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Is MRCP equivalent to ERCP for diagnosing biliary obstruction in orthotopic liver transplant recipients? A meta-analysis

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Abstract

Background—Biliary complications are the second leading cause of morbidity and mortality in orthotopic liver transplant (OLT) recipients. Endoscopic retrograde cholangiography (ERC) is considered the diagnostic criterion standard for post-orthotopic liver transplantation biliary obstruction, but incurs significant risks.

Objective—To determine the diagnostic accuracy of MRCP for biliary obstruction in OLT patients.

Design—A systematic literature search identified studies primarily examining the utility of MRCP in detecting post-orthotopic liver transplantation biliary obstruction. A meta-analysis was then performed according to the Quality of Reporting Meta-Analyses statement.

Setting—Meta-analysis of 9 studies originally performed at major transplantation centers.

Patients—A total of 382 OLT patients with clinical suspicion of biliary obstruction.

Interventions—MRCP and ERCP or clinical follow-up.

Main Outcome Measurements—Sensitivity and specificity of MRCP for diagnosis of biliary obstruction.

Results—The composite sensitivity and specificity were 0.96 (95% CI, 0.92–0.98) and 0.94 (95% CI, 0.90–0.97), respectively. The positive and negative likelihood ratios were 17 (95% CI, 9.4–29.6) and 0.04 (95% CI, 0.02–0.08), respectively.

Limitations—All but 1 included study had significant design flaws that may have falsely increased the reported diagnostic accuracy.

Conclusions—The high sensitivity and specificity demonstrated in this meta-analysis suggest that MRCP is a promising test for diagnosing biliary obstruction in patients who have undergone

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liver transplantation. However, given the significant design flaws in most of the component studies, additional high-quality data are necessary before unequivocally recommending MRCP in this setting.

Since 2004, more than 6000 orthotopic liver transplantations have been performed annually in the United States.¹ Despite improved surgical technique, biliary complications occur in 10% to 34% of liver transplant recipients, representing the second leading cause of morbidity and mortality after graft rejection.^{2–5} Endoscopic retrograde cholangiography (ERC) is considered the diagnostic criterion standard for post-orthotopic liver transplantation biliary obstruction⁴ and is commonly performed in this patient population.² ERC, however, incurs significant risks such as pancreatitis, bleeding, infection, perforation, and sedation-related cardiopulmonary complications in as many as 10% of patients^{6–8} as well as death in as many as 0.5% of patients.⁹ The risk profile of diagnostic ERC may not be justifiable in an era in which the accuracy of MRCP has been shown to be excellent in several studies.^{9–18}

The most recent National Institutes of Health Consensus Statement on ERCP for Diagnosis and Therapy states that MRCP, EUS, and ERCP have comparable sensitivity and specificity for the diagnosis of choledocholithiasis,¹⁹ although no clear recommendations were made with respect to biliary strictures, particularly in orthotopic liver transplant recipients. A recent high-quality meta-analysis of 67 studies evaluating the diagnostic accuracy of MRCP for diagnosing biliary obstruction found that MRCP has a sensitivity and specificity of 97% and 98%, respectively.⁹ This meta-analysis, however, did not specifically evaluate post-orthotopic liver transplantation biliary obstruction and raised concerns about the accuracy of MRCP in this setting. It has been reported that in less than 40% to 50% of transplant recipients with known anastomotic strictures, upstream biliary dilation develops, likely secondary to denervation and fibrosis of the donor biliary system.^{4,20,21} The lower incidence of ductal dilation has been hypothesized to limit the diagnostic utility of MRCP in transplant recipients.^{4,9} Several studies have compared MRCP with ERC for the diagnosis of post-transplantation biliary strictures, but sample sizes have been small.^{10–18} Given the growing concerns about the risks of diagnostic ERC and uncertainty regarding the accuracy of MRCP in diagnosing post-orthotopic liver transplantation biliary obstruction, we performed a meta-analysis to determine the overall sensitivity, specificity, and diagnostic accuracy of MRCP for post-orthotopic liver transplantation biliary obstruction.

METHODS

Search strategy

The study was conducted according to standard guidelines for systematic review and meta-analysis of diagnostic studies.^{22,23} A computer-assisted literature search of EMBASE and PubMed (MEDLINE) from inception until September 15, 2009 was conducted to identify potentially relevant articles using the exploded medical subject heading (MeSH) term liver transplantation OR free-text term liver transplantation AND the exploded MeSH term cholangiopancreatography, magnetic resonance OR free-text term magnetic resonance cholangiopancreatography OR MRCP. Manual searches of reference lists from potentially relevant articles were performed to identify any additional studies that may have been

missed by using the computer-assisted strategy. In addition, for each potentially relevant article found on PubMed, the “relevant article” option was used to identify similar articles.

Study selection

Two investigators (J.E.J., B.J.E.) independently reviewed titles and abstracts of all citations identified by the literature search. Potentially relevant studies were retrieved and selection criteria were applied. Eligible articles were reviewed and data were abstracted in a duplicate and independent manner by 2 investigators (J.E.J., B.J.E.). Disagreement was resolved by consensus.

Inclusion and exclusion criteria

The selection criteria for inclusion into the meta-analysis were (1) a study that primarily examined the utility of MRCP in diagnosing biliary obstruction after liver transplantation; (2) study that contained primarily subjects who underwent MRCP for a clinical suspicion of biliary obstruction (not for routine follow-up); (3) study that explicitly defined the reference standard as cholangiography, surgery, liver biopsy, clinical follow-up, or some combination thereof; and (4) study from which the raw numbers (true positive, false positive, true negative, false negative) necessary for meta-analysis are reported or can be calculated. Exclusion criteria were (1) data duplicated in another article; (2) animal studies; and (3) articles in a language other than English.

Data extraction

Two independent reviewers (J.E.J., B.J.E.) extracted the following data from the selected studies: first author's name, year of publication, journal of publication, patient characteristics, type of anastomosis, MRCP technique, indication for MRCP, reference standard used, duration of clinical follow-up, timing between MRCP and reference standard, blinding of radiologists and endoscopists, and outcomes (true positive, false positive, true negative, false negative). Two other independent reviewers (A.S., J.T.) assessed the quality of included studies by extracting the 14 items in the Quality Assessment Tool for Diagnostic Accuracy Systematic Review (QUADAS) guidelines.²⁴

Data synthesis and statistical analysis

The primary outcomes of interest were the sensitivity and specificity of MRCP for biliary obstruction in patients who had undergone orthotopic liver transplantation. We applied a bivariate mixed-effects regression model for synthesis of diagnostic test data assuming a binomial error distribution for sensitivity and specificity.^{25,26} Composite sensitivity, specificity, likelihood ratios, and diagnostic odds ratios were calculated.

Heterogeneity of outcomes between included studies was evaluated graphically by a Forest plot and summary receiver-operating characteristic curve. The χ^2 test of homogeneity and the inconsistency index (I^2) were used to statistically assess heterogeneity.²⁷ Publication bias was assessed with a Deek's funnel plot asymmetry test.²⁸ The MIDAS (Meta-analytical Integration of Diagnostic Accuracy Studies)²⁹ command in Stata 10.1 (StataCorp LP, College Station, Tex) was used to analyze the data by using a bivariate mixed-effects model.

RESULTS

Literature search

A total of 285 articles were retrieved by using the search criteria described. Title and abstract review identified 15 studies eligible for detailed review. Nine studies were included in the meta-analysis.^{10–18} There was 100% agreement between reviewers regarding study selection.

Excluded studies

Six studies were excluded.^{30–35} Zoepf et al³³ was excluded because the primary purpose of the study was to compare ERC with various noninvasive methods such as US, MRCP, and CT. The 2004 study by Boraschi et al³⁴ was excluded because it appeared to be a subset of their 2001 study, which was included in the final analysis. Linhares et al³⁰ and Ott et al³¹ were excluded because most of the MRCPs were performed for routine follow-up and not for suspicion of biliary obstruction. Bridges et al³⁵ was excluded because the study was a comparison of 2 types of MRCP rather than an evaluation of the diagnostic accuracy of MRCP. Ward et al³² was excluded because not all included subjects underwent liver transplantation, and we were unable to determine the raw numbers for transplanted patients.

Included studies

Demographics—The selected studies included 382 patients with 435 MRCP readings. MRCPs were performed 11 days to 10 years after transplantation. The studies that reported surgery type included 299 patients who underwent choledochocholedochostomy, and 46 patients who underwent choledochointerostomy.^{11–14,16–18} Eight articles provided specific information about the type of strictures identified^{10–12,14,16–18} and included 85 anastomotic strictures and 76 nonanastomotic strictures. Additional patient demographics of each included article are listed in Table 1.

Diagnostic accuracy—Our independent extraction of sensitivity and specificity matched the reported values in all but 2 studies. Kitazono et al¹⁰ reported the sensitivity and specificity of the 2 reading radiologists separately, but we opted to report only the results from the less-accurate radiologist. Fulcher and Turner¹⁶ reported the sensitivity for choledocholithiasis (86%) separately from stricture (100%), but we combined all findings for a combined sensitivity of 94%.

Statistical data for each included study are given in Table 1. The composite sensitivity of MRCP for diagnosing biliary obstruction in this meta-analysis was 0.96 (95% CI, 0.92–0.98). The composite specificity of MRCP for diagnosing biliary obstruction in this meta-analysis was 0.94 (95% CI, 0.90–0.97). The area under the summary receiver-operating characteristic curve was 0.99 (95% CI, 0.97–0.99) (Fig. 1). The Forest plots for sensitivity and specificity of MRCP for assessing biliary obstruction after orthotopic liver transplantation are illustrated in Figure 2. The diagnostic odds ratio was 378 (95% CI, 157–910). The heterogeneity I^2 for sensitivity was 0.0 and for specificity was 1.0, demonstrating absence of heterogeneity.

Evaluation of clinical utility

The positive likelihood ratio of MRCP for biliary obstruction was 17 (95% CI, 9.4–29.6). The negative likelihood ratio of MRCP for biliary obstruction was 0.04 (95% CI, 0.02–0.08). Because using MRCP as the initial diagnostic test is only appropriate in scenarios with low to moderate pretest suspicion for obstruction, we graphed posttest probability assuming pretest probabilities of 25% and 50%. In these situations, a positive MRCP results in posttest probabilities of 80% and 94%, respectively; a negative MRCP results in posttest probabilities of 1% and 4%, respectively (Figs. 3 and 4).

Assessment of study quality

The included studies fulfilled between 5 and 14 of the 14 QUADAS²⁴ items for methodological quality, with a mean of score of 9.7 (Table 2). Two studies had QUADAS scores less than 9.^{11,13} When these studies were excluded, the mean QUADAS score increased to 10.9 and the sensitivity and specificity were unchanged; however, many design flaws were noted, which may have introduced bias.

Potential biases

None of the studies used the ideal reference standard of ERCP and adequate clinical follow-up. Eight of the 9 studies did not use the same reference standard for positive and negative MRCP results.^{11–18} Of the studies that reported which patients were followed clinically, 121 patients with normal MRCPs were followed for 2 or more months, and none of the studies reported the need for direct cholangiography during the follow-up period in these patients. Table 1 provides details regarding the reference standard used in each study. Other design flaws are further elucidated in the discussion.

Assessment of publication bias

Although an imperfect test for assessing publication bias,³⁶ Deek's funnel plot asymmetry test was not significant ($P = .47$), nor was there a significant slope, suggesting that a large degree of publication bias was not present (Fig. 5).

DISCUSSION

Although there is adequate scientific evidence to support the use of MRCP for diagnosing biliary obstruction in general, it remains unclear whether these data can be extrapolated to liver transplant recipients. This meta-analysis suggests that MRCP may have excellent diagnostic accuracy for biliary obstruction in patients who have undergone orthotopic liver transplantation, with a composite sensitivity of 0.96 and a composite specificity of 0.94. When stratified by stricture site, there was little difference in sensitivity (97% for anastomotic strictures and 94% for nonanastomotic strictures). The overall positive and negative likelihood ratios were 17 and 0.04, respectively. The summary results had virtually no heterogeneity, implying that the component studies were uniform in their procedures, patient populations, and design.

All included studies adequately described the MRCP techniques used. Several studies used older 2-dimensional techniques (Table 1), and only 1 study¹⁰ used a combination of

techniques. A combination of 2- and 3-dimensional techniques with varying slice thickness has recently been shown to improve accuracy for diagnosing biliary complications in the post-liver transplantation population.³⁷ Even with these differences, all study protocols were considered good to excellent in quality by our contributing radiologist (M.A.). However, it should also be noted that the component studies were performed at centers with well-developed expertise in MRCP, so the results may not be applicable to centers with less MRCP expertise.

Despite these promising results, however, many of the component studies in this meta-analysis had methodological flaws that merit further discussion. First, none of the studies used the ideal reference standard of ERCP and adequate clinical follow-up. This combined reference standard is critical because the clinical significance of a biliary stricture is often not established until sufficient time has passed to determine whether the ERC-guided intervention (dilation or stenting) has resulted in biochemical and clinical improvement. In addition, because the ideal criterion standard was not used, an area under the curve of 0.99 means only that MRCP is almost as good as ERCP in isolation. Because the diagnostic accuracy of ERCP in isolation of clinical follow-up has not been determined, a “best” area under the curve for MRCP cannot be calculated but is likely to be significantly lower than 0.99.

Second, 8 of the 9 studies did not use the same reference standard for positive and negative MRCP results.^{11–18} MRCPs with positive findings were often followed by direct cholangiography or surgery, whereas patients with negative MRCP findings were often followed clinically^{11–15,17,18} (Table 1). Only 2 studies provided a final diagnosis for all the patients with negative MRCP findings who were followed clinically.^{11,17} These discrepancies may have caused a differential verification bias and could have falsely elevated the reported sensitivities. On the other hand, a sufficiently large number of patients with negative MRCP findings who underwent only clinical follow-up seem to have done well, without the need for direct cholangiography, making it less likely that a clinically significant obstruction was missed.

Several included studies did not report the time delay between MRCP and the reference standard^{13,18} or included a significant proportion of patients in whom the delay was greater than a week¹¹ or a month,¹⁶ thus raising the possibility of disease progression (strictures) or regression (spontaneously passed stones) bias. All but 1 of the studies reported blinding of the radiologists interpreting the MRCPs^{10,12–18}; however, most of studies did not specifically state that the person performing direct cholangiography or surgery was blinded to the results of the MRCPs,^{10,12–18} thus raising the possibility of review bias.

Finally, several studies included patients who were not representative of those who would typically be considered for MRCP in clinical practice or did not provide enough information to make this determination. For example, 2 studies included patients with suspicion of ascending cholangitis.^{12,18} Another study¹⁷ reported that 11 of the 23 patients had both biliary dilation and hyperbilirubinemia. In clinical practice, these patients would have been referred directly for ERC and should not have been included in a study evaluating the utility of MRCP. Few of the studies described the patients’ clinical status well enough to determine

the pretest probability of biliary obstruction, but rather imprecisely defined the inclusion criteria to be abnormal liver function test results.^{10–15,18} Only 1 study¹⁸ excluded recurrent viral hepatitis or rejection before study entry. Therefore, it is unclear whether these patients were appropriate for MRCP, suggesting the possibility of spectrum bias.

On the basis of these methodological flaws in the component studies, MRCP cannot be universally recommended as the diagnostic test of choice for post-orthotopic liver transplantation biliary obstruction in the absence of a definitive high-quality study. The ideal study should prospectively and consecutively enroll only post-orthotopic liver transplantation patients at low to moderate suspicion for biliary obstruction. Patients with cholestatic liver enzymes and biliary ductal dilation on transabdominal US or a clinical syndrome consistent with ascending cholangitis should be excluded, as these patients are most appropriate for ERC in clinical practice. If biliary dilation or bacterial cholangitis are absent, included patients should undergo MRCP followed within 24 hours by ERC or percutaneous transhepatic cholangiogram regardless of MRCP findings. The reference standard should include at least 8 weeks of clinical follow-up in addition to direct cholangiographic findings to determine whether the intervention performed during ERC or percutaneous transhepatic cholangiography has resulted in biochemical and clinical improvement. True negative MRCPs should be recorded only if the direct cholangiogram is unremarkable and an alternative etiology for liver function test result abnormalities is discovered. The time since transplantation should be recorded and evaluated to determine whether the utility of MRCP varies between early and late biliary complications. The type of ductal anastomosis should also be noted because a lower accuracy threshold may be tolerated for patients with Roux-en-Y anatomy given the difficulty in performing ERC in this patient population. Endoscopists and radiologists should be blinded in this study. A cost-utility and safety analysis should also be performed because the high incidence of biliary complications in the post-liver transplantation population may render MRCP cost-ineffective even in patients with low to moderate clinical suspicion of biliary obstruction.

In summary, this meta-analysis demonstrates that MRCP may have excellent sensitivity and specificity for diagnosing biliary obstruction in patients who have undergone orthotopic liver transplantation. The aggregate positive and negative likelihood ratios suggest that MRCP may be an appropriate test in patients with low to moderate suspicion for biliary obstruction, and the use of MRCP could potentially avoid the unnecessary risks of ERCP in this clinical scenario. However, given the significant methodological flaws in most of the component studies, a definitive high-quality clinical trial would be helpful before universally recommending MRCP in this setting.

Abbreviations

ERC	endoscopic retrograde cholangiography
OLT	orthotopic liver transplant
QUADAS	Quality Assessment Tool for Diagnostic Accuracy Systematic Review

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Take-home Message

- Although this meta-analysis demonstrated a high sensitivity and specificity, the overall quality of the component studies was poor. A definitive high-quality trial would be useful before universally recommending MRCP as the diagnostic test of choice for identifying and excluding biliary obstruction in orthotopic liver transplant recipients.

Figure 1. Summary receiver-operating characteristic (SROC) curve demonstrating composite sensitivity (SENS) and specificity (SPEC). AUC, area under the curve.

Figure 2.

Forest plot for the sensitivity and specificity of MRCP for assessing biliary obstruction in post-orthotopic liver transplantation patients. CI, confidence interval.

Figure 3.

Positive and negative likelihood ratios for MRCP for diagnosing biliary obstruction in post-orthotopic liver transplantation patients given a pretest likelihood ratio (LR) of 25%.

Post_Prob_Pos, posttest probability of a positive test; Post_Prob_Neg, posttest probability of a negative test.

Figure 4.

Positive and negative likelihood ratios for MRCP for diagnosing biliary obstruction in post-orthotopic liver transplantation patients given a pretest likelihood ratio (LR) of 50%.

Post_Prob_Pos, posttest probability of a positive test; Post_Prob_Neg, posttest probability of a negative test.

Figure 5.
Deeks funnel plot asymmetry test for identifying publication bias.

TABLE 1

Patient, study design, and statistical characteristics of included studies

Study (year)	No. of patients	Mean age, y	% Men	MRCP technique	Reference standard	TP	FP	FN	TN	Sens	Spec
Fulcher and Turner ¹⁶ (1999)	25	46	56	Thin RARE, thick RARE	24 ERC/PTC/tube, 1 surgery <24 h to >30 d after MRCP	16	0	1	8	94	100
Laghi et al ¹⁷ (1999)	23	46	78	3D TSE	15 + MRCP → ERC/PTC/tube within 24–48 h; 11 – MRCP → 3–10 mo clinical F/U	15	0	0	11	100	100
Meersshaut et al ¹¹ (2000)	12	57	50	Thin TSE, thick RARE	5 ERC/PTC 7–18 d before or after MRCP 7 clinical F/U of unclear duration	12	0	0	3	100	100
Boraschi et al ¹⁴ (2001)	113	50	80	Thin FSE, thick FSE	50 ERC, 5 PTC within 7 d, 11 surgery 58 with normal MRCP findings >6 mo clinical F/U + US	38	6	3	74	93	93
Valls et al ¹⁸ (2005)	63	53	75	Thin TSE, thick FSE	41 + MRCP → direct cholangiogram 22 – MRCPs → clinical F/U for 2–48 mo	42	1	2	20	96	95
Beltran et al ¹² (2005)	46	55	67	3D TSE	24 ERC, 10 PTC, 5 surgery 30 – MRCP → <6 mo clinical F/U + US	28	1	2	40	93	98
Kitazono et al ¹⁰ (2007)	8	57	75	Multiple 3D RARE	ERC in all patients within 24 h of MRCP	6	1	0	2	100	67
Maj et al ¹³ (2007)	40	44	43	3D RARE, thick RARE	17 direct cholangiogram, 2 fistulogram, 3 path, 2 surgery, 25 clinical F/U	45	1	0	5	100	83
Boraschi et al ¹⁵ (2008)	52	NS	NS	Thin FSE, thick FSE	31 + MRCPs → ERC or PTC 21 – MRCPs → PTC, ERC, surgery, bx, imaging	30	1	2	19	94	95
Totals	382					232	11	10	182	96	94

bx, Biopsy; 3D, 3-dimensional; ERC, endoscopic retrograde cholangiography; FN, false negative; FP, false positive; FSE, fast spin echo; F/U, follow-up; N/S, not supplied; PTC, percutaneous transhepatic cholangiogram; RARE, rapid acquisition with refocused echoes; Sens, sensitivity; Spec, specificity; TN, true negative; TP, true positive; TSE, turbo spin echo.

TABLE 2
Quality Assessment Tool for Diagnostic Accuracy Systematic Review of quality criteria of included studies

Criteria	Study								
	Fulcher and Turner ¹⁶	Laghi et al ¹⁷	Meerschaert et al ¹¹	Borascchi et al ¹⁴	Valls et al ¹⁸	Beltran et al ¹²	Kitazono et al ¹⁰	Maj et al ¹³	Borascchi et al ¹⁵
Patient spectrum representative?	–	+	?	–	–	–	+	?	+
Selection criteria described?	+	+	–	+	+	+	+	+	+
Reference standard appropriate?	+	+	?	+	+	+	+	?	+
Time between tests appropriate?	–	+	–	+	?	?	+	?	?
Uniform verification by reference standard?	+	+	?	+	+	+	+	?	+
Same reference test used?	–	–	–	–	–	–	+	–	–
Reference standard independent?	+	+	+	+	+	+	+	+	+
Index test described adequately?	+	+	+	+	+	+	+	+	+
Reference standard described adequately?	+	+	–	+	–	+	+	–	–
Blinding to reference standard results?	+	+	?	+	+	+	+	+	+
Blinding to index test results?	?	?	?	?	?	?	+	?	?
Appropriate clinical data available?	+	+	+	+	+	+	+	+	+
Uninterpretable data reported?	+	+	+	+	+	+	+	+	+
Withdrawals explained?	+	+	+	+	+	+	+	+	+
No. of criteria met out of 14	10	12	5	11	9	10	14	6	10

+, Criteria met; –, criteria not met; ?, unable to determine whether criteria were met.