Diagnostic utility of clinical and biochemical parameters in pancreatic head malignancy patients with normal carbohydrate antigen 19-9 levels

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Abstract

Background: Carbohydrate antigen (CA)19-9 that is the most widely used biomarker for pancreatic cancer has certain limitations in diagnosis, which results in a tough job to distinguish pancreatic cancer from benign tumors with normal CA19-9. The aim of this study was to investigate the diagnostic utility of clinical parameters and serum markers in patients with pancreatic head masses but without elevated CA19-9.

Methods: Retrospectively, 106 (69 malignant, 37 benign) of 487 patients admitted for pancreatic head masses were enrolled with CA19-9 level of <37u/ml. Clinical parameters and serum biomarkers were assessed. Among the patients with pancreatic head mass, male individuals ($p=0.025$) and elder individuals ($p<0.001$) were more likely to have cancer; and cancer patients were more likely to present with abdominal-pain ($p=0.023$), weight-loss ($p=0.013$) and jaundice ($p<0.001$). Serum bilirubin levels among malignancies, including total bilirubin ($p<0.001$), direct bilirubin ($p<0.001$) and indirect bilirubin ($p<0.001$), were considerably higher than those of benign ones. Logistic regression further concluded that age-distribution, abdominal-pain and direct-bilirubin were three independent factors correlating with final diagnosis. However, CEA ($p=0.156$) was not sufficient enough to exclude pancreatic cancer.

Conclusions: In patients with pancreatic head masses and CA19-9 of <37u/ml, age-distribution, abdominal-pain and direct bilirubin might be helpful in differential diagnosis. CEA was insufficient for exclusion of malignancy.

Key words: pancreatic head malignancy, diagnosis, clinical parameter, biomarker

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Introduction

Pancreatic cancer is one of the most lethal malignant tumors, with a 5-year survival of less than 0.4% to 5% [1-3]. Only 20% of patients are considered eligible for surgery at the time of diagnosis, and only half of them are suitsble for curative resection[1]. The most beneficial treatment of this disease is complete surgical resection in its early stage. Therefore, early and accurate diagnosis of patients with a suspicious pancreatic mass is critical. However, it is difficult to preoperatively distinguish malignancies from benign tumors with currently available diagnostic modalities at an early stage.

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At present, clinical diagnosis depends mainly on a variety of imaging technologies and a single serum carbohydrate antigen(CA)19-9 level[2-5]. Serum CA19-9 has a reported sensitivity of 70% to 90%, specificity of approximately 90%, positive predictive value of about 69%, and negative predictive value of about 90% in screening for pancreatic carcinoma[6]. However, elevated CA19-9 levels have also been found in several benign diseases, including chronic/acute pancreatitis, cholangitis, and lymphoepithelial cyst of the pancreas[2,7,8]. In addition, CA19-9 could not be detected in subjects with Lewis a-b- genotype[9]. Furthermore, only about 50% of patients with pancreatic carcinomas of <3cm had

elevated CA19-9 levels, and poorly differentiated malignant tumors secreted lower concentrations of CA19-9 than medium/well- differentiated ones did[10]. Given these limitations, malignant carriers with normal CA19-9 levels but positive imaging findings would appear even more difficult in distinguishing from benign ones.

Approximately 70% to 80% of patients with pancreatic cancer, mostly located in pancreatic head, presented with obstructive jaundice[11], and in some studies carcinoembryonic antigen (CEA) was proven to increase diagnostic accuracy of pancreatic cancer[12,13]. Therefore, serum bilirubin and CEA levels may serve as helpful complements to imaging and single CA19-9 measurement. Since the correlation between those parameters (both biochemical markers and clinical characteristics) and pancreatic head cancer haven't clearly been defined yet, the aim of this study was to assess the utility of these factors in diagnosis of pancreatic malignancies with imaging evidence and normal CA19-9 levels.

Material and methods

Details of all referrals with a pancreatic head mass that was proven by instrumental examinations before medical intervention were retrospectively collected and maintained in an original database. Instrumental examinations consisted of computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and endoscopic retrograde cholangiopancreatography (ERCP). Complete data was taken with the permission of the hospital from the records of all patients admitted to the Department of Surgery, Second Affiliated hospital, College of Medicine, Zhejiang University between January 2003 and December 2009. Clinical database was explored with the permission of the hospital. The clinical decision of malignancy or benign was determined by final pathological diagnosis, which was based on results of operative biopsies, endoscopic biopsies, or surgical specimens. Patients among the original database with serum CA19-9 levels of <37u/ml, which was recommended in most literature as normal level[2,6,14,15], were enrolled for further study. Patients lacking imaging support or pathological diagnosis as well as patients with metastasis were excluded. Patients without complete medical records were also eliminated.

With informed consent,all patients enrolled for further study underwent complete standard blood examinations, including serum bilirubin (total bilirubin(TB), direct bilirubin(DB) and indirect bilirubin(IB)), CA19-9, and CEA levels. Clinical symptoms that might appear during the development of diseases included abdominal pain, back pain, weight loss, fever, and jaundice. The CA19-9 cutoff value was described above as 37u/ml. Patients with serum TB levels of >2mg/dl were considered to be jaundiced according to the testing reagent manufacturer's specification for the reference range. All blood tests were performed by our clinical laboratory using the same manufacturer's specified testing reagents and standard testing procedure.

Statistic analysis was performed with SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL, US), and statistical significance was accepted at the $p<0.05$ level. Nonparametric tests were preferred when data distribution was not certain. Comparison of serum marker levels between the malignant and benign groups were obtained with the Mann–Whitney U test. Differences in frequencies for categorical variables were assessed by chi-square test. Multivariable analysis for detecting pancreatic head cancer was carried out using binary logistic regression. To further estimate the diagnostic abilities, receiver operating characteristics (ROC) curves were built. The area under the curve (AUC) was calculated for assessment of malignancy-detecting ability.

Results

Data of 487 patients was recorded in the original database at the beginning of the study. According to the aforementioned criteria, 106 patients with CA19-9 levels of <37 u/ml were finally enrolled. Pathological diagnosis proved that 69 (65.09%) of these 106 patients carried malignant tumors (Group 1), and the remaining 37 (34.91%) carried benign ones (Group 2). Clinical parameters and serum biomarkers were summarized in Table 1.

In group 1, 68 patients had pancreatic ductal adenocarcinoma and the remaining one had mucinous cystadenocarcinoma. Among group 2, eight had mucinouscystadenoma, seven had chronic pancreatitis, seven had solid- pseudopapillary tumor, six had insulinoma, five had serous cystadenoma and four had intraductal papillary mucinous tumor. group 1 was comprised of 40 men and 29 women with a median age of 62 years (range, 30–82 years), while group 2 consisted of 13 men and 24 women with a median age of 53 years (range, 16–80 years) (Table 1). In group 1, 44 (63.77%) patients

Table 1. Clinical andbiochemicalcharacteristicsofthepatients

	Malignant (%)	Benign (%)	*P*
Gender			
Male	40 (57.97)	13 (35.14)	
Female	29 (42.03)	24 (64.86)	0.025
Age	61.65±11.77	49.84±16.16	< 0.001
Abdominal pain	44 (63.77)	17 (45.95)	0.023
Back pain	12 (17.39)	5 (13.51)	0.604
Weight loss	20 (28.99)	3 (8.11)	0.013
Fever	4 (5.80)	0 (0.00)	0.295
Jaundice	29 (42.03)	1 (2.70)	< 0.001
Pathology			
Ductal adenocarcinoma	68 (98.55)		
Mucinous cystadenocarcinoma	1 (1.45)		
Mucinous cystadenoma		9 (24.32)	
Chronic pancreatitis		7 (18.92)	
Solid pseudopapillary tumor		6 (16.22)	
Insulinoma		6 (16.22)	
Serous cystadenoma		5 (13.51)	
Intraductal papillary mucinous tumor		4 (10.81)	
Common bile duct (cm)	1.00±0.49	0.73±0.30	0.002
Tumor size (cm)	4.54±2.60	4.34±2.77	0.599
Total bilirubin (mg/dl)	5.46±14.43	0.71±0.51	< 0.001
Direct bilirubin	3.11±9.67	0.19±0.14	< 0.001
Indirect bilirubin	2.35±4.84	0.52±0.38	< 0.001
CEA[1] (ng/ml)	8.79±28.27	4.37±6.99	0.156
CA19-9[2] (u/ml)	13.16±9.45	10.39±7.63	0.154

1: CEA equals Carcinoembryonic antigen.

2: CA19-9 equals Carbohydrate antigen19-9

suffered from abdominal pain and 12 (17.39%) suffered from back pain. In group 2, 17 (45.95%) patients experienced abdominal pain and 5 (13.51%) experienced back pain. Twenty of 69 (28.99%) and 3 of 37 (8.11%) patients underwent weight loss. Only 4 of the total 106 people developed a fever, and they were all cancer patients (Table 1). Besides sex ratio (p=0.025) and age distribution (p<0.001), abdominal-pain (p=0.023), weight-loss (p=0.013) and jaundice (p<0.001) were also statistically different in two groups; while back-pain (p=0.604) and fever (p=0.295) were not (Table 1).

The serum total bilirubin (TB) level in group 1(median, 1.27; range, 0.18–116.10 mg/dl) was significantly higher than that of group 2 (median, 0.64; range, 0.17–3.14 mg/dl) (p<0.001), and the same results were observed when direct and indirect bilirubin levels were compared between two groups (both p<0.001) (Table 1). To assess the severity of obstruction in the common bile duct (CBD), which resulted from the pancreatic head mass and gave rise to high hyperbilirubinemia (especially direct bilirubin), the tumor size and diameter of the CBD in both groups were measured according to the screenage data. However, although no difference (p=0.599) was found in tumor size(benign median, 3.65; range, 1.60–15.50 cm versus malignant median, 4.00; range, 1.30–13.00 cm) between 2 groups, statistical significance was obtained in the dilation of CBD (benign median, 0.60; range, 0.60–1.70 cm versus malignant median, 0.80; range, 0.60–2.50 cm) (p=0.002). When considering the TB cutoff value of 2mg/dl, 29 of 69 (42.3%) patients in group 1 and 1 of 37 (2.7%) in group 2 were positive for jaundice (p<0.001) (Table 1). Compared with benign disease (median, 1.50; range, 0.50–31.40ng/ml), no statistical difference (p=0.156) of serum CEA level was observed in the malignant group (median, 2.65; range, 0.00–210.20ng/ml) (Table 1). Similarly, no considerable bias of serum CA19-9 level was obtained (benign median, 7.70; range, 2.00–30.10u/ml versus malignant median, 10.70; range,1.70–36.90u/ml, p=0.154) in the Mann–Whitney U test (Table 1).

We subsequently performed binary logistic regression and pearson correlation analysis to find out those essential factors that were helpful in detection of malignancy. We found that, age distribution (p=0.002), abdominal-pain (p=0.044) and serum DB level (p=0.034) were fully confirmed as three independent elements mostly influencing the final diagnosis (Table 2). The other parameters were excluded either because of less impact or strong multicollinearity (Table 2).

Table 2. The statistic assessment on diagnostic utility of clinical and biochemical parameters

	Variables in the Equation not in the Equation(Sig)		Variables	AUC of the ROC Curve
	Sig	If Removed		
Gender			0.701	
Age	0.002	< 0.001		0.714
Abdominal pain	0.044	0.032		
Back pain			0.720	
Weight loss			0.346	
Fever			0.649	
Common bile duct			0.755	
Tumor size			0.554	
Total bilirubin			0.182	
Direct bilirubin	0.034	< 0.001		0.769
Indirect bilirubin			0.177	
CEA[1]			0.406	
CA19-9[2]			0.776	
Constant	0.001			

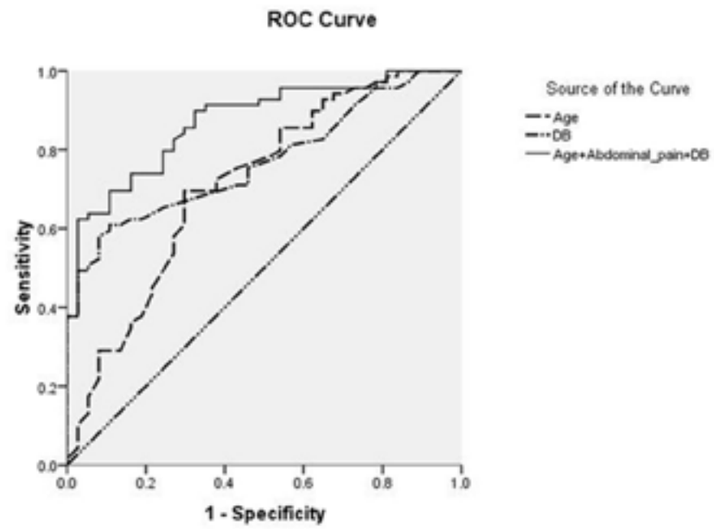
1: CEA equals Carcinoembryonic antigen.

2: CA19-9 equals Carbohydrate antigen19-9

We further built the ROC curve to assess the diagnostic utility of those candidates (Fig.1). The AUC of age-curve was 0.714 with a 95% confidence interval of 0.608 to 0.820. The sensitivity and specificity were 69.6% and 70.3% respectively with the most efficient cutoff value of 57 years according to the largest Youden index. Similarly, sensitivity of 60.9% and specificity of 89.2% were obtained with a cutoff value of 0.27mg/dl in ROC curve of DB (AUC=0.769, 95% confidence interval, 0.682 to 0.857). The combination of three variables inferred from the equation was proven to be better with a bigger AUC of 0.867(95% confidence interval of0.800 to 0.934).

Discussion

Figure 1. ROC curves of the differential diagnosis utility of age distribution, serum direct bilirubin and combination of three independent factors concluded by logistic regression



Diagnosis of pancreatic head masses remains a tough job. In the present study, we systemically evaluated the role of clinical parameters as well as serum bilirubin and CEA levels in diagnosing of pancreatic head cancer. We found that age distribution, abdominal pain and direct bilirubin were three independent factors that could probably improve the detection of malignancy when patients presented with imaging support but normal CA19-9 level.

The correlation between patients' age and pancreatic cancer was controversial. There was evidence that advanced age was a significant risk factor of pancreatic cancer among those suspicious[16]; while there was opposite outcomes provided by Kudo et al that onset age did not act as an important factor for developing pancreatic cancer[17]. Age distribution in our study (p<0.001), as same as the former, proved to be one of the essential elements that had the most sharp statistical difference, and logistic regression further proved that it (p=0.002, removed sig p<0.001) was an independent factor influencing the clinical diagnosis. The ROC curve with an AUC of 0.714 demonstrated its medium utility in detecting pancreatic head cancer among normal CA19-9 group, and it seemed that the age of 57 was the best cutoff point.

69.57% of malignant carriers and 29.73% of benign patients presented after the age of 57 in the study. Compared with a cutoff age of 50 (93% positive in cancer patients) suggested by Zubarik R et al as a high risk of pancreatic malignancy[16], the difference of our conclusion mainly might result from different study objects(different subpopulation more precisely), and different enrolled criteria.

Besides age, abdominal pain (p=0.023, logistic sig

p=0.044, removed sig p=0.032) appeared as another useful clinical feature in detecting pancreatic head cancer. Patients bearing malignant tumors in pancreatic head were more likely to present with abdominal pain (63.77% versus 45.95% in our study). Although abdominal pain was nonspecific[18], it was the most frequent onset symptom in pancreatic cancer[15,19], and it was proven to have certain relation with tumor location in pancreatic adenocarcinoma[20]. On the other hand, patients with benign lesions did not often appear with abdominal pain until it reached considerable size and gave rise to the obstruction of the pancreatico-biliary duct[21]. Therefore, abdominal pain probably correlated with malignancy more closely, and this kind of potential tendency might be amplified on the condition that patients' CA19-9 levels were under 37u/ml.

Sex ratio (p=0.025) and weight-loss (p=0.013) were other two clinical factors with statistical differences in two groups at first. However, according to the subsequent logistic analysis, neither the sex ratio nor the weight-loss appeared to be helpful. Although 4 patients with fever all belonged to group 1, no significant difference (p=0.295) was observed in two groups and logistic equation further confirmed its helplessness in differential diagnosis. The same result was also obtained on the symptom of back pain (p=0.604). There were some similar findings that above four clinical features were not significant risk factors for developing pancreatic cancer and they often did not appear until the tumor was locally advanced or metastatic[16,17,22]. Study on cystic lesions of pancreas also revealed that benign tumors of pancreas were often asymptomatic at early stage, and the symptoms such as back pain would not present until adjacent organs were involved[22]. Hence in accordance with our study, sex-ratio, back-pain, fever and weight-loss were not sufficient enough to distinguish malignancies from benign ones.

Since malignant patients with onset symptom of jaundice were more likely to have tumors located in the pancreatic head[20] and jaundice closely correlated with serum bilirubin[20], the serum bilirubin level was supposed to serve as a helpful diagnostic candidate. In our study, the difference of bilirubin levels between malignant and benign tumors was substantial (pTB<0.001,pDB<0.001,pIB<0.001). Compared with group 2, patients in group 1 had extremely higher (>15-fold) concentrations of direct bilirubin (DB) on average, while total bilirubin (TB) and indirect bilirubin (IB) in group 1 were more than four times as much as in benign group. In addition, logistic regression recommended DB (p=0.034, removed sig p<0.001) as an independent predictor and ROC analysis(AUC=0.769) concluded a reasonable cut-off value of 0.27mg/dl with sensitivity of 60.9% and specificity of 89.2%. All these results demonstrated that DB was a possible important factor among serum markers to screen cancer patients when the CA19-9 level is <37u/ml.

The nature of the correlation between pancreatic cancer and bilirubin was not yet clearly defined. Pancreatic head masses, which would lead to obstructive jaundice, were more likely to present as malignancies in some researches[10,20,23]. The same result was obtained in the present study as well. And accordingly, the diameter of CBD was no doubt statistically different in two groups (p=0.002), which demonstrated the sharp difference in the extent of CBD dilation. However on the other hand, the sizes of tumors in both groups were almost the same (p=0.599). This interesting contradiction revealed that the character of pancreatic head mass, whether benign or not, did play an important role in this type of malignant jaundice.

This contradiction might be explained as followings. Firstly, obstructive jaundice was described in over 90% of patients with pancreatic head carcinoma as a result of either invasion or compression of the common bile duct[24]; while cystic lesions located in pancreatic head were proven to be less likely to cause obstructive jaundice for their less progressive growth[22]. Secondly, compared with benign patients or healthy volunteers, pancreatic adenocarcinoma individuals presented considerably higher level of TNF-alpha[25] which was demonstrated to have toxic effect on cholangiocytes[26-28]. The susceptibility of cholangiocytes to TNF-alpha's cytotoxicity could be enhanced during biliary tract obstruction, which would result in severe liver damage and hyperbilirubinemia[26,27,29]. Given these interpretations, hyperbilirubinemia might more closely be correlated with pancreatic cancer, and serum direct bilirubin seemed quite sufficient in differential diagnosis of pancreatic head masses with CA19-9<37u/ml

CEA was another serum biomarker of interest for this study because it had been, and would likely continue to be, one of the most extensively used clinical tumor markers[30-32]. Pancreas was proven to be one of few tissues that can express CEA[31], and several studies had indicated that CEA was helpful in the diagnosis of pancreatic malignancy[33-35]. However, the present series demonstrated that patients in the benign group did not have statistically different CEA levels (p=0.156) as that of the cancer group. Thus, CEA had very low accuracy in the diagnosis of pancreatic head malignancies in patients with a suspicious mass but normal CA19-9 level (<37u/ml). The poor diagnostic utility was probably due to the fact that the serum CEA level did not correlate with its genetic level, but with tumor stage[35,36].

Conclusion

In patients with suspicious pancreatic head masses and CA19-9 levels of <37u/ml, age distribution, abdominal pain and direct bilirubin might be useful aid in differentiation between the malignant and the benign. Interestingly, compared with benign tumors, malignancies of pancreatic head were more likely to cause obstructive jaundice despite of the sizes of tumors. CEA, however, may not be sufficient enough to exclude malignancy. Large scale cohort of forward clinical research studies need to be carried out to confirm our findings.

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