprit in pancreatic disease, and CA19-9 promotes pancreatitis and pancreatic tumourigenesis[17]. CA19-9 is also correlated with worse overall survival and disease-free survival in IPMN[18]. Therefore, we infer that CA19-9 elevation not only indicates the malignancy of IPMNs but also contributes to the development of IPMNs into more invasive pathological subtypes.

As mentioned before, false positives and false negatives have restrained the efficacy of CA19-9 in clinical practice. Previous studies have investigated the efficacy of CA19-9 in distinguishing malignant and benign IPMNs, and the sensitivity of CA19-9 ranged from 40.8–74.0%[18,19], which means that CA19-9 is limited because of its considerable false negative rate. The unsatisfactory sensitivity of CA19-9 can be partially attributed to the heterogeneity of the Lewis blood group. Approximately 5%-7% of the population belongs to the Lewis^{a-b-} subgroup and has defects in synthesizing sialyl Lewis a, i.e., CA19-9. CA19-9 negativity may be caused by the absence of some enzymes and some types of metabolic disorders. For example, patients with FUT3 deficiency are not able to synthesize CA19-9, patients with overexpressed

FUT2 will consume the substrate for CA19-9 synthesis, and patients with secretor 21 deficiency are not able to secrete CA19-9 into serum[20].

Nonetheless, CA19-9 is the best biomarker for recognizing malignant IPMNs, but its limitations require the assistance of other biomarkers in clinical practice. Our study reveals that when combined with CA19-9, CA125 could increase the efficacy of predicting IPMN malignancy. The application of CEA in distinguishing benign and invasive IPMNs of the pancreas is less than satisfactory, and the combination of CEA and CA19-9 has no promotion of diagnostic value.[19] These conclusions were supported by our study. We readjusted the CA125 cut-off value according to the ROC curve and demonstrated that CA125 is superior to CEA in assisting CA19-9 in predicting malignant IPMNs. The combination of CA125 and CA19-9 improved the sensitivity to recognize invasive IPMNs. In addition, in CA19-9-negative patients, serum CA125 levels were significantly elevated in the carcinoma subgroup, whereas CEA levels were not.

Another major challenge of CA19-9 is the false positivity rate. Conditions of inflammation and nonpancreatic cancer are also accompanied by CA19-9 elevation, and efforts have been made to find more accurate serum metabolites[21]. Cholestasis and cholangitis are closely associated with CA19-9 elevation as well. Because CA19-9 is also excreted by normal biliary epithelial cells, CA19-9 has a significantly higher serum level in patients with bile tract obstruction[22]. Nonetheless, the reported specificity of CA19-9 in distinguishing IPMNs with invasiveness ranges from 84.5–85.9%[19,18], which means false positivity is not the major limitation of the clinical application of CA19-9. Nevertheless, it is valuable to adjust the cut-off values of CA19-9 according to patients' serum bilirubin levels to improve the efficacy of CA19-9. Multivariate analysis including serum bilirubin level and other factors is needed in future studies.

Our research has the strength of solely focusing on pathologically diagnosed IPMN patients, which makes our study more homogenous. In addition, we included 381 IPMN patients in our study, which is comparatively large and makes our results more convincing. Moreover, we separately analysed the serological biomarkers in patients with CA19-9-negative IPMNs to show the significance of CA125 in these patients. To the best of our knowledge, no previous study has demonstrated that CA125 can supplement CA19-9 in recognizing invasive IPMNs of the pancreas. The primary limitation of our study is that it is a surgical cohort. Besides, we did not match serological biomarkers with bilirubin levels and morphological subtypes. Different morphological subtypes of IPMNs have different biological behaviours, and patients with main ductal IPMN have a higher risk of malignancy[23]. Morphological subtypes are mainly detected by CT or MRI; therefore, radiological methods cannot be omitted in the preoperative assessment of IPMN malignancy. Additionally, it has been reported that CA19-9 is also correlated with worse overall survival and disease-free survival in IPMN[18], but there were no data on survival in our study.

In conclusion, our study demonstrated that CA19-9 is the best serological biomarker to predict IPMN malignancy, and CA125 contributes to helping CA19-9 distinguish histological subtypes of IPMN in Lewis-negative patients.

Abbreviations

AUC
areas under the curve
CA125
Carbohydrate antigen 125
CA19-9
Carbohydrate antigen 19-9
CEA
carcinoembryonic antigen
CT
cross-sectional computerized tomography
EUS
endoscopic ultrasonography
IAP
The International Association of Pancreatology
IPMN
intraductal papillary mucinous neoplasm
MRI
magnetic resonance imaging
ROC
receiver operating characteristic

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Board of Shanghai Cancer Center, Fudan University, and all patients involved in this study provided informed consent for the use of their personal data for research purposes.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests in this section.

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Authors' contributions

Conceptualization and Funding acquisition: Xianjun Yu and Chen Liu. Project Administration and Supervision: He Cheng. Validation: He Cheng, Yusheng Chen and Xuan Zou. Visualization: Yu Liu, Ruijie Wang, Shengming Deng and Xuan Lin. Writing - original draft: Yunzhen Qian and Yitao Gong. Writing – review editing: Xu Wang and Guopei Luo.

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References

1. Conlon KC. Intraductal papillary mucinous tumors of the pancreas. J Clin Oncol. 2005;23(20):4518–23. doi:10.1200/JCO.2005.22.517.
2. Stark A, Donahue TR, Reber HA, Joe Hines O. Pancreatic cyst disease a review. JAMA - J Am Med Assoc. 2016;315(17):1882–93. doi:10.1001/jama.2016.4690.
3. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6(1-2):17–32. doi:10.1159/000090023.
4. Werner J, Fritz S, Büchler MW. Intraductal papillary mucinous neoplasms of the pancreas - A surgical disease. Nat Rev Gastroenterol Hepatol. 2012;9(5):253–9. doi:10.1038/nrgastro.2012.31.
5. Pulvirenti A, Margonis GA, Morales-Oyarvide V, et al. Intraductal Papillary Mucinous Neoplasms. *Ann Surg*. 2019;Publish Ah(Xx):1-8. doi:10.1097/sla.0000000000003703.
6. Tanaka M. Controversies in the management of pancreatic IPMN. Nat Rev Gastroenterol Hepatol. 2011;8(1):56–60. doi:10.1038/nrgastro.2010.193.
7. Kim H, Kang KN, Shin YS, et al. Biomarker panel for the diagnosis of pancreatic ductal adenocarcinoma. Cancers (Basel). 2020;12(6):1–11. doi:10.3390/cancers12061443.
8. Luo G, Liu C, Guo M, et al. Potential Biomarkers in Lewis Negative Patients With Pancreatic Cancer. Ann Surg. 2017;265(4):800–5. doi:10.1097/SLA.0000000000001741.

9. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76(2):182–8. doi:10.1111/his.13975.
10. Liu C, Guopei L, Xianjun Y. Roles of CA19-9 in pancreatic cancer: biomarker, predictor and promoter. *BBA - Rev Cancer*. 2020.
11. Tanday S. Biomarkers in blood could help to detect pancreatic cancer. Lancet Oncol. 2014;15(3):e108. doi:10.1016/s1470-2045(14)70033-6.
12. Postlewait LM, Ethun CG, Mcinnis MR, et al. Association of preoperative risk factors with malignancy in pancreatic mucinous cystic neoplasms a multicenter study. JAMA Surg. 2017;152(1):19–25. doi:10.1001/jamasurg.2016.3598.
13. Felder M, Kapur A, Gonzalez-Bosquet J, et al. MUC16 (CA125): Tumor biomarker to cancer therapy, a work in progress. Mol Cancer. 2014;13(1):1–15. doi:10.1186/1476-4598-13-129.
14. Henderson JT, Webber EM, Sawaya GF. Screening for ovarian cancer updated evidence report and systematic review for the US preventive services task force. JAMA - J Am Med Assoc. 2018;319(6):595–606. doi:10.1001/jama.2017.21421.
15. Gold P. Carcinoembryonic Antigen Medicine among the Managers. *Br Mediacal J*. 1972; (September):600–601.
16. McDermott U, Longley DB, Johnston PG. Molecular and biochemical markers in colorectal cancer. *Ann Oncol*. 2002;13(SUPPL. 4):235-245. doi:10.1093/annonc/mdf665.
17. Engle DD, Tiriac H, Rivera KD, et al. The glycan CA19-9 promotes pancreatitis and pancreatic cancer in mice. Science. 2019;364(6446):1156–62. doi:10.1126/science.aaw3145.
18. Ciprani D, Morales-Oyarvide V, Qadan M, et al. An elevated CA 19-9 is associated with invasive cancer and worse survival in IPMN. Pancreatology. 2020;20(4):729–35. doi:10.1016/j.pan.2020.04.002.
19. Fritz S, Hackert T, Hinz U, Hartwig W, Büchler MW, Werner J. Role of serum carbohydrate antigen 19-9 and carcinoembryonic antigen in distinguishing between benign and invasive intraductal papillary mucinous neoplasm of the pancreas. Br J Surg. 2011;98(1):104–10. doi:10.1002/bjs.7280.
20. Guo M, Luo G, Lu R, et al. Distribution of Lewis and Secretor polymorphisms and corresponding CA19-9 antigen expression in a Chinese population. FEBS Open Bio. 2017;7(11):1660–71. doi:10.1002/2211-5463.12278.
21. Mayerle J, Kalthoff H, Reszka R, et al. Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis. Gut. 2018;67(1):128–37. doi:10.1136/gutjnl-2016-312432.
22. Kim HJ, Kim MH, Myung SJ, et al. A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: Analysis using a receiver operating characteristic curve. Am J Gastroenterol. 1999;94(7):1941–6. doi:10.1111/j.1572-0241.1999.01234.x.
23. Salvia R. Differences between main-duct and branch-duct intraductal papillary mucinous neoplasms of the pancreas. World J Gastrointest Surg. 2010;2(10):342. doi:10.4240/wjgs.v2.i10.342.

Figures

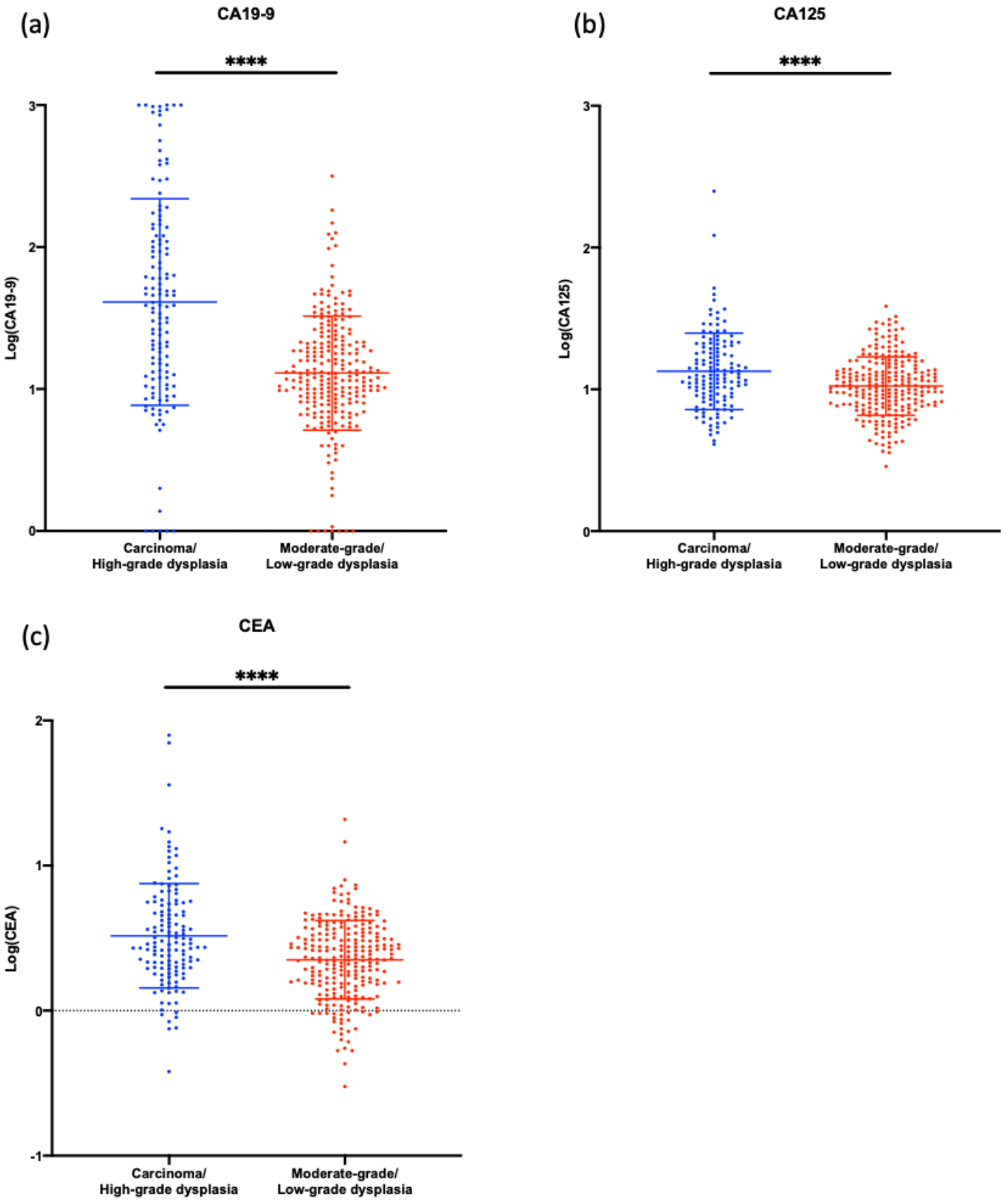

Figure 1

Serum levels of CA19-9, CA125 and CEA in relation to histological grade of IPMN. Comparisons between different histological grades of IPMN in CA19-9 levels (a), CA125 levels (b), and CEA levels (c). ****: $p < 0.0001$, P values derived from Students' t test. Abbreviations: CA19-9 Carbohydrate antigen 19-9, CA125

Carbohydrate antigen 125, CEA carcinoembryonic antigen, IPMN intraductal papillary mucinous neoplasm.

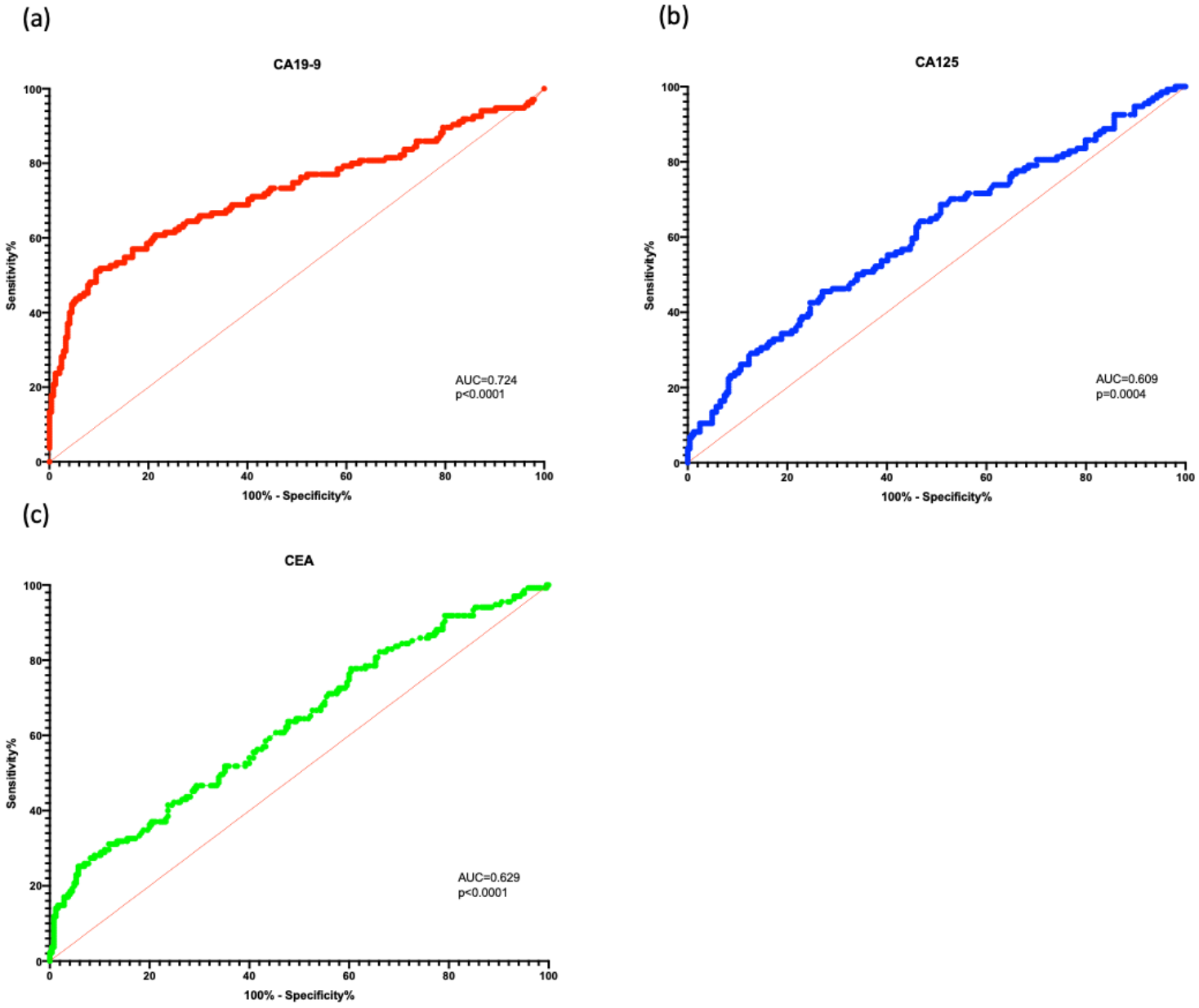

Figure 2

Receiver operating characteristic curves for serum levels of CA19-9, CA125 and CEA Receiver operating characteristic curves of CA19-9 (a), CA125 (b) and CEA (c) for predicting malignant IPMNs. Abbreviations: AUC area under curve, CA19-9 Carbohydrate antigen 19-9, CA125 Carbohydrate antigen 125, CEA carcinoembryonic antigen, IPMN intraductal papillary mucinous neoplasm.

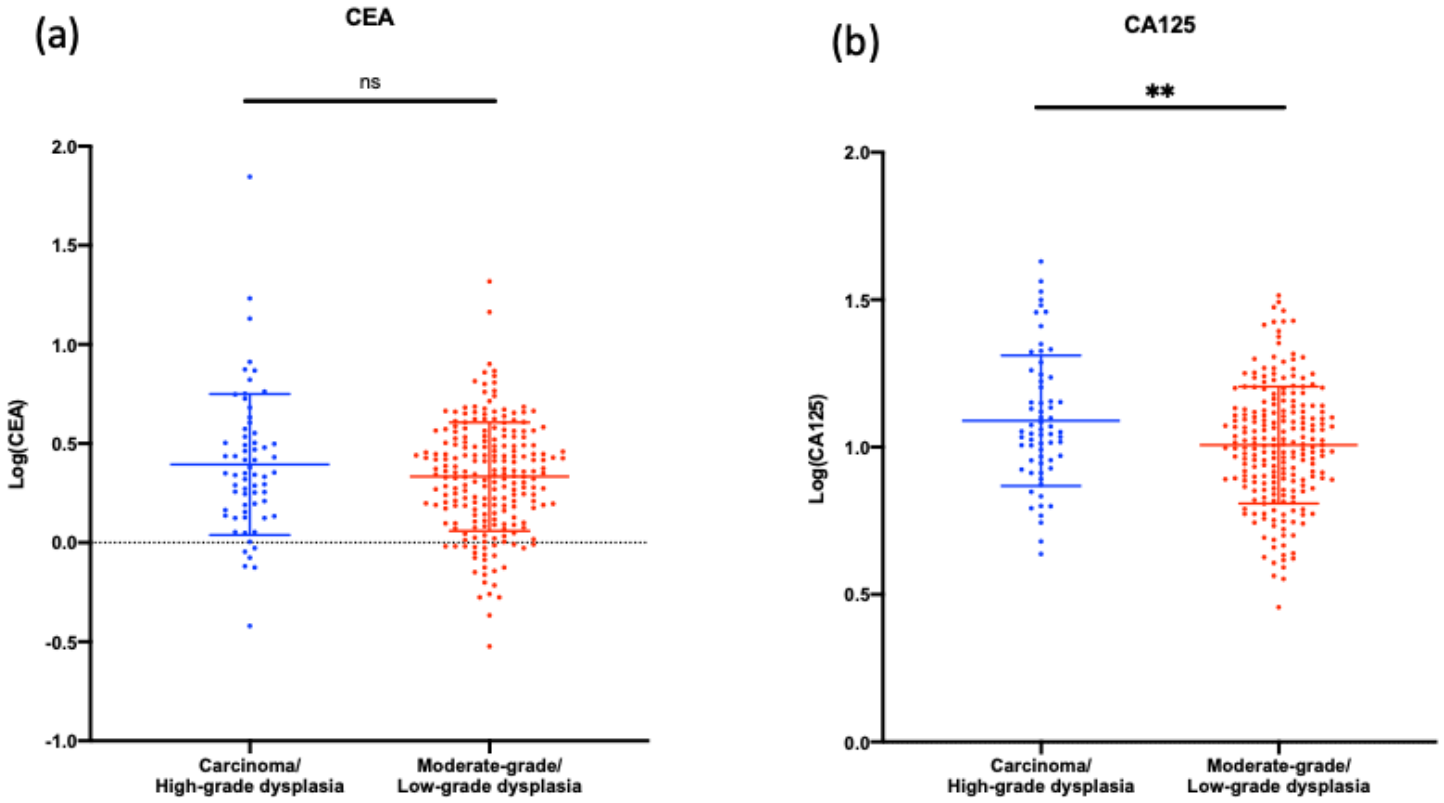

Figure 3

Serum levels of CA125 and CEA in relation to histological grade of IPMN in CA19-9 negative patients Comparisons between different histological grades of IPMN without CA19-9 elevation in CEA levels (a) and CA125 levels (b). **: p < 0.01, ns: not significant, P values derived from Students' t test. Abbreviations: CA19-9 Carbohydrate antigen 19-9, CA125 Carbohydrate antigen 125, CEA carcinoembryonic antigen, IPMN intraductal papillary mucinous neoplasm.

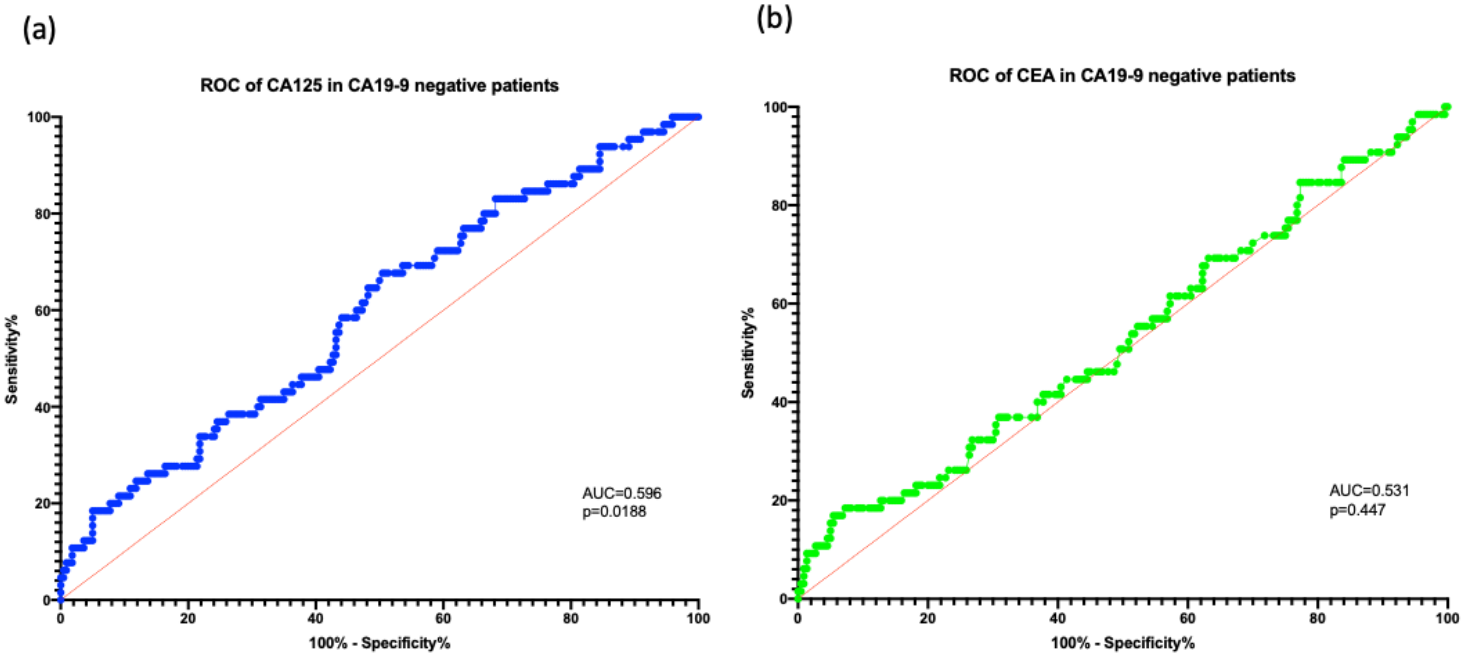

Figure 4

Receiver operating characteristic curves for CA125 and CEA in CA19-9 negative patients Receiver operating characteristic curves of CA125 (a) and CEA (b) for predicting malignant IPMNs in CA19-9-negative patients. Abbreviations: AUC area under curve, CA19-9 Carbohydrate antigen 19-9, CA125 Carbohydrate antigen 125, CEA carcinoembryonic antigen, IPMN intraductal papillary mucinous neoplasm, ROC receiver operating characteristic curves.