Original Article
Diagnostic value of IMP3 in pancreatic cancer: a meta-analysis

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Abstract: Background and objectives: An increasing number of studies have examined the ability of IMP3 (insulin-like growth factor 2 messenger RNA binding protein 3) to be a marker for the diagnosis of pancreatic cancer (PCa). The exact role of IMP3 needs to be elucidated. The aim of this study is to determine the overall accuracy of IMP3 in PCa through a meta-analysis of published studies. Materials and methods: Publications addressing the accuracy of IMP3 in the diagnosis of PCa were selected from Pubmed, Embase, Cochrane Library, Web of Science, and The Chinese Journals Full-text Database (CNKI). The following indexes of test accuracy were computed for each study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). The diagnostic threshold identified for each study was used to plot a summary receiver operating characteristic (SROC) curve. Statistical analysis was performed by Meta-Disc 1.4 and STATA 12.0 software. Results: 10 studies met the inclusion criteria. The summary estimates for IMP3 in the diagnosis of PCa were: sensitivity 0.82 (95% CI, 0.78-0.85), specificity 0.87 (95% CI, 0.83-0.90), positive likelihood ratio (PLR) 15.04 (95% CI, 1.83-123.26), negative likelihood ratio (NLR) 0.21 (95% CI, 0.10-0.46) and diagnostic odds ratio 70.10 (95% CI, 16.74-293.56). The SROC curve indicated that the maximum joint sensitivity and specificity (Q-value) was 0.87; the area under the curve was 0.94. Conclusion: Our findings suggest that IMP3 may be a useful diagnostic adjunctive tool for confirming PCa. However, further large scale studies are needed to confirm these findings.

Keywords: Pancreatic cancer, IMP3, diagnosis, accuracy, meta-analysis

Introduction

Pancreatic cancer (PCa) is one of the most difficult cancers to treat with increasing incidence and mortality worldwide [1]. Despite surgical resection, radiation, and chemotherapy, more than 94% of people with PCa do not survive beyond 5 years [2]. Most PCa patients are diagnosed with metastatic disease at the time of presentation, with median survival duration less than 6 months [3]. Therefore, to make an early and accurate diagnosis will be very importance to the treatment and prognosis of PCa. Diagnosis of PCa mainly relies upon pathology findings together with radiological information or clinical and cytological data [4-7]. However, a wide range of histopathologic features may present in PCa and mimic other kinds of cancers. Similarly, cytological analysis requires the distinction of malignant pancreatic epithelial cells from reactive pancreatic and bile duct cells as well as other gastrointestinal contaminants, which often makes the diagnosis difficult [8]. One potential way of improving diagnostic accuracy is to use immunohistochemical (IHC) biomarkers as an adjunct in difficult to diagnose cases [9]. Several diagnostic IHC biomarkers have been investigated both as single biomarkers and as part of biomarker panels to improve the diagnosis of PCa. IMP3, a 40-kD phosphatidyl-inositol linked cell-surface glycoprotein, has been observed in an increasing number of human malignancies [10, 11], but not in normal pancreatic ductal epithelium [12, 13]. Therefore, IMP3 may have utility as a marker for discriminating between benign and malignant pancreatic epithelium.

Although an increasing number of studies have examined the ability of IMP3 to be a marker for
the diagnosis of PCa [14-25], the exact role of IMP3 needs to be elucidated. As meta-analysis is an essential tool for accurately and reliably summarizing evidence, we performed this meta-analysis to assess the potential value of IMP3 in the diagnosis of PCa, which, to the best of our knowledge, has not been previously performed.

Material and methods

Search strategy and study selection

Electronic databases Pubmed, Embase, Cochrane Library, Web of Science, and The Chinese Journals Full-text Database (CNKI) (updated to June 30, 2014) were searched for suitable studies. The search terms were “pancreatic cancer/pancreatic carcinoma/pancreatic adenocarcinoma/pancreatic ductal adenocarcinoma/pancreatic neoplasm”, “IMP3/KOC”, “sensitivity”, “specificity”, and “diagnosis”. The reference lists of all articles reviewed were also searched for eligible studies. A study was included if it met the following inclusion criteria: (1) e-clinical studies on evaluation of IMP3 in the diagnosis of PCa, (2) each study contains more than ten specimens, and (3) studies must provide sufficient data to calculate both sensitivity and specificity. Conference abstracts, reviews and letters to editor were excluded because of the limited data.

Data extraction and quality assessment

The final set of articles was assessed independently by two reviewers. The following data from each publication were collected: author, publication year, study of state, diagnostic standard, patient number, specimen, test method, IMP3 expression signature, sensitivity and specificity data and methodological quality. The methodological quality of each study was assessed by QUADAS (quality assessment for studies of diagnostic accuracy, an evidence-based quality assessment tool for use in systematic reviews of diagnostic accuracy studies, maximum score 14) [26].

Statistical analysis

The standard methods recommended for diagnostic accuracy were used in this meta-analysis [27]. Analyses were performed using two statistical software programs: Stata, version 12 (Stata Corporation, College Station, TX, USA) and Meta-Disc 1.4 for Windows (XI Cochrane Colloquium, Barcelona, Spain). The following indexes of test accuracy were computed for each study: sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR). The diagnostic threshold identified for each study was used to plot a summary receiver operating characteristic (SROC) curve [28]. To detect cut-off threshold effects, the relationship between sensitivity and specificity was evaluated by the Spearman correlation coefficient. The chi-square-based test and the inconsistency index I² were used to detect statistically significant heterogeneity across studies. When a significant Q test (\(P < 0.05\) or \(I^2 > 50\%\)) indicated heterogeneity among studies, the random-effect model (DerSimonian-Laird method) was conducted for the meta-analysis to calculate the pooled sensitivity, specificity, and other related indexes of the studies; Otherwise, the fixed-effect model (Mantel-Haenszel method) was chosen. Chi-square test was used to detect statistically significant heterogeneity across studies. If there were enough studies, meta-regression was performed to investigate the source of heterogeneity within the included studies (inverse variance weighted) [29]. Since publication bias is of concern for meta-analyses of diagnostic studies, we tested...
Table 1. Summary of the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Country</th>
<th>Specimen type</th>
<th>Cut-off</th>
<th>Sample size</th>
<th>TP</th>
<th>FP</th>
<th>FN</th>
<th>TN</th>
<th>QUADAS scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yantiss RK (a)</td>
<td>2005</td>
<td>America</td>
<td>FNA</td>
<td>Cytoplasmic staining</td>
<td>191</td>
<td>52</td>
<td>15</td>
<td>5</td>
<td>119</td>
<td>12</td>
</tr>
<tr>
<td>Yantiss RK (b)</td>
<td>2007</td>
<td>America</td>
<td>FNA</td>
<td>Cytoplasmic staining</td>
<td>55</td>
<td>11</td>
<td>0</td>
<td>1</td>
<td>43</td>
<td>12</td>
</tr>
<tr>
<td>Zhao H</td>
<td>2007</td>
<td>America</td>
<td>FNA</td>
<td>Cytoplasmic or membranous staining</td>
<td>48</td>
<td>35</td>
<td>0</td>
<td>5</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Ligato S</td>
<td>2008</td>
<td>America</td>
<td>FNA</td>
<td>Cytoplasmic staining</td>
<td>44</td>
<td>22</td>
<td>1</td>
<td>2</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>Toll AD</td>
<td>2009</td>
<td>America</td>
<td>surgical</td>
<td>&gt; 75% cells with 3 + intensity cells staining</td>
<td>36</td>
<td>10</td>
<td>0</td>
<td>7</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Li J</td>
<td>2011</td>
<td>China</td>
<td>Unclear</td>
<td>mean + 3SD of normal human sera</td>
<td>46</td>
<td>5</td>
<td>0</td>
<td>18</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Wachter DL</td>
<td>2011</td>
<td>Germany</td>
<td>surgical</td>
<td>&gt; 10% cells moderately staining or &gt; 10% cells strong cytoplasmic staining</td>
<td>68</td>
<td>25</td>
<td>1</td>
<td>1</td>
<td>41</td>
<td>11</td>
</tr>
<tr>
<td>Liu H</td>
<td>2012</td>
<td>America</td>
<td>surgical</td>
<td>≥ 5% cells stained</td>
<td>100</td>
<td>54</td>
<td>8</td>
<td>6</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Ali A</td>
<td>2014</td>
<td>UK</td>
<td>surgical</td>
<td>Cytoplasmic and membranous staining</td>
<td>198</td>
<td>73</td>
<td>0</td>
<td>26</td>
<td>99</td>
<td>8</td>
</tr>
<tr>
<td>Lok T</td>
<td>2014</td>
<td>America</td>
<td>FNA</td>
<td>Cytoplasmic staining</td>
<td>101</td>
<td>54</td>
<td>37</td>
<td>6</td>
<td>4</td>
<td>10</td>
</tr>
</tbody>
</table>

TP, true positive; FP, false positive; FN, false negative; TN, true negative; FNA, fine-needle aspiration.
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for the potential presence of this bias using Deeks’ funnel plots [30]. All statistical tests were two-sided and P < 0.05 was considered to indicate a statistically significant result.

Results

Quality of reporting and study characteristics

The literature selection process were presented in a flow chart in Figure 1. In accordance with the inclusion and exclusion criteria, 10 publications dealing with IMP3 for diagnosis of PCa were included in the present meta-analysis. The clinical characteristics of these studies, along with QUADAS score, were outlined in Table 1. Overall, 10 selected studies including 887 patients were available for analysis. All patients with PCa were diagnosed based on the histological evaluation of surgically resected tissue specimens or endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) biopsy and/or clinical data. Of the 10 articles included, 6 had QUADAS scores ≥ 10.

Quantitative data analysis

The $I^2$ of sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and DOR were 86.6% (P < 0.0001), 95.2% (P < 0.0001), 98.5% (P < 0.0001), 93.7% (P < 0.0001), and 80.3% (P < 0.0001), respectively. Since heterogeneity is obvious in the study, the random effects model was used for calculating pooled sensitivity, specificity, PLR, NLR and DOR. The pooled sensitivity and specificity of IMP3 test for the diagnosis of PCa calculated was 0.82 (95% CI, 0.78-0.85) and 0.87 (95% CI, 0.83-0.90), respectively. The forest plots of sensitivity and specificity of each included study were shown in Figure 2. The summary positive and negative likelihood ratios were 15.04 (95% CI, 1.83-123.26) and 0.21 (95% CI, 0.10-0.46). The pooled diagnostic odds ratio was 70.10 (95% CI, 16.74-293.56) (Figure 3). Figure 4 dis-

Figure 2. Forest plots of the sensitivity and specificity for IMP3 in the diagnosis of PCa for all studies. The point estimates of sensitivity and specificity for each study are shown as solid circles and the size of each solid circle indicates the sample size of each study. Error bars are 95% confidence intervals.

Figure 3. Summary receiver operating characteristic (SROC) curve for IMP3 in the diagnosis of PCa for all studies. Solid circles represent each study included in the meta-analysis. The size of each solid circle indicates the size of each study. The regression SROC curve summarizes the overall diagnostic accuracy.
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plays the SROC curve, which presents a global summary of test performance and shows the tradeoff between sensitivity and specificity [31]. As a global measure of test efficacy we used the Q-value, the intersection point of the SROC curve with a diagonal line from the left upper corner to the right lower corner of the ROC space, which corresponds to the highest common value of sensitivity and specificity for the test. This point does not indicate the only or even the best combination of sensitivity and specificity for a particular clinical setting but represents an overall measure of the discriminatory power of a test. In the present meta-analysis, the maximum joint sensitivity and specificity was 0.87 (the Q value), the AUC was 0.94, indicating the level of overall accuracy was good.

Publication bias

Publication bias was explored through Deeks’ funnel plots. The shape of the funnel plot of the pooled DOR of IMP3 for the diagnosis of PCa did not reveal any evidence of obvious asymmetry (Figure 5), while the Deeks’ test showed a statistically non-significant value (P = 0.802), indicating that there was no potential publication bias.

Discussion

The diagnosis of PCa is an important clinical challenge because of the late clinical presentation with advanced disease. In recent years, molecular techniques such as serial analysis of gene expression and RNA-based global gene expression profiling have identified several potential new markers of pancreatic cancer. Among these, IMP3 expression is reported to distinguish benign from malignant pancreatic tissue [12, 13] and an increasing number of diagnostic tests have focused on the value of IMP3 in the differential diagnosis of benign and malignant pancreatic diseases, but the results remain controversial because of several factors, including the differences in study designs, sample size, statistical methods, etc [32]. As meta-analysis is an essential tool for accurately and reliably summarizing evidence, we performed this meta-analysis to comprehensively assess the diagnostic accuracy of IMP3 for PCa.

In our meta-analysis, the data has shown that the pooled sensitivity and specificity were 0.82...
and 0.87, respectively, suggesting its potential diagnostic value of PCa, though the relatively low sensitivity of IMP3 may be not sufficient to screen PCa. The SROC curve presents a global summary of test performance, and shows the trade-off between sensitivity and specificity. The DOR, the ratio of the odds of positivity in disease relative to the odds of positivity in the non-diseased, is a single indicator of diagnostic test performance [33] that combines the data from sensitivity and specificity into a single number. The value of a DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance (higher accuracy). A DOR of 1.0 indicates that a test cannot discriminate between patients with the disorder and those without it. In this meta-analysis, the maximum joint sensitivity and specificity (Q value) was 0.87 while the AUC was 0.94, and the pooled DOR was 70.1, suggesting a moderate diagnostic accuracy for diagnosing PCa. However, the SROC curve and the DOR are not easy to interpret and use in clinical practice, while the likelihood ratio (PLR and NLR) is more clinically meaningful for our measures of diagnostic accuracy. A PLR value of 15.04 suggests that patients with PCa have about 15-fold higher chance of being IMP3-positive compared to non-PCa, and this was high enough for the clinical practice. On the other hand, the NLR was 0.21, which means that the probability of having PCa in IMP3-negative patients is 21% in theory, which is not low enough to rule out PCa.

The results of the present meta-analysis suggest that IMP3 may, to a certain extent, play a role in the diagnosis of malignant effusions. However, no single biomarker is 100% perfect; therefore, different biomarkers should be investigated in various combinations, to select an optimum panel for potential clinical application. Some biomarkers were proved to be useful in distinguishing PCa from other benign pancreatic diseases. For instance, Lok T et al. have reported that S100P and MUC5AC were frequently expressed in pancreatic ductal adenocarcinomas, seen in 95% and 67% cases, respectively [34]. In addition, it has been reported that using a panel of KOC, S100P and IMP3 with at least 2 positive biomarkers achieved almost 100% sensitivity and specificity in detecting pancreaticobiliary adenocarcinomas [25]. Nevertheless, due to the varying degrees of diagnostic accuracy of identical markers reported between studies, it remains unclear which marker has a superior performance. Therefore, more immunomarkers should be comprehensively evaluated for their diagnostic accuracy and larger sample-size diagnostic tests are needed to find the optimum panel of antibodies for the diagnosis of malignant effusions [35].

This meta-analysis has limitations. First of all, we excluded conference abstracts and letters to the editor, which may have contributed to the observed publication bias. Secondly, the small sample-sized studies appeared to overestimate the true diagnostic accuracy of IMP3 for the diagnosis of PCa and might be vulnerable to selection bias. Third, the diagnosis of PCa was made by histological assessment (gold standard) in some studies, while other PCa patients were diagnosed on the basis of clinical course. This issue of diagnostic accuracy may have caused non-random misclassification, leading to biased results. Also, because of a lack of required data reported in the original publications, it was not possible to analyse the effect of factors such as laboratory infrastructure, expertise with immunotechnology, patient spectrum and setting on the accuracy of the IMP3 measurements. In addition, due to the limited numbers of the studies included, we did not use the STARD and QUADAS scores to perform the meta-regression analysis to assess the effect of study quality on the relative DOR of IMP3 in the diagnosis of PCa. And for the same reason, we could not explore whether the study design, such as blinded, cross-sectional, consecutive/random and prospective design, affects the diagnostic accuracy, either. Therefore, further studies are still needed to evaluate the diagnostic accuracy of IMP3 in clinical applications.

Despite the above limitations, our meta-analysis used a statistical approach to combine the results of multiple studies. The data demonstrated that IMP3 may be a useful adjunct to conventional diagnostic tools for detecting PCa, while the results of immunostaining should be interpreted in parallel with the gold standard of morphology and clinical findings.

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Disclosure of conflict of interest
None.

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