

## Retrospective Study

# Risk factors of biliary intervention by imaging after living donor liver transplantation

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## Abstract

**AIM:** To determine the risk factors of biliary intervention using magnetic resonance cholangiopancreatography (MRCP) after living donor liver transplantation (LDLT).

**METHODS:** We retrospectively enrolled 196 patients who underwent right lobe LDLT between 2006 and 2010 at a single liver transplantation center. Direct duct-to-duct biliary anastomosis was performed in all 196 patients. MRCP images routinely taken 1 mo after LDLT were analyzed to identify risk factors for biliary intervention during follow-up, such as retrograde cholangiopancreatography or percutaneous transhepatic biliary drainage. Two experienced radiologists evaluated the MRCP findings, including the anastomosis site angle on three-dimensional images, the length of the filling defect on maximum intensity projection, bile duct dilatation, biliary stricture, and leakage.

**RESULTS:** Eighty-nine patients underwent biliary intervention during follow-up. The anastomosis site angle [hazard ratio (HR) = 0.48; 95% confidence interval (CI), 0.30-0.75,  $P < 0.001$ ], a filling defect in the anastomosis site (HR = 2.18, 95%CI: 1.41-3.38,

$P = 0.001$ ), and biliary leakage (HR = 2.52, 95%CI: 1.02-6.20,  $P = 0.048$ ) on MRCP were identified in the multivariate analysis as significant risk factors for biliary intervention during follow-up. Moreover, a narrower anastomosis site angle (*i.e.*, below the median angle of  $113.3^\circ$ ) was associated with earlier biliary intervention ( $38.5 \pm 4.2$  mo *vs*  $62.1 \pm 4.1$  mo,  $P < 0.001$ ). Kaplan-Meier analysis comparing biliary intervention-free survival according to the anastomosis site angle revealed that lower survival was associated with a narrower anastomosis site angle (36.3% *vs* 62.0%,  $P < 0.001$ ).

**CONCLUSION:** The biliary anastomosis site angle in MRCP after LDLT may be associated with the need for biliary intervention.

**Key words:** Magnetic resonance cholangiopancreatography; Liver transplantation; Living donor; Biliary intervention; Endoscopic retrograde cholangiopancreatography; Percutaneous transhepatic biliary drainage

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**Core tip:** Biliary complications and interventions are common after living donor liver transplantation (LDLT). Identifying patients who are at high risk for biliary interventions early after LDLT could help clinicians with patient follow-up. Magnetic resonance cholangiopancreatography (MRCP) imaging was performed 1 mo after LDLT to determine risk factors for biliary intervention. The anastomosis site angle, a filling defect in the anastomosis site, and biliary leakage on MRCP were identified as significant risk factors. Moreover, a narrower anastomosis site angle was related to earlier biliary intervention. Here, for the first time, we have shown that the anastomosis site angle might be associated with the need for biliary intervention.

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## INTRODUCTION

Biliary complications occur commonly after liver transplantation (LT)<sup>[1]</sup> and are the main cause of morbidity and mortality in LT recipients<sup>[2]</sup>. Magnetic resonance cholangiopancreatography (MRCP), a non-invasive tool used to visualize the biliary tract, has 88% sensitivity and 94% specificity for detecting biliary complications following LT<sup>[3]</sup>. Therefore, MRCP is the

recommended diagnostic modality for detecting biliary complications after LT<sup>[3]</sup>. Biliary interventions, such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic biliary drainage (PTBD) are generally used to manage these complications<sup>[4]</sup>.

Several investigators have documented risk factors influencing the development of biliary complications. Perioperative risk factors include a Model for End-stage Liver Disease (MELD) score  $> 35$ , donor age  $> 60$  years, and primary sclerosing cholangitis<sup>[5,6]</sup>. Intraoperative risk factors include cold ischemic time and anastomosis method (duct-to-duct *vs* hepaticojejunal methods)<sup>[5,6]</sup>. Cytomegalovirus infection and hepatic artery thrombosis have been reported as postoperative risk factors<sup>[5,6]</sup>.

However, no study has investigated the risk factors associated with the future need for intervention based on MRCP findings shortly after living donor LT (LDLT). Identifying patients at high risk for biliary intervention by MRCP, a non-invasive and accurate tool, during the early post-transplant period would be clinically helpful for managing and following patients who have undergone LT.

The purpose of this study was to determine factors, specifically the anastomosis site angle, that increase the requirement for biliary intervention during follow-up in LDLT recipients on MRCP images 1 mo after LT.

## MATERIALS AND METHODS

### Study population

We retrospectively reviewed the records of 270 patients who underwent LDLT at Seoul St. Mary's Hospital between 2006 and 2010. Of these 270 patients, 74 patients were excluded for the following reasons: two subjects underwent ERCP or PTBD within 1 mo after LDLT, 38 had no MRCP images taken 1 mo after LDLT, 13 had no three-dimensional (3D) reconstruction or maximum intensity projection (MIP) images or had poor quality images with severe artefacts, 3 underwent choledochojejunostomy as the biliary anastomosis method, and 18 died  $< 1$  mo after LDLT (bleeding, 4; sepsis, 11; graft failure, 3). Finally, 196 consecutive LDLT recipients who underwent MRCP 1 mo after LT were included in this study. The present study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (KC13RISI0788).

### Type of graft liver and anastomosis method

All 196 patients underwent right lobe living donor transplantation<sup>[7]</sup>. Biliary anastomosis was performed according to the anatomy of the hepatic duct: single duct-to-duct anastomosis for a single hepatic duct and double duct-to-duct anastomosis, or hepaticoplasty, for double hepatic ducts. Hepaticoplasty for double hepatic ducts was performed to create one lumen in cases of a short distance between the two hepatic

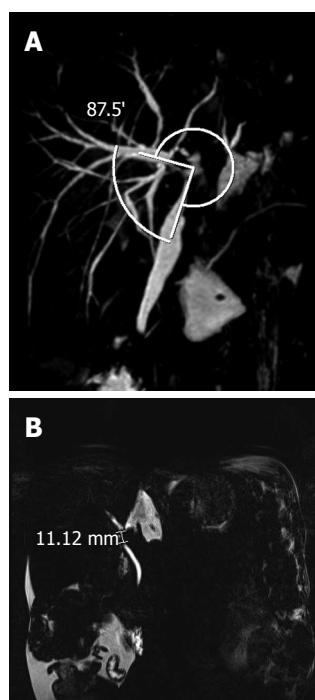


Figure 1 Representative magnetic resonance cholangiopancreatographic image showing the anastomosis site angle (A) and the filling defect (B).

ducts<sup>[8]</sup>. Alternatively, double duct-to-duct anastomosis was performed such that each duct was anastomosed to the left and right hepatic ducts individually.

#### Timing of biliary intervention during follow-up

Biliary intervention was defined as procedures involving ERCP and PTBD. During follow-up, these procedures were performed when the following criteria were met: (1) abnormal laboratory findings of biliary-associated factors, such as serum bilirubin, alkaline phosphatase and  $\gamma$ -glutamyl transferase; and (2) radiologically determined bile duct stricture with dilatation above the stricture site<sup>[9]</sup>.

#### MRCP image analysis

MRCP was performed 1 mo after LDLT. The anastomosis site angle was measured using 3D reconstruction imaging. The anastomosis site angle was defined as the angle between the donor hepatic duct and the recipient's common hepatic duct (Figure 1A). If there were two anastomosis sites, the smaller one was chosen. To improve the accuracy of measurement of the anastomosis site, we checked the measurements on every 3D image rendered and chose the smallest site. We also identified the presence of a filling defect and the length of the filling defect on MIP images. Every image was reviewed, and the filling defect with the longest length was chosen (Figure 1B). The presence of bile duct dilatation, biliary stricture, and leakage was also verified. MRCP images were reviewed by two experienced radiologists (Lee YJ and Yeo DM) without knowledge of the patient's clinical status, and

the measurements were made in consensus.

#### Statistical analysis

The patient characteristics are expressed as the means  $\pm$  SD (range) or counts, as appropriate. The inter-observer correlation coefficient (ICC) was determined to evaluate agreement between the two radiologists for the anastomosis site angle and the length of the filling defects. The Cox proportional hazards model was used to determine risk factors for biliary intervention, such as ERCP or PTBD, after LDLT. Variables with  $P$  values  $< 0.2$  in the univariate Cox regression analysis were considered potential variables for the multivariate Cox regression analysis. A forward selection method was adopted to identify significant risk factors with  $P$  values  $< 0.05$ . Kaplan-Meier analysis was also performed to estimate biliary intervention-free survival according to the anastomosis site angle. All statistical analyses were performed using SPSS ver. 15.0 (SPSS, Chicago, IL, United States).

## RESULTS

#### Patient characteristics

Of the 196 patients, 136 (70.0%) were men, and the mean recipient age was  $49.7 \pm 10.1$  years. The underlying causes for LT were hepatocellular carcinoma ( $n = 80$ , 40.8%), decompensated liver cirrhosis (LC) associated with hepatitis B ( $n = 51$ , 26.0%), alcoholic LC ( $n = 27$ , 13.8%), and hepatitis C-associated LC ( $n = 4$ , 2.0%). Eighty-nine patients (45.4%) underwent biliary intervention (Table 1). At the time of biliary intervention, jaundice (80.5%) and itching sensation (33.3%) were the main manifestations. In laboratory findings, mean total bilirubin was 5.2 (1.7–32.4); mean alkaline phosphatase was 433.1 (130–1465) and mean  $\gamma$ -glutamyl transpeptidase was 502.7 (92.9–2000.0).

Single duct-to-duct anastomosis was the most common anastomosis type ( $n = 145$ , 74.0%). Biliary stricture ( $n = 91$ , 46.4%) and a filling defect on an MIP image ( $n = 90$ , 45.9%) were the most common findings. Biloma and hematoma were noted in 13 (6.6%) and 10 (5.1%) patients, respectively (Table 2).

The mean anastomosis site angles were  $112.9^\circ$  and  $109.2^\circ$  according to radiologists 1 and 2, respectively, and the ICC was 0.896 ( $P < 0.001$ ). The lengths of the filling defects on the MIP images were 3.4 mm according to both radiologists, and the ICC was 0.921 ( $P < 0.001$ ) (Table 3).

#### Factors predicting biliary intervention

Factors with  $P$  values  $< 0.20$  in the univariate analysis were the anastomosis site angle on a 3D image [hazard ratio (HR) = 0.42, 95% confidence interval (CI), 0.27–0.65,  $P < 0.001$ ], recipient age  $> 65$  years (HR = 2.10, 95%CI: 0.85–5.20,  $P = 0.110$ ), a filling defect on an MIP image (HR = 2.44, 95%CI: 1.58–3.75,  $P < 0.001$ ), length of the filling defect on an MIP image

**Table 1** Baseline characteristics of the patients *n* (%)

Variable	
Recipient age (yr) <sup>1</sup>	49.7 ± 10.1 (13-68)
Older age patients (> 65 yr)	6 (3.1)
Recipient sex (M/F)	138 (70.0)/58 (30.0)
Donor age (yr) <sup>1</sup>	34.0 ± 10.9 (16-64)
Older donor age (> 60 yr)	2 (1.0)
Donor sex (M/F)	114 (58.2)/82 (41.8)
Age difference (recipient age - donor age)	15.7 ± 14.4 (-22 to 42)
MELD score	17.4 ± 10.4 (2.1 to 58.1)
High score patients (> 35)	13 (6.6)
Cause	
LC-B	51 (26.0)
LC-C	4 (2.0)
Alcohol	27 (13.8)
Hepatocellular carcinoma	80 (40.8)
Combined	5 (2.6)
Hepatitis A	9 (4.6)
Other (drug, autoimmune, unknown)	20 (10.2)
Total ischemic time	91.5 ± 16.0 (60-145)
Group 1 <sup>2</sup>	93.7 ± 17.9
Group 2 <sup>2</sup>	88.8 ± 15.1
Number of patients with biliary intervention	89 (45.4)
ERCP	38
PTBD	12
Both (ERCP and PTBD)	38
Re-operative intervention	0
Mean duration without biliary intervention (mo)	33.5 ± 28.6 (1-89)

<sup>1</sup>Mean age; <sup>2</sup>The groups were categorized according to the anastomosis site angle (median angle = 113.3°); group 1, angle > 113.3°; group 2, angle ≤ 113.3. MELD: Model for end-stage liver disease; ERCP: Endoscopic retrograde cholangiopancreatography; PTBD: Percutaneous transhepatic biliary drainage; LC: Liver cirrhosis.

**Table 2** Clinical profiles of the patients analyzed *n* (%)

Variable	Number of patients
Using T-tube	13 (6.6)
Anastomosis method	
Type 1 <sup>1</sup>	145 (74.0)
Type 2 <sup>2</sup>	51 (26.0)
MRI findings	
Filling defect on MIP image	90 (45.9)
Diffuse bile duct dilatation	29 (14.8)
Biliary stricture	91 (46.4)
Biliary leakage	6 (3.1)
Biloma	13 (6.6)
Hematoma	10 (5.1)
Thrombus, infarct	3 (1.5)
Common bile duct stone	2 (1.0)

<sup>1</sup>Type 1, single duct-to-duct anastomosis; <sup>2</sup>Type 2, double duct-to-duct anastomosis including hepatoplasty. MRI: Magnetic resonance imaging; MIP: Maximum intensity projection.

(HR = 1.04, 95%CI: 1.01-1.06, *P* = 0.010), biliary leakage (HR = 2.49, 95%CI: 1.01-6.14, *P* = 0.049), hematoma (HR = 1.80, 95%CI: 0.78-4.10, *P* = 0.179), and diffuse bile duct dilatation (HR = 1.59, 95%CI: 0.93-2.70, *P* = 0.088) (Table 4).

The significant risk factors in the multivariate

**Table 3** Patient characteristics and inter-observer agreement

	Radiologist 1	Radiologist 2	Inter-observer agreement
Anastomosis site angle (°)	112.9 (32.5-168.4)	109.2 (31-173)	0.896 ( <i>P</i> < 0.001)
Length of filling defect (mm)	3.4 (0-33.9)	3.4 (0-33)	0.921 ( <i>P</i> < 0.001)

**Table 4** Cox regression model for factors predicting biliary intervention

Variable	Univariate		Multivariate	
	Exp (B)	95%CI	Exp (B)	95%CI
Recipient age	1.01	0.99-1.04		
Older age (> 65 yr)	2.10	0.85-5.20		
Recipient sex	1.11	0.69-1.70		
Donor age	1.00	0.98-1.02		
Older donor age (> 60 yr)	0.92	0.13-6.51		
Donor sex	0.84	0.55-1.28		
Age difference <sup>1</sup>	1.01	0.99-1.02		
MELD score <sup>2</sup>	1.00	0.99-1.02		
High MELD score (> 35) <sup>2</sup>	0.97	0.42-2.22		
Anastomosis method <sup>3</sup>				
Type 2 vs 1	1.14	0.72-1.80		
T-tube	0.98	0.43-2.24		
MRI findings				
Anastomosis site angle <sup>4</sup>				
Group 2 vs group 1 <sup>4</sup>	0.42	0.27-0.65	0.48	0.30-0.75
Filling defect <sup>5</sup>	2.44	1.58-3.75	2.18	1.41-3.38
Length of filling defect <sup>5</sup>	1.04	1.01-1.06		
Diffuse bile duct dilatation	1.59	0.93-2.70		
Biliary stricture	1.03	0.68-1.56		
Biliary leakage	2.49	1.01-6.14	2.52	1.02-6.20
Biloma	1.54	0.74-3.19		
Hematoma	1.80	0.78-4.10		
Thrombus, infarct	0.64	0.09-4.59		

<sup>1</sup>Recipient age-donor age; <sup>2</sup>MELD, model for end-stage liver disease;

<sup>3</sup>Type 1, single duct-to-duct anastomosis; type 2, double duct-to-duct anastomosis; <sup>4</sup>Checked on the three-dimensional image; the groups were categorized according to the anastomosis site angle (median angle = 113.3°); group 1, angle > 113.3°; group 2, angle ≤ 113.3°; <sup>5</sup>Checked on the maximum intensity projection image. MRI: Magnetic resonance imaging.

analysis were a filling defect on an MIP image (HR = 2.18, 95%CI: 1.41-3.38, *P* = 0.001), biliary leakage (HR = 2.52, 95%CI: 1.02-6.20, *P* = 0.048), and the anastomosis site angle (HR = 0.48, 95%CI: 0.30-0.75, *P* < 0.001) (Table 4).

### Anastomosis site angle and biliary intervention

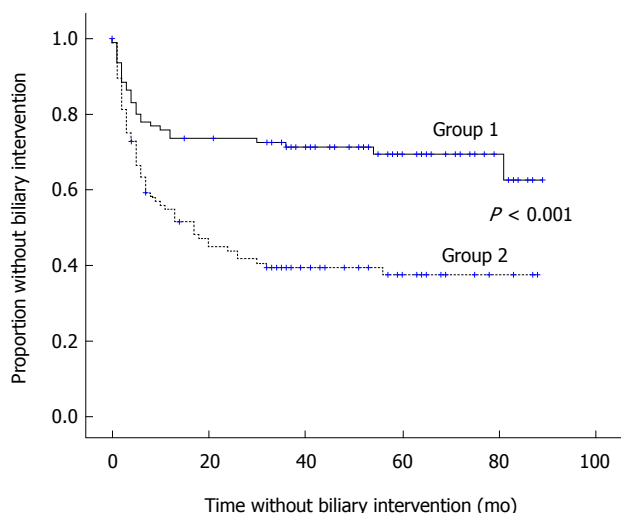
Two groups were created according to the median value of the anastomosis site angle (median angle = 113.3°): group 1, angle > 113.3° and group 2, angle ≤ 113.3°. The biliary intervention rate was significantly lower in group 1 (30.6% vs 60.2% in group 2, *P* < 0.001), and the mean time to biliary intervention was longer in group 1 (62.1 ± 4.1 vs 38.5 ± 4.2 in group 2, *P* < 0.001) (Table 5). Kaplan-Meier analysis comparing biliary intervention-free survival between groups 1 and 2 revealed higher survival in group 1 (Figure 2).



**Table 5** Biliary intervention rate by anastomosis site angle<sup>1</sup>

Variable	Total number	Number of events	Rate of events	P value	Mean time interval to events (mo)	P value
Group 1	98	30	30.6%	$P < 0.001$	62.1 ± 4.1	$P < 0.001$
Group 2	98	59	60.2%		38.5 ± 4.2	

<sup>1</sup>The groups were categorized according to the anastomosis site angle (median angle = 113.3°); group 1, angle > 113.3°; group 2, angle ≤ 113.3°.



**Figure 2** Kaplan-Meier curves for all biliary interventions according to the anastomosis site angle<sup>1</sup>. The Kaplan-Meier curves show that group 1 had a significant survival advantage without biliary intervention compared with group 2 (62.0% vs 36.3%,  $P < 0.001$ ). <sup>1</sup>The groups were categorized according to the anastomosis site angle (median angle = 113.3°); group 1, angle > 113.3°; group 2, angle ≤ 113.3°.

## DISCUSSION

Biliary complications after LDLT are an important cause of morbidity and mortality; however, the risk factors for biliary complications that can be determined from an MRCP image after LT have yet to be determined. In the present study, we identified biliary leakage, the presence of a filling defect on an MIP image, and the anastomosis site angle as significant risk factors on MRCP images associated with future biliary intervention.

In our analysis, neither the anastomosis method nor the presence of a T-tube was a risk factor for biliary intervention. Consistent with our results, several studies have demonstrated that the presence of a T-tube is not a risk factor for biliary complications<sup>[10,11]</sup>; however, some have argued the opposite<sup>[2]</sup>. Because it is widely accepted to be more physiologically appropriate and has a therapeutic advantage over Roux-en-Y choledochojejunostomy, duct-to-duct anastomosis was performed in our study<sup>[12]</sup>. We investigated the relationship between increases in the number of duct-to-duct anastomoses and increases in biliary intervention rate. Our findings agree with those of Tsui *et al.*<sup>[13]</sup>; however, they differ from the results of other studies<sup>[14,15]</sup>.

Our results demonstrate that biliary leakage on

MRCP was predictive of biliary intervention after LDLT. Biliary leakage can cause complications, such as infection or biliary stricture<sup>[16]</sup>. Moreover, ERCP and PTBD are the mainstays for managing biliary leakage<sup>[17]</sup>. Therefore, our result that biliary leakage was a risk factor for biliary intervention is in accordance with previous findings.

A filling defect on MIP images was also a risk factor for biliary intervention. Several studies have indicated the significance of a filling defect detected on MRCP and have suggested that a filling defect could be a sign of bile duct carcinoma or papillomatosis<sup>[18-20]</sup>. In addition, intra-ductal debris, sludge, and stones could be causes of a filling defect after LT<sup>[21]</sup>. For these reasons, a filling defect on MIP images should be considered a risk factor for biliary intervention.

However, donor age > 60 years and a MELD score > 35 were not determined to be significant predictors of biliary intervention. Some studies have shown that these are risk factors for biliary complications<sup>[5,6]</sup>. These inconsistencies could be due to the lower proportion of patients with a donor age > 60 years or a high MELD score (> 35) in our study.

Finally, the anastomosis site angle on a 3D image was shown to be a risk factor for biliary intervention. We demonstrated that a wider anastomosis site angle (*i.e.*, above the median angle of 113.3°) resulted in a lower and delayed incidence of biliary intervention. No study has investigated the relationship between the anastomosis site angle and biliary complications or interventions after LDLT. Thus, we documented, for the first time, that a decrease in the anastomosis site angle on MRCP after LT could be a risk factor for biliary intervention during the follow-up period.

Several limitations of our study should be discussed. First, the design was retrospective. To improve the accuracy of the results, we reviewed every possible factor blinded to biliary outcome. Further prospective studies are warranted to confirm these results. Second, we could not obtain data on patient cold ischemic time, which is a well-known risk factor for biliary complications in deceased donor liver transplantation (DDLTL). Generally, however, cold ischemic time is very short during LDLT. Third, the biliary intervention rate we observed in our study was slightly higher than that reported by previous studies. Unfortunately, the reason for the observed high biliary intervention rate remains unknown.

Biliary complications after LDLT are commonly compared with those following DDLT<sup>[5]</sup>. Thus, pre-

dicting a future need for biliary intervention using a non-invasive method, such as MRCP, could be useful for hematologists and liver transplant surgeons.

In summary, we suggest that MRCP findings of a filling defect on MIP images, biliary leakage, and anastomosis site angle results 1 mo after LDLT can be used to determine the need for future biliary intervention. A further prospective clinical study will be needed to confirm the clinical implications of MRCP 1 mo after LDLT.

## COMMENTS

### Background

Biliary complications commonly occur after liver transplantation (LT) and are the main cause of morbidity and mortality in LT recipients. Magnetic resonance cholangiopancreatography (MRCP), a non-invasive and accurate tool, is the recommended diagnostic modality for detecting biliary complications after LT. Biliary interventions, such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic biliary drainage (PTBD), are generally used to manage these complications. Several investigators have documented risk factors influencing the development of biliary complications. However, no study has investigated the risk factors associated with the future need for intervention based on MRCP findings shortly after living donor LT (LDLT). The purpose of this study was to determine factors, specifically the anastomosis site angle, that increase the requirement for biliary intervention during follow-up in LDLT recipients on MRCP images 1 mo after LT.

### Research frontiers

In this study, the authors documented several risk factors for biliary complication by MRCP. They suggest that MRCP findings of a filling defect on maximum intensity projection (MIP) images, biliary leakage, and anastomosis site angle results 1 mo after LDLT can be used to determine the need for future biliary intervention.

### Innovations and breakthroughs

No study has investigated the relationship between the anastomosis site angle and biliary complications or interventions after LDLT. Thus, current study documented, for the first time, that a decrease in the anastomosis site angle on MRCP after LT could be a risk factor for biliary intervention during the follow-up period.

### Applications

Biliary complications after LDLT are an important cause of morbidity and mortality. Thus, predicting a future biliary intervention using a non-invasive method, such as MRCP, could be useful for hematologists and liver transplant surgeons.

### Terminology

MRCP: A non-invasive magnetic resonance imaging tool used to visualize the biliary tract with high sensitivity and specificity. ERCP: An endoscopic procedure specialized for viewing the biliary system and treating biliary complications such as stone and stricture. PTBD: An invasive procedure used to approach the biliary system and treat biliary complications via a percutaneous route.

### Peer-review

Lee *et al* analyzed MRCP imaging performed 1 mo after LDLT to determine risk factors for biliary intervention. The anastomosis site angle, a filling defect in the anastomosis site, and biliary leakage on MRCP were identified as significant risk factors. Moreover, a narrower anastomosis site angle was related to earlier biliary intervention. For the first time, they showed that the anastomosis site angle may be associated with the need for biliary intervention. A further prospective clinical study will be needed to confirm the clinical implications of MRCP mo after LDLT.

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