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Nomogram to predict malignancy in branch duct type intraductal papillary mucinous neoplasms

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Abstract

Prediction of malignancy in branch duct (BD)-type intraductal papillary mucinous neoplasms (BD-IPMNs) is difficult. In this retrospective study, we showed the performance of imaging biomarker and biochemical biomarker in identifying the malignant BD-IPMNs. A total of 97 patients with pathological proved BD-IPMNs were included in this study. Imaging data were collected from magnetic resonance imaging (MRI). Malignant BD-IPMNs were defined as those with high grade dysplasia and invasive carcinoma. There were 10 patients with malignant BD-IPMNs (10.3%). Significant difference was found in prevalence of mural nodule and tumor size >3.0 cm between patients with and without malignant BD-IPMNs (44.4% vs 3.1%, $P < .01$; 80.0% vs 33.3%, $P < .01$). Significant differences were observed in mural nodule and elevated carbohydrate antigen 19-9 (CA19-9) between patients with and without invasive carcinoma (40.0% vs 7.6, $P = .05$; 60% vs 15.3%, $P = .04$). Mural nodule and tumor size >3.0 cm were the independent associated factor for malignant BD-IPMNs. The odds ratio (OR) was 5.22 (95% confidence interval [CI]: 1.04–31.16) for mural nodule and was 6.80 (95% CI: 1.16–39.71) for cyst size >3.0 cm. The combined model of mural nodule and tumor size showed good performance in identifying malignant BD-IPMNs (area under the curve [AUC] = 0.82, 95%CI: 0.67–0.97). Our data show that mural nodule and cystic size can be used as predictor of malignancy in BD-IPMN. The predictive performance is acceptable.

Abbreviations: AUC = area under the curve, BD = branch duct, CA19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, CI = confidence interval, IPMN = intraductal papillary mucinous neoplasms, MD = main duct, MPD = main pancreatic duct, MRI = magnetic resonance imaging, MT = mixed type, OR = odds ratio, ROC = receiver operating characteristic.

Keywords: intraductal papillary mucinous neoplasms, invasive carcinoma, malignancy, mural nodule

1. Introduction

Intraductal papillary mucinous neoplasms (IPMNs) are 1 of pancreatic cystic lesions. The detection rate of IPMNs has increased due to widely use of cross-sectional imaging.[1,2] IPMNs have malignant potentials. More than 40% of IPMNs may have malignant features, including high-grade dysplasia or invasive carcinoma.[3] Based on the presence or absence of main pancreatic duct (MPD) involvement, IPMNs are divided into 3 types: main duct (MD), branch duct (BD), and mixed type (MT). MD-IPMN is less common but had higher risk of malignancy than BD-IPMNs.[4] Surgical resection is usually recommended for IPMN with MPD involvement because the high incidence of malignancy.[5] However, the treatment strategies for BD-IPMNs have not totally answered.[6] It would be valuable to identify potential biomarkers for malignancy in BD-IPMNs.

High-risk stigmata and worrisome features, such as diameter of MPD and presence of mural nodule (>5.0 mm), have been used to identify or predict malignant IPMNs.[7] In addition, tumor biomarkers, such as carbohydrate antigen 19-9 (CA19-9)[8–10] and carcinoembryonic antigen (CEA),[8,9] also showed acceptable performance in predicting malignancy in IPMNs. However, those studies did not separately analyze the role of above biomarkers in MPD involved IPMNs and BD-IPMNs. Few studies compare the performance of those biomarkers in identifying malignant IPMNs. Only 1 recent study showed that MD dilatation is the best predictor of malignant IPMNs.[11]

Although the associated factors for malignancy in IPMNs have been reported, few studies have identified associated factors for malignancy in BD-IPMNs.[12–15] Hwang et al[13] showed mural nodule and size of cyst were independent associated factors. Oyama et al[14] showed that size of IPMN and diameter of the MPD were associated with the incidence of carcinoma at follow-up. Different biomarkers were identified in these studies and conflict results were reported. Recent 2 meta analysis showed that tumor markers and imaging features were all valid.[16,17] However, they did not compare the performance of those biomarkers in identifying malignancy in BD-IPMNs.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Moreover, MT IPMNs may be also included in these studies. One study also developed nomogram model for the differentiation of malignant BD-IPMNs based on age, cyst size, duct dilatation, mural nodule, serum CA19-9, and CEA.[18] This model looks complicated. A model based on simple parameters is welcome for clinical use. However, the performance of nomogram based on a few associated factors is still unclear. In the current study, we showed the performance of CA19-9, CEA, cyst size, MPD diameter and presence of mural nodule in identifying malignant BD-IPMNs. We also developed a simple nomogram model to identify malignant BD-IPMNs based on the predominant associated factors.

2. Materials and Methods

2.1. Patients

We searched the medical database of our institutions. There were 185 patients with histological proven IPMNs during 2011 to 2020. After excluding MD and MT IPMN (n = 88), a total of 97 patients with BD-IPMNs were included in this study. All patients had magnetic resonance imaging (MRI) data. We also collected the clinical information, such as preoperative symptoms and tumor biomarkers (serum CA19-9) and serum CEA, and pathological features from medical records. The medical history of pancreatitis, diabetes and fasting plasma glucose levels were also harvested from medical records. This retrospective study was approved by the Institutional Ethic Review Board of Hangzhou Xiaoshan Hospital of Traditional Chinese Medicine and informed consent was waived because this was a retrospective study.

2.2. MRI examinations

Contrast enhanced MRI scans of the abdomen and pelvis were performed using the following machines: Siemens Magnetom Avanto 1.5Tesla (Germany) and Philips Ingenia 3Tesla scanner (the Netherlands). Gadopentetate dimeglumine (Magnevist, Bayer Healthcare) was used as contrast-agent (injection rate of 2 mL/s). MR cholangiopancreatography was also performed using the following parameters: TR 1800 ms; TE 642 ms; FOV 375 × 100 mm^2; Slice thickness 1 mm for Siemens machine; TR 2560 ms; TE 740 ms; FOV 250 × 231 mm^2; slice thickness 0.47 mm for 3.0T Fillips machine. The following imaging information was collected: tumor location (head-neck or body-tail), cyst size, MPD diameter, presence or absence of mural nodule (contrast-enhanced solid component). If the lesion is large, the location is evaluated based on the center of the cyst. If there were multiple lesions, the location and the size were evaluated based on the largest cyst. BD IPMN was defined when the lesions communicated with MPD. All the MRI images were re-reviewed blindly by a dedicated abdominal radiologist.

2.3. Histological examinations

The histological evaluation of BD-IPMN was based on the World Health Organization guidelines. BD-IPMN was divided into 3 grade: low-intermediate dysplasia, high-grade dysplasia, and invasive carcinoma. The lesions with high grade dysplasia and invasive carcinoma were regarded as malignant BD-IPMNs. We also collected the histological information of lymph node metastasis (yes vs no) and peripancreatic extension (organs invasion and vascular invasion).

2.4. Statistics

Data analysis was performed with SPSS16.0 (Chicago, III, USA). Data was shown as mean ± standard deviation (continuous data) or number (qualitative data). Continuous data were evaluated by Independent-sample *t* test or Mann–Whitney *U* test (MPD diameter, CEA and Ca19-9). Qualitative data were analyzed by Chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curves were used to show the performance of cyst diameter, MPD diameter, CA19-9, CEA and mural node in predicting malignant IPMN and invasive carcinoma were evaluated through calculation of the area under the curve (AUC) using ROC curve analysis. Subsequently, univariable and multivariable logistic regression analyses were performed to identify associated factor for malignant IPMNs. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated. Based on the identified associated factors, we developed a nomgram to predict malignancy in IPMNs. Two-sided *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of patients with malignant and nonmalignant BD-IPMNs

Patient clinicopathological features are shown in Table 1. There were 10 patients with malignant BD-IPMN (10.3%). Significant difference was found in mural node and cystic size between patients with and without malignant BD-IPMNs (44.4% vs 3.1%, $P < .01$; 80.0% vs 33.3%, $P < .01$). The glucose level of patients with malignant BD-IPMN was slightly lower than that in nonmalignant 1 ($P = .09$). For other variables, such as age, tumor size, MPD diameter, CA19-9 and CEA levels, no significant differences were found. Mural node and cystic size were 2 important factors for malignancy in BD-IPMNs.

3.2. Characteristics of patients with and without invasive carcinoma

Subsequently, we analyzed the clinicopathological features in BD-IPMN patients with and without invasive carcinoma (Table 2). The incidence of invasive carcinoma was 5.2%. No significant differences were observed in age, gender, tumor size, MPD diameter, and CEA levels between patients with and without invasive carcinoma. The glucose level of patients with invasive carcinoma was slightly lower than that in noninvasive carcinoma, but no significant difference was found. Obvious difference was found in mural node and elevated CA19-9 levels between patients with and without invasive carcinoma (40.0% vs 7.6%, $P = .055$; 60% vs 15.3%, $P = .04$). Mural node and elevated CA19-9 levels were the 2 important factors for invasive carcinoma in BD-IPMNs.

3.3. ROC analysis

Subsequently, ROC curve analysis was used to show the performance of serum CEA, CA19-9, size, mural node and/or pancreatic duct diameter in identifying malignant IPMNs (Fig. 1A) and invasive carcinomas (Fig. 1B). Cyst size had the highest performance in predicting malignant IPMNs (the AUC = 0.74, 95% CI: 0.58–0.89), followed by mural nodule (AUC = 0.67, 95% CI: 0.47–0.88) and CA19-9 (AUC = 0.62, 95% CI: 0.42–0.84) (Fig. 1A). CA19-9 also showed the highest performance in predicting invasive carcinomas, the AUC was (AUC = 0.72, 95% CI: 0.46–0.98), followed by mural nodule (AUC = 0.66, 95% CI: 0.38–0.0.95) and CEA (AUC = 0.55, 95% CI: 0.28–0.83). Cyst size, mural nodule and CA19-9 had acceptable performance in identifying malignant BD-IPMNs.

3.4. Associated factors with malignant BD-IPMNs

Next, we used univariable and multivariable logistic regression analyses to show the association between mural node

Table 1

Clinical data in malignant and nonmalignant branch duct intraductal papillary mucinous neoplasms.

	Total (n = 97)	Malignant (n = 10)	Nonmalignant (n = 87)	*P*
Age (yr)	61.80 ± 9.61	57.49 ± 12.31	62.30 ± 9.01	.14
Size (cm)	3.74 ± 2.34	4.27 ± 2.02	3.67 ± 2.38	.47
Sex(male/female)	57/40	7/3	50/37	.47
Dysplasia				
Low-intermediate grade	87	/	87	
High-grade	5	5	0	
Invasion	5	5	0	
Location				.23
Head-neck	58	6	52	
Body and tail	39	4	35	
CEA (ng/ml)	3.19 ± 1.78	2.80 ± 1.58	3.29 ± 2.63	.39
CEA > 5.0	10	1	9	.97
CA19-9 (U/ml)	42.13 ± 62.54	45.82 ± 48.06	39.86 ± 119.4	.87
>37	17	4	13	.05
MPD diameter (cm)	0.31 ± 0.14	0.28 ± 0.11	0.31 ± 0.14	.50
Glucose (mmol/L)	5.53 ± 1.41	5.26 ± 1.34	5.59 ± 1.42	.09
Pancreatitis	4	0	4	1.0
Abdominal Symptoms	42	4	38	.92
Diabetes	15	2	13	.65
Lymph node metastasis (yes vs no)	0	0	0	
Peripancreatic extension	0	0	0	
Mural nodule	9	4	5	<.01
Cyst size > 3.0 cm	37	8	29	<.01

Malignant IPMNs were defined as those with high grade dysplasia and associated invasive carcinoma.
CA 19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, MPD = main pancreatic duct.

Table 2

Clinical data in intraductal papillary mucinous neoplasms with and without invasive carcinoma.

	Invasive carcinoma (n = 5)	Noninvasive carcinoma (n = 92)	*P*
Age (yr)	61.48 ± 11.39	63.34 ± 9.04	.26
Size (cm)	4.34 ± 2.57	3.40 ± 2.21	.36
Sex(male/female)	2/3	38/54	.80
Location			.57
Head-neck	1	55	
Body and tail	4	37	
Glucose (mmol/L)	5.12 ± 1.53	5.58 ± 1.41	.48
CEA (ng/ml)	4.48 ± 3.34	2.76 ± 1.56	.028
CEA > 5.0	1	9	.43
CA19-9 (U/ml)	65.38 ± 55.43	39.11 ± 116.31	.62
>37	3	14	.037
MPD diameter (cm)	0.25 ± 0.12	0.31 ± 0.13	.33
Mural nodule	2	7	.055

CA 19-9 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, MPD = main pancreatic duct.

and malignant BD-IPMNs (Table 3) and invasive carcinoma (Table 4). Univariable and multivariable analysis both showed that mural node and cyst size were the independent associated factor for malignant BD-IPMNs. The OR was 5.22 (95% CI: 1.04–31.16) for mural nodule and was 6.80 (95% CI: 1.16–39.71) for tumor size in multivariable analysis (Table 3). CA19-9 was the only 1 independent associated factors for invasive carcinoma (Table 4). The OR was 8.25 (95%CI: 1.26–53.94) for univariable analysis and 6.57 (95% CI: 1.00–47.05) for multivariable analysis (Table 4).

3.5. Nomogram for identification of malignant BD-IPMNs

Base on the 2 independent associated factors, cyst size and mural nodule, we developed a nomogram to identify malignant BD-IPMNs (Fig. 2A). The AUC of the model was 0.82 (95%CI: 0.67–0.97). The C-index was 0.81. Bootstrap calibration with 1000 repetitions showed that our nomogram was acceptable in distinguishing malignancy from nonmalignancy (Fig. 2B). Nomogram had good performance in identifying malignant BD-IPMNs.

4. Discussion

Surgical resection is usually performed on MPD involved IPMN due to the high risk of malignant transformation. However, management of BD-IPMN has not reached a consensus. Several markers have been used to identifying the malignant BD-IPMNs, such as cyst size, MPD diameter and mural nodule.[14] In the present study, we compared the predictive performance of imaging biomarkers and biochemical biomarkers in identifying malignant IPMN and invasive carcinoma. Our data showed that cyst size and mural nodule had the highest diagnostic ability in predicting malignant BD-IPMNs. A nomogram based on the 2 imaging biomarkers showed acceptable identifying performance.

The incidence of malignant BD-IPMNs and invasive carcinoma are 10.3% and 5.2% in our population which is lower than that in MPD involved IPMNs. Previous studies also indicated that the risk of cancer in BD-IPMNs is low (1%–2%)[6,19] which was slightly lower than our data. High risk malignant IPMNs (18%) or invasive carcinoma (7.5%) was also reported in several studies.[10,20] Our data was close to the results of previous report.

Several guidelines have shown the potential predictive stigmata in identifying malignant IPMNs.[6] However, those guidelines were based on all type of IPMNs. It is not clear whether those high-risk stigmata or worrisome features are also fit for BD-IPMNs. Few studies also showed several risk factors for malignancy in BD-IPMNs, including MPD diameter, cyst size, mural nodule, and tumors biomarkers.[14,15] However, these studies did not compared the diagnostic performance of the biomarkers. Our data showed the cyst size is the best 1, followed by mural nodule. 40% of malignant BD-IPMNs had mural nodule. Interestingly, a Meta analysis also indicated that mural nodule had a good diagnostic pooled OR and AUC, and was the highly

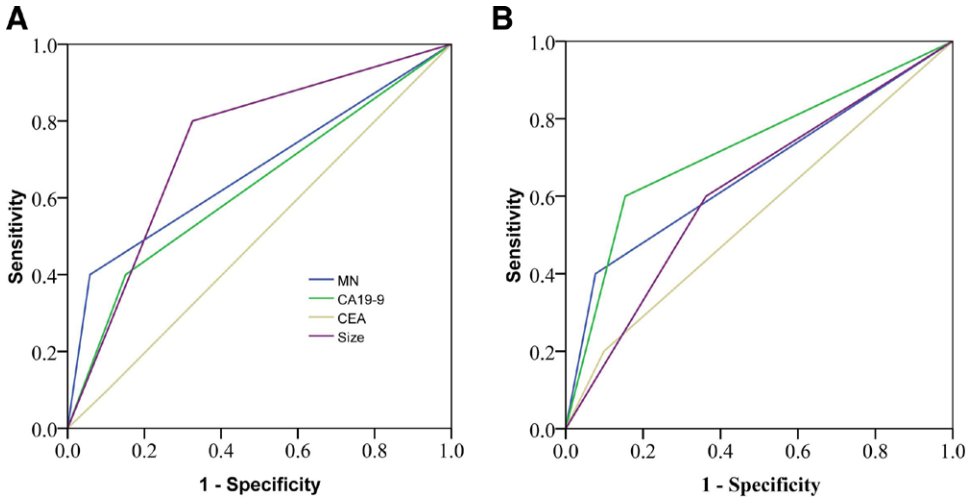

Figure 1. The receiver operating characteristic (ROC) curves of serum carbohydrate antigen 19-9 (CA19-9) level, serum carcinoembryonic antigen (CEA) levels, mural node, cyst size in predicting malignant intraductal papillary mucinous neoplasm (IPMN) (A) and invasive carcinoma (B).

Table 3

Associated factors with malignant intraductal papillary mucinous neoplasms.

	Univariable	Multivariable	
Variables	OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Age (yr)	0.95 (0.88–1.02)	0.97 (0.90–1.04)	0.93 (0.85–1.01)
Size > 3.0 cm (yes vs no)	8.00 (1.60–40.12)	7.44 (1.23–44.1)	6.80 (1.16–39.71)
MPD diameter (cm)	1.24 (0.01–170.5)	5.59 (0.01–300.2)	6.32 (0.01–316.5)
Mural node (yes vs no)	10.93 (2.31–51.73)	5.30 (1.09–32.78)	5.22 (1.04–31.16)
CA19-9 (>37 vs <37 U/ml)	3.74 (0.93–15.12)	4.42 (0.76–25.78)	3.33 (0.62–18.00)

Model 2 was additionally adjusted with diabetes.

CA 19-9 = carbohydrate antigen 19-9, CI = confidence interval, MPD = main pancreatic duct.

Table 4

Associated factors with invasive carcinoma.

	Univariable	Multivariable
Variables	**OR (95% CI)**	**OR (95% CI)**
Age (yr)	0.93 (0.83–1.05)	0.97 (0.88–1.06)
Size > 3.0 cm (yes vs no)	2.56 (0.41–16.09)	1.73 (0.19–15.62)
Mural node (yes vs no)	8.09 (1.15–56.79)	4.88 (0.46–51.86)
CA19-9 (>37 U/ml vs ≤37 U/ml)	8.25 (1.26–53.94)	6.57 (1.00–47.05)

CA 19-9 = carbohydrate antigen 19-9, CI = confidence interval.

suspicious for malignancy in BD-IPMNs.[21] Our multivariate regression analysis and ROC analysis also supported those findings. Moreover, our data also indicated that cyst size >3.0 cm is another independent predictor for malignancy in BD-IPMNs which was in accordance with previous studies.[13,14]

Few studies have identified the associated factors for invasive carcinoma of IPMN. In the present study, univariable regression analysis showed that mural nodule and elevated CA19-9 are associated factors. Multivariable analysis showed that elevated CA19-9 remained to be an independent associated factors. ROC curve also showed CA19-9 had acceptable performance (AUC = 0.72) in discriminating invasive carcinoma from IPMNs. However, further study is needed due to small sample size of invasive carcinoma.

We also developed a nomogram model to identify malignant IPMNs based on 2 main biomarkers, cyst size and presence of mural nodule. The model showed good performance with a AUC of 0.82 which is better than cyst size or mural nodule alone. Most of studies just identify associated factors of malignancy. Few studies have developed model to identify malignancy in IPMNs. Jang et al showed a nomogram model based on a large database for IPMNs.[18] Interestingly, cyst size and mural nodule were also included in their model. Other biomarkers, such as pancreatic duct diameter, CA19-9 and CEA were also included in their model. The AUC of the model with these 5 variables and age was 0.783 which was slightly lower than AUC (0.82) of our model with only 2 biomarkers. One reason may be that categorical data of cyst size was used in this study. Our study showed a more simple model than that in previous study.

There are several limitations in our study. First, the sample size of BD-IPMNs is small because IPMNs are rare disease, especially for malignant IPMNs and invasive carcinoma. The generalization of our results should be confirmed by a study with large sample size. Second, our study is a retrospective study and selection bias cannot be avoided. Third, it would be better to perform a follow-up study in patients with surveillance.

In conclusion, our data show that the prevalence of malignancy and invasive carcinoma in BD-IPMNs is 10.3% and 5.2%, respectively. Cyst size and mural nodule are the dominant predictor for identifying malignant BD-IPMNs. CA19-9 may be also a valuable biomarker for identifying invasive carcinoma of IPMN. Moreover, we developed a nomogram model to identify malignant BD-IPMNs using only 2 biomarkers which showed better performance than models previous published.

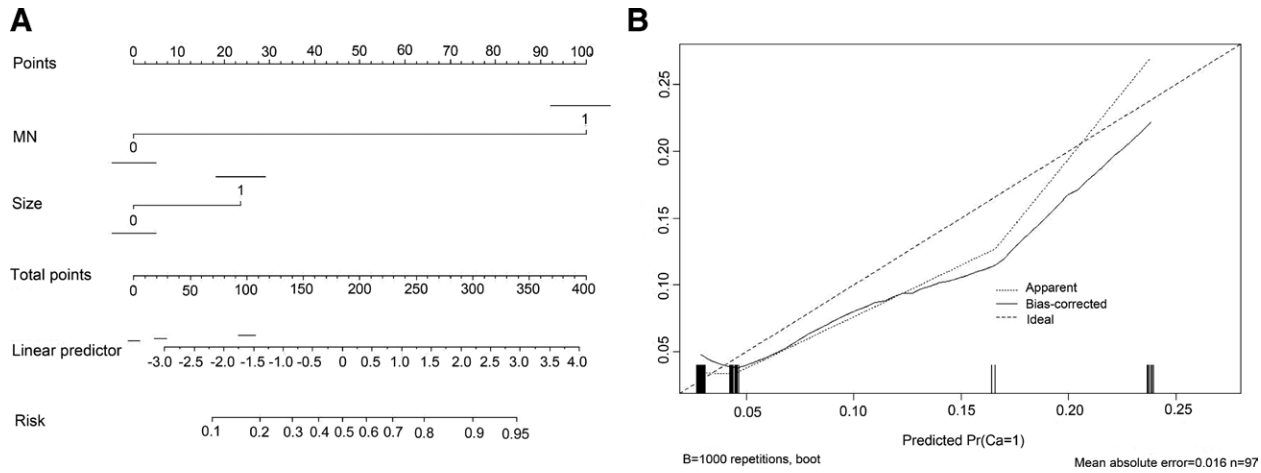

Figure 2. The nomogram to identify malignant intraductal papillary mucinous neoplasm (IPMN) (A) and the calibrate curve (B).

Author contributions

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