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

Xiaoli Jin1, Yulian Wu2

1. Department of Surgery, Sir Run Run Shaw Hospital College of Medicine, Zhejiang University, 3 Qingchun Road East, Hangzhou, Zhejiang Province 310016, P.R. China E-mail: Jinxl@srrsh.com
2. Department of Surgery, Second Affiliated Hospital, College of Medicine, Zhejiang University, 88 Jiefang Road, Hangzhou, Zhejiang Province 310009, P.R. China

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 suitable for curative resection1. 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.

At present, clinical diagnosis depends mainly on a variety of imaging technologies and a single serum carbohydrate antigen(CA)19-9 level2-5. Serum CA19-9 has reported a 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 carcinoma6. However, elevated CA19-9 levels have also been found in several benign diseases, including chronic/acute pancreatitis, cholangitis, and lymphoepithelial cyst of the pancreas7,8. In addition, CA19-9 could not be detected in subjects with Lewis a-b- genotype9. Furthermore, only about 50% of patients with pancreatic carcinomas of <3cm had
and poorly differentiated malignan
tumors secreted lower concentrations of CA19-
9 than medium-well-differentiated ones did. 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 pancreat-
ic cancer, mostly located in pancreatic head, presented
with obstructive jaundice, and in some studies carcino-
embryonic antigen (CEA) was proven to increase
diagnostic accuracy of pancreatic cancer. Therefore,
serum bilirubin and CEA levels may serve as helpful
complements to imaging and single CA19-9 measure-
ment. Since the correlation between those param-
eters (both biochemical markers and clinical char-
acteristics) 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 ex-
aminations 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 admit-
ted 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 hos-
pital. The clinical decision of malignancy or benign
determined by final pathological diagnosis, which was
based on results of operative biopsies, endoscopic bi-
opside, or surgical specimens. Patients among the origi-
nal database with serum CA19-9 levels of <37 μ/ml,
which was recommended in most literature as normal
level, were enrolled for further study. Patients lack-
ing 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 fur-
ther study underwent complete 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 abdomi-
nal pain, back pain, weight loss, fever, and jaundice.
The CA19-9 cutoff value was described above as 37 μ/ml. Patients with serum TB levels of >2 mg/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. Non-
parametric tests were preferred when data distribution
was not certain. Comparison of serum marker levels
between the malignant and benign groups were ob-
tained with the Mann–Whitney U test. Differences in
frequencies for categorical variables were assessed by
chi-square test. Multivariable analysis for detecting pan-
creatic 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 da-
tabase at the beginning of the study. According to the
abovementioned criteria, 106 patients with CA19-9 lev-
els of <37 μ/ml were finally enrolled. Pathological di-
agnosis 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 adenocar-
cinoma and the remaining one had mucinous cystadeno-
carcinoma. Among group 2, eight had mucinoseystad-
cardenoma, 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>
<thead>
<tr>
<th>Gender</th>
<th>Malignant (%)</th>
<th>Benign (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40 (57.97)</td>
<td>13 (35.14)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29 (42.03)</td>
<td>24 (64.86)</td>
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<tr>
<td>&lt;37 u/ml</td>
<td>61.65±11.77</td>
<td>49.84±16.16</td>
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</tr>
<tr>
<td>≥37 u/ml</td>
<td>79.35±2.49</td>
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<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>44 (63.77)</td>
<td>17 (45.95)</td>
<td>0.023</td>
</tr>
<tr>
<td>Back pain</td>
<td>12 (17.39)</td>
<td>5 (13.51)</td>
<td>0.604</td>
</tr>
<tr>
<td>Weight loss</td>
<td>20 (28.99)</td>
<td>3 (8.11)</td>
<td>0.013</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (5.80)</td>
<td>0 (0.00)</td>
<td>0.295</td>
</tr>
<tr>
<td>Jaundice</td>
<td>29 (42.03)</td>
<td>1 (2.70)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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
Tumor size (cm) 4.54±2.60
Total bilirubin (mg/dl) 5.46±1.43
Direct bilirubin 3.11±0.67
Indirect bilirubin 2.35±0.84
CEA 1 (ng/ml) 8.79±28.27
CA19-9 2 (u/ml) 13.16±9.45

1: CEA equals Carcinoembryonic antigen.
2: CA19-9 equals Carbohydrate antigen.
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=0.032), 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 (p<0.001). 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, 0.50–31.40 mg/ml), no statistical difference (p=0.156) of serum CE A level was observed in the malignant group (median, 2.65; range, 0.00–210.20 mg/ml) (Table 1). Similarly, no considerable bias of serum CA19-9 level was obtained (benign median, 7.70; range, 2.00–30.10 U/ml versus malignant median, 10.70; range, 1.70–36.90 U/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

<table>
<thead>
<tr>
<th>Variables in the Equation Not in the</th>
<th>Variables If Removed</th>
<th>AUC of the ROC Curve</th>
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<td>Sig</td>
<td>Equation(Sig)</td>
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<tr>
<td>Gender</td>
<td>0.002</td>
<td>&lt; 0.001</td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
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<td>0.032</td>
</tr>
<tr>
<td>Back pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>0.720</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>0.346</td>
<td></td>
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<tr>
<td>Common bile duct</td>
<td>0.649</td>
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<tr>
<td>Tumor size</td>
<td>0.755</td>
<td></td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>0.554</td>
<td></td>
</tr>
<tr>
<td>Direct bilirubin</td>
<td>0.034</td>
<td>&lt; 0.001</td>
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<tr>
<td>Indirect bilirubin</td>
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</tr>
<tr>
<td>CEA</td>
<td>0.177</td>
<td>0.406</td>
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<tr>
<td>CA19-9</td>
<td>0.061</td>
<td>0.406</td>
</tr>
<tr>
<td>Constant</td>
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</table>

1: CEA equals Carcinoembryonic antigen.
2: CA19.9 equals Carbohydrate antigen 19.9

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 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 suspicious14; while there was opposite outcomes provided by Kudo et al that onset age did not act as an important factor for developing pancreatic cancer15. 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, removable 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 Zubariak R et al. as a high risk of pancreatic malignancy14, 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
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 patients. The results demonstrated that DB was a possible important factor among serum markers to screen cancer patients when the CA19-9 level is <37u/ml. 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. CA19-9, 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.

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. Furthermore, 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; while cystic lesions located in pancreatic head were proven to be less likely to cause obstructive jaundice for their less progressive growth. Secondly, compared with benign patients or healthy volunteers, pancreatic adenocarcinoma individuals presented considerably higher level of TNF-alpha which was demonstrated to have toxic effect on cholangiocytes. 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. 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.

References

17. Kudo Y, Kamisawa T, Anjiki H, Takuma K, Egawa N: Incidence of and risk factors for developing...


