**Magnetic Resonance Cholangiopancreatography in the Diagnosis of Pancreas Divisum**

*ORIGINAL ARTICLE*

**A Systematic Review and Meta-analysis**

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**Objective:** This study aimed to perform a structured meta-analysis of all eligible studies to assess the overall diagnostic use of magnetic resonance cholangiopancreatography (MRCP) alone or with secretin enhancement (secretin-enhanced MRCP [S-MRCP]) in the detection of pancreas divisum.

**Methods:** Two authors independently performed a comprehensive search of PubMed, MEDLINE, and the Cochrane Library from inception to September 2013. Studies were included if they allowed construction of 2 × 2 contingency tables of MRCP and/or S-MRCP compared with criterion standard. DerSimonian-Laird random effect models were used to estimate the pooled sensitivity, specificity, and quantitative receiver operating characteristics.

**Results:** Of 51 citations, 10 studies with 1474 patients were included. Secretin-enhanced MRCP had a higher overall diagnostic performance than MRCP (S-MRCP: pooled sensitivity, 86% [95% confidence interval (CI), 77%–93%; specificity, 97% [95% CI, 94%–99%]; and area under the curve, 0.93 ± 0.056 compared with MRCP: sensitivity, 52% [95% CI, 45%–59%]; specificity, 97% [95% CI, 94%–99%]; and area under the curve, 0.76 ± 0.104). Pooled diagnostic odds ratios were 72.19 (95% CI, 5.66–938.8) and 23.39 (95% CI, 7.93–69.02) for S-MRCP and MRCP, respectively. Visual inspection of the funnel plot showed low potential for publication bias.

**Conclusions:** Secretin-enhanced MRCP has a much higher diagnostic accuracy than MRCP and should be preferred for diagnosis of pancreas divisum.

**Key Words:** pancreas divisum, ERCP, MRCP, secretin

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Pancreas divisum, with a reported prevalence of 2.7% to 22%, is the most common congenital anatomical variant of pancreatic ductal development. The dorsal and ventral pancreatic buds of the foregut fail to fuse during the seventh week of intrauterine life and results in pancreas divisum, in which the duct of Wirsung drains the minor part of the pancreas, that is, ventral pancreas, through the major papilla, whereas the dominant duct of Santorini drains the major part of the pancreas, that is, the dorsal pancreas, through the minor papilla. Because the major part of the pancreatic secretion must flow through the minor papilla, pancreas divisum could predispose to obstructive pancreatopathy, causing both acute pancreatitis and pancreatic type pain, and be implicated in the development of severe chronic pancreatitis.

The best option for the diagnosis of pancreas divisum currently is an endoscopic retrograde cholangiopancreatography (ERCP), which is considered the criterion standard for diagnosing pancreas divisum. Diagnostic ERCP, however, is associated with significant complications. Magnetic resonance cholangiopancreatography (MRCP) has emerged as a noninvasive imaging modality for the diagnosis of pancreas divisum. Secretin enhancement has been shown to improve visualization of pancreas, particularly pancreatic ductal anatomy. Therefore, secretin-enhanced MRCP (S-MRCP) has been suggested to enhance the detection of congenital pancreaticobiliary malformations, including pancreas divisum. However, despite the recent advances in MRCP pancreas divisum may not be detected in a significant portion of cases, and as such, several studies on the diagnostic accuracy of MRCP and S-MRCP have yielded conflicting results. The aim of this study was to perform a structured meta-analysis of all eligible studies to assess the overall diagnostic use of MRCP alone or with secretin enhancement (S-MRCP) in the detection of pancreas divisum. This meta-analysis and systematic review was written in accordance with the proposal for reporting by Quality of Reporting of Meta-analyses statement.

**METHODS**

**Literature Search**

A comprehensive search of the literature was performed to identify articles that examined the diagnostic accuracy of MRCP and S-MRCP for the detection of pancreas divisum. We systematically searched PubMed, MEDLINE, and the Cochrane Library for studies published until September 2013. Search terms included “magnetic resonance cholangiopancreatography” and “diagnostic test” in combination with “secretin,” “pancreas divisum,” and/or “endoscopic retrograde cholangiopancreatography.” No language restriction was applied to the search filter. The titles and abstracts of all potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed for additional articles. Two reviewers (T.R. and B.N.) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Interreviewer discrepancies were resolved by referring to the original article and by mutual agreement.

**Study Selection Criteria**

Only studies investigating the use of MRCP and/or S-MRCP for the detection of pancreas divisum were included. Only studies with data available for the construction of 2 × 2 contingency tables with true-positive, false-negative, false-positive, and true-negative values were eligible for inclusion.
The exclusion criteria were as follows:
1. studies that did not evaluate MRCP and/or S-MRCP for the detection of pancreas divisum compared with criterion standard;
2. studies with insufficient data;
3. reviews, editorials, and correspondence letters that did not report their own data; and
4. case reports and studies with fewer than 10 patients.

Quality of Studies
Currently, there is no consensus or criteria to evaluate the quality of studies without a control arm. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) questionnaire was used to evaluate the quality of selected studies. A total of 14 items were appraised in this study, and items were rated as “yes,” “no,” or “unclear.”

Statistical Analysis
Meta-analysis for the accuracy of MRCP and/or S-MRCP for the detection of pancreas divisum was performed by calculating pooled estimates of sensitivity, specificity, likelihood ratios (LRs), and diagnostic odds ratio (DOR). The DOR was an independent indicator ranging from 0 to infinity, which represented how much greater the odds of having pancreas divisum were for patient with a positive MRCP and/or S-MRCP result than for patient with a negative result. The higher the DOR, the better the discriminatory ability of the test. Pooling was performed using the DerSimonian-Laird method (random effects model), and empty cells were handled using a 0.5 continuity correction. Forest plots were constructed to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the Forest plots corresponded to the assigned weight of the study. Heterogeneity was assessed by using $\chi^2$ statistics, $I^2$ measure of inconsistency, and Cochran $Q$ test.

A summary receiver operating characteristic (SROC) curve was constructed based on the Moses-Shapiro-Littenberg method as a way to summarize the true-positive and false-positive rates from different studies. The proximity of the area under the curve (AUC) to 1 is a well-validated overall representation of the diagnostic accuracy of a test. The robustness of the meta-analysis to publication bias was assessed by funnel plots and bias indicators, including the Begg-Mazumdar test and the Harbord-Egger test.

Sensitivity Analysis
A sensitivity analysis was conducted for every study to determine whether any single study was incurring undue weight in the analysis. We systematically removed 1 set of study data and checked the pooled results for the remaining studies to see if there was any significant change in test performance.

Combined weighted sensitivity, specificity, positive LR (LR+), negative LR (LR−), DOR, summary receiver operating characteristic curve, and meta-regression were determined by using Meta-DiSc version 1.4 (Unit of Clinical Biostatistics, Ramon y Cajal Hospital, Madrid, Spain).

RESULTS
Eligible Studies and Quality Assessment
Fifty-one potentially relevant studies were identified by our primary search of the electronic databases for published work on the subject. Of these studies, 21 were excluded after further review of the title and abstract for irrelevant topics, and an additional 20 were excluded for duplication of the reports, meeting exclusion criteria or lack of data for evaluation. The detailed process of this literature search is shown in Figure 1. After careful review, 10 studies with a total of 1474 subjects were included in this meta-analysis. The characteristics of each included study are shown in Table 1.

The quality of the eligible studies as assessed by the QUADAS criteria is reported in Figure 2. For most QUADAS items (10/14), all studies were classified as high quality.

Magnetic Resonance Cholangiopancreatography
For MRCP (n = 1361; 9 studies), the pooled sensitivity and specificity for diagnosis of pancreas divisum were 52% (95% confidence interval [CI], 45–59%) and 97% (95% CI, 94–99%), respectively (Fig. 3). The pooled LR+ was 7.88 (95% CI, 3.03–20.48), and the LR− was 0.47 (95% CI, 0.34–0.64). The positive predictive value was 0.93 (95% CI, 0.86–0.97), and the negative predictive value (NPV) was 0.72 (95% CI, 0.67–0.77). The pooled DOR was 23.39 (95% CI, 7.93–69.02). The results of DOR did not show significant heterogeneity ($P < 0.16$; Cochran $Q$, 11.76; $I^2 = 32$%). The AUC value was 0.76 ± 0.104 (Supplemental Digital Content 1, Figure 1, http://links.lww.com/MPA/A294).

Secretin-Enhanced MRCP
For S-MRCP (n = 951; 5 studies), the pooled sensitivity and specificity for diagnosis of pancreas divisum were 86% (95% CI, 77–93%) and 97% (95% CI, 94–99%), respectively (Fig. 4). The pooled LR+ was 12.31 (95% CI, 4.35–35.23), and the LR− was 0.19 (95% CI, 0.06–0.62). The positive predictive value was 0.92 (95% CI, 0.84–0.97), and the NPV was 0.94 (95% CI, 0.89–0.97). The pooled DOR was 72.19 (95% CI, 5.66–938.8). The AUC value was 0.93 ± 0.056 (Supplemental Digital Content 2, Figure 2, http://links.lww.com/MPA/A295).

Sensitivity Analysis
We systematically removed 1 data set at a time and recalculated the DOR and AUC values for the remaining studies. The largest change occurred when removing the data set from Kim et al. which changed the pooled DOR for MRCP from 23.39 to 21.62 (−7.8%), and the corresponding change in the AUC value was from 0.76 to 0.75 (−1.32%). Similar results were
obtained for S-MRCP. These results indicated that no single data set carried enough weight to significantly influence the pooled test performance reported for MRCP or S-MRCP in the diagnosis of pancreas divisum.

**Publication Bias**

The Begg-Mazumdar indicator for bias gave a Kendall $\tau_b$ of 0.22 ($P = 0.19$), and Egger test, another indicator for publication bias, was $t = 0.59$ (95% CI, $-0.79$ to 0.29; $P = 0.26$). Both of these values indicated no significant publication bias. Visual inspection of funnel plot further confirms that publication bias is not a major determinant of pooled diagnostic accuracy in this meta-analysis (Fig. 5).

**DISCUSSION**

Pancreas divisum is the most common congenital variant of the pancreas; however, it is of clinical importance in only a small percentage of patients causing recurrent acute pancreatitis, chronic pancreatitis, or pancreatic-type pain. Endoscopic retrograde cholangiopancreatography is currently the criterion standard for diagnosing pancreas divisum but is an invasive test requiring sedation and carries a 10% to 15% complication rate, with up to 10% of patients developing post-ERCP pancreatitis. In addition, the difficulty and the level of expertise required in achieving endoscopic access to the minor papilla makes this a less-than-desirable first-line diagnostic tool. Given these drawbacks of ERCP, several noninvasive or minimally invasive tests such as MRCP, multidetector computed tomography, and endoscopic ultrasound have been considered as alternative options for the detection of pancreas divisum.

Magnetic resonance cholangiopancreatography was first introduced in 1991 as a noninvasive diagnostic technique to illustrate the dilated common bile duct in a way that was similar to what clinicians were accustomed to with ERCP. Over the next few years, the MRCP technique was further developed to not only obtain images in short time of 2 to 20 seconds compared with the original publication, which took 6 minutes, but also to be able to provide images of the pancreatic duct, which is significantly smaller, approximately 3 mm in diameter. Magnetic resonance cholangiopancreatography was first introduced in 1991 as a noninvasive diagnostic technique to illustrate the dilated common bile duct in a way that was similar to what clinicians were accustomed to with ERCP. Over the next few years, the MRCP technique was further developed to not only obtain images in short time of 2 to 20 seconds compared with the original publication, which took 6 minutes, but also to be able to provide images of the pancreatic duct, which is significantly smaller, approximately 3 mm in diameter.

Studies evaluating the accuracy of MRCP in detecting pancreas divisum, however, have yielded varying results. Although earlier studies reported high sensitivity and specificity, approaching 100%, recent studies show a more modest accuracy.

### TABLE 1. Detection Rate of Pancreas Divisum and Characteristics of the 10 Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bret et al</td>
<td>1996</td>
<td>310</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Ueno et al</td>
<td>1998</td>
<td>93</td>
<td>44.4</td>
<td>98.82</td>
</tr>
<tr>
<td>Manfredi et al</td>
<td>2000</td>
<td>107</td>
<td>44.44</td>
<td>88.89</td>
</tr>
<tr>
<td>Matos et al</td>
<td>2001</td>
<td>279</td>
<td>74.19</td>
<td>96.77</td>
</tr>
<tr>
<td>Kim et al</td>
<td>2003</td>
<td>47</td>
<td>36.36</td>
<td>100</td>
</tr>
<tr>
<td>Lai et al</td>
<td>2004</td>
<td>43</td>
<td>60</td>
<td>88.89</td>
</tr>
<tr>
<td>Kamisawa et al</td>
<td>2007</td>
<td>32</td>
<td>73.33</td>
<td>100</td>
</tr>
<tr>
<td>Carnes et al</td>
<td>2008</td>
<td>405</td>
<td>40.6</td>
<td>66.67</td>
</tr>
<tr>
<td>Mosler et al</td>
<td>2012</td>
<td>113</td>
<td>73.68</td>
<td>96.81</td>
</tr>
<tr>
<td>Kushnir et al</td>
<td>2013</td>
<td>45</td>
<td>60</td>
<td>93.75</td>
</tr>
</tbody>
</table>

**FIGURE 2.** Quality of the eligible studies as assessed by the QUADAS criteria.
rate. Many explanations have been attributed to the disparities in the results. Exclusion and verification biases with regard to the criterion standard test used and the relatively small number of patients with pancreas divisum in earlier studies might have accounted for a high diagnostic accuracy of MRCP. Various techniques for performing MRCP exist, and thus, there exists a large degree of institutional variability. Performance of MRCP at nonacademic institutions has been shown to have lower overall sensitivity and specificity.

FIGURE 3. Forest plot of sensitivity and specificity of MRCP in diagnosing pancreas divisum.

FIGURE 4. Forest plot of sensitivity and specificity of S-MRCP in diagnosing pancreas divisum.
Another important factor that might account for variation in results is the proportion of patients with chronic pancreatitis included in the study. Patients with chronic pancreatitis have a high percentage of false-negative and false-positive diagnoses on MRCP. Mosler and colleagues compared the diagnostic accuracy of S-MRCP in the subgroup of patients with and without chronic pancreatitis and found a significant difference (57% vs 83% sensitivity and 91% vs 99% specificity in patients with and without chronic pancreatitis, respectively).

Evaluating a patient for pancreas divisum requires determining where the pancreatic duct enters into the duodenum. Often, this location is very difficult to see, and secretin can provide a significant advantage by better defining the prepapillary part of the pancreatic duct. Secretin stimulates secretion of fluid and bicarbonate by the pancreas, engorging the pancreatic duct with extra fluid, which improves its visualization. Most of the recent studies have shown a significantly higher diagnostic accuracy of S-MRCP for pancreas divisum when performed with secretin stimulation, except for few studies with small sample sizes. In our meta-analysis, S-MRCP yielded a much higher overall sensitivity, DOR, and AUC compared with MRCP, suggesting improved visualization of pancreatic ductal anatomy for the detection of pancreas divisum with secretin stimulation.

In this study, S-MRCP had a high pooled DOR of 72.19 (95% CI, 5.66–938.8). This means that if S-MRCP shows pancreas divisum, the patient has 72 times higher chance in having a true diagnosis. The LR+ of a test is a measure of how well the test identifies the disease, and the LR− is a measure of how well the same test performs in excluding the disease state. Likelihood ratios greater than 10 and less than 0.1 provide strong evidence to rule a diagnosis in or out, respectively. In our study, the pooled LR+ for S-MRCP was 12.31 (95% CI, 0.43–353.2), and the pooled LR− was 0.19 (95% CI, 0.06–0.62). This indicates that S-MRCP is reliable in diagnosing pancreas divisum and in excluding normal ductal anatomy. Along with its high NPV (0.94), it might be considered as diagnostic test of choice for excluding pancreas divisum without exposing patients to discomfort and risks associated with ERCP.

Secretin-enhanced MRCP has good diagnostic accuracy even in presence of chronic pancreatitis. In a study by Matos et al., S-MRCP was shown to have a high correlation with ERCP (98.5%) in the subgroup of patients with severe chronic pancreatitis. However, as with MRCP, the diagnostic accuracy of S-MRCP has been reported to decrease in patients with chronic pancreatitis. Kim et al. reported significant improvement in image quality after administration of secretin in all patients, but the improvement scale was significantly lower in patients with chronic pancreatitis compared with other groups. Mosler et al. noted ERCP finding of chronic pancreatitis to be more frequent among incorrect S-MRCP interpretations than among correct interpretations (odds ratio, 5.5 [95% CI, 1.3–25.3]). The difficulty in the detection of pancreas divisum in patients with chronic pancreatitis has been attributed to a poorer-than-average secretin response and the presence of stones and strictures in either the ventral or dorsal pancreatic ducts.

All new magnetic resonance scanners have the capability of adding secretin stimulation, and this technique can be used anywhere; its use does not need to be reserved for major academic centers. However, the use of secretin has been limited by its cost, availability, and concerns for potential adverse effects. Although a normal MRCP is a totally noninvasive procedure, adding the secretin component changes this to an invasive approach because intravenous access is acquired. In clinical trials, secretin has been associated with some adverse effects, such as abdominal pain and nausea; however, these are minor and can be easily monitored in patients undergoing MRCP. None of the 5 S-MRCP studies (n = 85) reported any significant adverse event or complication related to secretin.

Although the results of this meta-analysis are clinically useful, our meta-analysis also has a number of limitations. Pancreas divisum is a relatively rare disease, and hence, high-quality studies are scarce. The other major problem with meta-analysis is ensuring appropriate data comparison. In our study, as in most meta-analysis of diagnostic studies, a considerable degree of heterogeneity was present, which is a very frequent observation in meta-analysis of diagnostic studies. We, however, used a random effects model and meta-regression to control for heterogeneity. More so, the sensitivity analysis did not identify a consistent source of heterogeneity. Publication bias and selection bias can influence the summary estimates. This bias can be estimated by bias indicators and by drawing funnel plots. In this meta-analysis and systematic review, bias calculation using Egger bias indicator and Begg-Mazumdar indicator showed no statistically significant bias, and this was confirmed by the symmetrical funnel plot.

In conclusion, this study is the first meta-analysis, to the best of our knowledge, to summarize all the available evidence regarding the diagnostic performance of MRCP and S-MRCP in the detection of pancreas divisum. Secretin-enhanced MRCP has a much higher diagnostic accuracy than MRCP and should be preferred for diagnosis of pancreas divisum. Magnetic resonance cholangiopancreatography without secretin should be obsolete if the detection of pancreas divisum is desired.

REFERENCES


