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Evaluating Utility of Scoring System to Predict Malignancy and Invasiveness of Intraductal Papillary Mucinous Neoplasms of the Pancreas at a Single Center

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Abstract

Background: The management of pancreatic intraductal papillary mucinous neoplasia (IPMN) is dependent on their risk of malignant progression to invasive IPMN. Recently a 5- point scoring system has been proposed as a useful clinical tool to predict the malignancy of IPMNs; however, this tool has not been validated. Here, we investigate the ability of the 5 point scoring system to predict malignancy in patients with IPMNs who had surgical resection of their IPMNs.

Methods: A total of 179 patients underwent pancreatic resection for IPMN from 1998 to 2011 at our institute. Data was entered prospectively. Following review of scoring system from Shin et al. [4] (World J Surg 2010), primary data extracted from the database included the following information for each patient: age, presence of mural nodule, MPD dilation, CA19-9, history of pancreatitis, tumor size, duct communication (side, main, or mixed), and final pathology reports. This scoring system uses five independent variables: the presence of mural nodules, MPD diameter >6 mm, CA 19-9 >37 U/mL, history of pancreatitis, and age ≥60 years. One point was given to each variable. Validation of the scoring system was performed using a ROC analysis.

Results: Records of 98 patients included all five variables. Analysis showed that a cut-off of 3 points had the highest discriminating power. The associated risk ratio (RR) was 3.13 (95% CI: 1.51-6.49) and could predict IPMN malignancy with a sensitivity of 73.2% and a specificity of 80.7% (AUC: 0.81, 95% CI: 0.73-0.89). Additional analysis performed on side-branch variant of IPMN and mixed type (71 cases) for the cut-off of 3 points also showed the highest discrimination in predicting malignancy in IPMN. The RR was 6.49 (95% CI: 2.41-17.7) with a sensitivity of 84.6% and specificity of 86.7% (AUC: 0.90, 95% CI: 0.82-0.96).

Conclusion: The 5-point scoring system described by Shin et al. [4] was successfully validated and can be used to reliably predict malignancy in IPMN in both main branch and side/mixed cases of IPMN. This scoring system may assist clinicians in predicting malignancy in the preoperative patient with IPMN and is especially useful with the side branch and mixed variant.

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Introduction

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas have been increasing in recognition across the world.[1] IPMN is characterized by cystic dilation of the pancreatic ducts, involving either the main pancreatic duct or its branches or both, due to copious production of mucin by papillary epithelium [1]. Unregulated, intraductal proliferation continues and results in the formation of a clinically and macroscopically detectable mass. IPMNs include a wide spectrum of malignant potential, ranging from low-grade, moderate, and high-grade dysplasia to invasive adenocarcinoma [2]. The progression of non-invasive IPMN to invasive IPMN as well as the need for conservative versus surgical therapy is determined by the grading of IPMN. Therefore, it is imperative to pre-operatively classify these tumors by their malignant potential. Studies have been done in Asia identifying several preoperative risk factors, such as age, presence of mural nodule,

Table 1: Demographic profiles of the patients included in the study and value coding for the scoring system.

Variable	All patients (n=98)	Score Coding
Gender		
Male	46 (47%)	
Female	52 (53%)	
Age		
<60	20 (20%)	0
>=60	78 (80%)	1
Pancreatitis		
No	45 (46%)	0
Yes	53 (54%)	1
MPD diameter (mm)		
<=6	57 (58%)	0
>6	41 (42%)	1
Mural nodules		
No	94 (86%)	0
Yes	4 (12%)	1
CA-19-9 (U/mL)		
<=37	57 (58%)	0
>37	41 (42%)	1
Duct type		
Branch	27 (38%)	0
Main/mixed	71 (62%)	1
Diagnosis		
Invasive	41 (42%)	
Benign	57 (58%)	

Table 2: Comparison of surgical pathology with 5-point scoring system.

Score	Benign (n = 57)	Malignant (n = 41)	Risk ratio of carcinoma	95% C.I.
0	6	0	0	-
1	20	3	0.21	0.07-0.66
2	20	8	0.56	0.27-1.14
3	8	18	3.13	1.51-6.49
4	3	12	5.56	1.68-18.46
5	0	0	-	-

elevated CA 19-9, tumor size, etc. and have applied them into scoring systems [3-7]. Among all the scoring systems, the most widely used has been the model by Shin et al. [4]. However, external validation of the scoring system in an independent sample of IPMN patients has not been performed which is very important to establish the reliability. Furthermore, the validation of the scoring system proposed by Shin et al. [4] has yet to be determined in Western hemisphere as the patients used in the original model primarily were in Asia. Therefore, the aim of the proposed study was to assess the external validity of IPMN scoring systems by Shin et al. [4] in a cohort of IPMN patients.

Methods

Data source

At H. Lee Moffitt Cancer Center, an IRB-approved, ongoing project has been following all patients with IPMN since 1989. This database includes several demographic, clinical, endoscopic, radiographic, and histologic features.

Table 3: Sensitivities and specificities associated with 5-point scoring system including main duct IPMN.

Score	Sensitivity	Specificity	AUC	LR+	LR-
(>= 0)	100.00%	0.00%	41.84%	1	
(>= 1)	100.00%	10.53%	47.96%	1.1176	0
(>= 2)	92.68%	45.61%	65.31%	1.7042	0.1604
(>= 3)	73.17%	80.70%	77.55%	3.7916	0.3324
(>= 4)	29.27%	94.74%	67.35%	5.561	0.7466
(> 4)	0.00%	100.00%	58.16%		1

Table 4: Sensitivities and specificities associated with 5-point scoring system excluding main duct IPMN.

Score	Sensitivity	Specificity	Classified Correctly	LR+	LR-
(>= 0)	100.00%	0.00%	36.62%	1	
(>= 1)	100.00%	13.33%	45.07%	1.1538	0
(>= 2)	100.00%	53.33%	70.42%	2.1429	0
(>= 3)	84.62%	86.67%	85.92%	6.3462	0.1775
(>= 4)	26.92%	95.56%	70.42%	6.0577	0.7648
(> 4)	0.00%	100.00%	63.38%		1

Scoring System by Shin et al. [4]

The scoring system proposed by Shin et al. [4] was proposed in 2010 which uses five variables: the presence of mural nodules, main pancreatic duct (MPD) diameter >6 mm, Carbohydrate Antigen (CA) 19-9 >37 U/mL, history of pancreatitis, and age ≥60 years. These were each found to be independent predictors of invasive IPMN. Each variable was given weight with dichotomous responses as either Yes (1 point) or No (0 points). This scoring system was chosen due to its ease of application as it uses data that will be easily accessible in outpatient setting as well as the simplicity of the scoring system overall.

Data Collection

All consecutive patients with IPMN who underwent resection between 1998 and 2011 were extracted from the surgical database at H. Lee Moffitt Cancer Center. Primary data extracted from database included: pre-operative age, gender, presence of mural nodule, MPD diameter, CA19-9, history of pancreatitis, and duct type (branch or main or both). Pathology reports of each resected specimen were also collected to determine malignancy, which we defined as adenocarcinoma. Patients were excluded if any of the variables or pathology reports were not available.

Statistical analysis

Each patient received a score, which consisted of the sum of dichotomous expressions of age, presence of mural nodule, MPD diameter, CA19-9, and history of pancreatitis. The cutoff points used to generate the dichotomous values are shown in Table 1. For each score, we measured the number of patients for whom the surgical pathology indicated malignant or benign IPMN and the associated risk ratio (RR) along with 95% confidence intervals (CI) were calculated. Finally, we performed non-parametric Receiver Operating Characteristics (ROC) analysis to identify the score with highest classification accuracy. The summary results from ROC analysis are reported as area under the curve (AUC) along with 95% CI. Additional analysis was performed for side-branch IPMN by

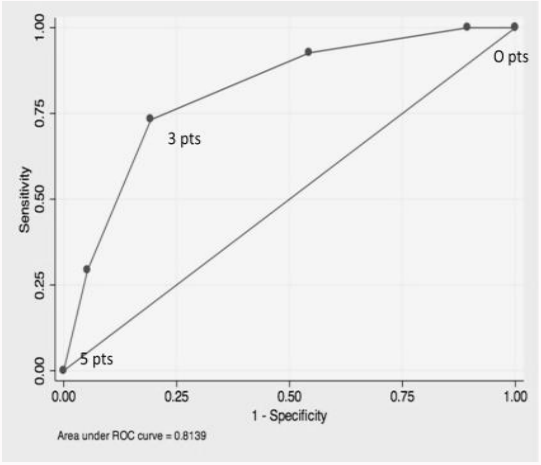

Figure 1: Receiver operating characteristics (ROC) curve for scoring system used to predict malignancy in IPMN including main duct IPMN.

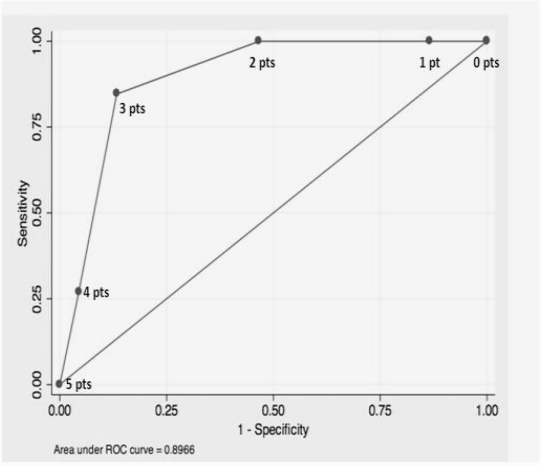

Figure 2: Receiver operating characteristics (ROC) curve for scoring system used to predict malignancy in IPMN excluding main duct IPMN.

excluding patients with main and mixed brunch type. All analyses were performed using STATA statistical analysis software.

Results

A total of 179 patients records were extracted from the database. 81 patient records were excluded because of missing values. The final dataset consisted of 98 complete patient records. Characteristics of all included patients are illustrated in Table 1. Based on the scoring system presented by Shin et al. [4] we calculated a score for each patient. Table 2 summarizes the relationship between these scores and the number of patients who were found from the surgical pathology with benign or malignant IPMN. There was a statistically significant association between higher score and increased risk for malignancy. While a score of ≤2 was not associated with malignancy (RR = 0.56; 95% CI 0.27 to 1.14), a score of 3 was associated with a statistically significant increase in risk for malignancy (RR = 3.13; 95% CI 1.51 to 6.49). Similarly, a score of 4 was also associated with a statistically significant increase in risk for malignancy (RR = 5.56; 95% CI 1.68 to 18.46). The results of ROC analysis is presented in Table 3. ROC analysis showed that a score equal to 3 was associated a sensitivity of 73.17% and specificity of 80.7%, classifying correctly 77% of the patient population. With increase in score the specificity increased to 94.74%, but the value of sensitivity decreased to 29.27% without further increase in accuracy. Therefore, the score 3 was associated with highest discriminating power to classify IPMN as malignant or benign. As shown in Figure 1, the AUC for overall performance of the scoring system was 81.39% (95% C.I. 73% to 90%) on ROC analysis. We also performed sensitivity analysis in a subgroup of patients with side-branch IPMN by excluding main duct type which consisted of 71 patients of which 26 (37%) were benign and 46 (63%) were malignant. Similar to the main analysis there was a statistically significant association between increase in score and risk for malignancy. While a score of ≤2 was not associated with malignancy (RR = 0.46; 95% CI 0.16 to 1.24), a score of 3 was associated with a statistically significant increase in risk for malignancy (RR = 6.49; 95% CI 2.41 to 17.5). Similarly, a score of 4 was also associated with a statistically significant increase in risk for malignancy (RR = 6.06; 95% CI 1.36 to 27.03). The results of ROC analysis for the subgroup are presented in Table 4. A score of 3 points predicted malignancy with a sensitivity of 84.62% and a specificity of 86.67%. Using score 3 as cutoff point is again associated with highest accuracy at 85.92% and the resultant AUC was 89.6% (95% C.I. 82% to 96%; see Figure 2).

Discussion

Intraductal papillary mucinous neoplasm is a disease with a wide range of malignant potential ranging from benign adenomatous disease up to invasive adenocarcinoma. For this reason, a reliable and non-invasive method of risk stratifying patients is needed as surgical intervention may be required. To our knowledge, this is the first external validation of the scoring system developed by Shin et al. [4] in a cohort of IPMN patients. The results show that accuracy of the model in predicting IPMN is very high and can serve as an important and reliable tool to inform management of IPMN. The results are similar to the original findings by Shin et al. [4] Assessment of our patients using the same scoring system mirrored these results. At a 3-point cutoff, malignancy was predicted with 73.17% sensitivity and 80.7% specificity. AUC at this cutoff was 0.8139 (95% C.I. 0.73148, 0.89624). Although our 3-point cutoff yielded slightly higher risk ratio, sensitivity and specificity, the results did show consistency as the score increased from three to four points. This three point cutoff had the highest discriminating power in our patient sample. As we were only attempting to validate this scoring system, no tests for statistical significance were performed. As is well-known, main duct IPMN is associated with malignancy in 43.1% of cases; therefore, surgical resection is strongly recommended as per the most recent international consensus guidelines [8]. Side-branch IPMN is not as frequently associated with invasive adenocarcinoma at 17.7%. As a result, management of side-branch IPMN is not as straightforward. In order to determine if the scoring system was applicable to side-branch types, additional analysis was performed on our patients excluding main-duct IPMN. We demonstrated that this 5-point scoring system gave just as reliable results with 3 points able to predict malignancy with 84.62% sensitivity and 86.67% specificity. While the findings are informative, the study also has some limitations. It first suffers from selection bias. Given the sample of patients chosen, this study suffers in that it only includes patients who underwent surgical resection. As a result, it may tend to reflect more robust results of screening test. This may be improved with future studies including all patients with IPMN and not just those who had resection. Secondly, the results were associated with wide confidence intervals due to small sample size in our dataset. Nevertheless, given the rarity of the disease, we did include all consecutive patients at our center and all patients had

an accurate classification of malignancy based on pathology reports. Additionally, this is still one of the largest cohorts used for external validation of a scoring system. Further investigation to determine whether this scoring system can be integrated with other predictive models for IPMN malignant risk to improve the sensitivity and specificity of the scoring system is warranted.

Conclusion

In summary, the scoring system proposed by Shin et al. [4] reliably predicts malignancy in IPMN for both main duct as well as side-branch and mixed cases. This scoring system is based on standard clinical, imaging and laboratory data and therefore can easily be applied to any practice setting without additional cost or effort. Application of this scoring system offers an objective tool to guide management decisions such as surgical resection versus surveillance. Based on this clinical score one can design clinical algorithms with surveillance intervals. Future studies with a larger sample size are needed for reproducibility of findings from our study.

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