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TOPIC HIGHLIGHT

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Postoperative biliary adverse events following orthotopic liver transplantation: Assessment with magnetic resonance cholangiography

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Abstract

Biliary adverse events following orthotopic liver transplantation (OLT) are relatively common and continue to be serious causes of morbidity, mortality, and transplant dysfunction or failure. The development of these adverse events is heavily influenced by the type of anastomosis during surgery. The low specificity of clinical and biologic findings makes the diagnosis challenging. Moreover, direct cholangiographic procedures such as endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography present an inadmissible rate of adverse events to be utilized in clinically low suspected patients. Magnetic resonance (MR) maging with MR cholangiopancreatography is crucial in assessing abnormalities in the biliary system after liver surgery, including liver transplant. MR cholangiopancreatography is a safe, rapid, non-invasive, and effective diagnostic procedure for the evaluation of biliary adverse events after liver transplantation, since it plays an increasingly important role in the diagnosis and management of these events. On the basis of a recent systematic review of the literature the summary estimates of sensitivity and specificity of MR cholangiopancreatography for diagnosis of biliary adverse events following OLT were 0.95 and 0.92, respectively. It can provide a non-invasive method of imaging surgical reconstruction of the biliary anastomoses as well as adverse events including anastomotic and non-anastomotic strictures, biliary lithiasis and sphincter of Oddi dysfunction in liver transplant recipients. Nevertheless, conventional T2-weighted MR cholangiography can be implemented with T1-weighted contrast-enhanced MR cholangiography using hepatobiliary contrast agents (in particular using Gd-EOB-DTPA) in order to improve the diagnostic accuracy in the adverse events' detection such as bile leakage and strictures, especially in selected patients with biliary-enteric anastomosis.

Key words: Liver transplantation; Bile ducts; Biliary adverse events; Magnetic resonance cholangiography; Contrast-enhanced magnetic resonance cholangiography

Core tip: Biliary adverse events continue to be serious causes of morbidity, mortality, and transplant dysfunction or failure after orthotopic liver transplantation. In this article, we review the technique as well as the diagnostic role of magnetic resonance (MR) imaging with cholangiopancreatographic sequences in the assessment of adverse events following orthotopic liver transplantation. The features of the main types of biliary adverse events on MR cholangiopancreatography are presented and the recently developed techniques are also discussed in this setting, according to the biliary reconstruction and liver transplant procedure performed.

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INTRODUCTION

Orthotopic liver transplantation (OLT) has become an accepted therapy for acute and chronic end-stage liver disease[1,2]. Today, liver transplant patients have a 5-year survival rate of approximately 75%. The improvement in survival can be attributed to better patient selection and preparation, advances in organ preservation, improved immunosuppressive therapy agents, and refinement of surgical techniques[2,3].

Patients candidates for OLT are those with fulminant liver failure or with hepatic chronic diseases in which conventional therapies are no longer effective. In patients with fulminant hepatic failure (prevalently affecting young people) a large portion of the liver parenchyma is quickly destroyed and this causes liver dysfunction, infections, hepatic encephalopathy, and acute renal failure. Chronic hepatitis B and C, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, alcoholic liver disease, and liver injury induced by drugs are the most common chronic liver diseases that may be treated by transplantation. Patients affected by disorders of metal metabolism such as hemochromatosis and Wilson disease also may benefit from liver transplant.

BILIARY ADVERSE EVENTS AFTER ORTHOTOPIC LIVER TRANSPLANTS

Although over the years there has been a continuous improvement in survival after OLT, a significant number of adverse events is still reported. One of the most important complications following OLT is acute rejection whose diagnosis is generally obtained by graft biopsy and histologic examination. The other main adverse events are represented by arterial and venous stenosis and thrombosis; biliary strictures, lithiasis and leak; hepatic abscesses; right adrenal gland hemorrhage; fluid collections and hematomas; hepatitis virus C infection; lymphoprolifeative disease and tumors. Imaging techniques play a central role in excluding the other adverse events that may have clinical signs and symptoms as those of acute rejection[4,5].

Biliary tract adverse events are the most common complications after OLT and remain a major source of morbidity in liver transplant patients, with an incidence of 5%-32%. Adverse events such as bile leaks, anastomotic and non-anastomotic strictures, biliary stones, sludge and casts are encountered more commonly as a result of increased number of liver transplantations and the prolonged survival of transplant patients[6]. Early adverse events are those occurring within three months, whereas the late ones can be observed a few months to several years after OLT.

A major determinant of biliary adverse events' risk after OLT is represented by the choice of biliary anastomosis[7,8]. Choledochocholedochostomy (CC) and biliodigestive or choledochojejunostomy (CJ) are the most frequent types of surgical reconstruction. The first technique is a duct-to-duct anastomosis between donor and recipient choledochal ducts. Since it is simple, physiologic and allows preservation of the sphincter of Oddi, this biliary anastomosis is performed in most of liver transplant patients. On the other hand, the biliodigestive technique is an anastomosis between the donor choledochal duct and a jejunal loop of the recipient and is used in selected recipients. Since infectious colonization of the biliary tract is possible, episodes of cholangitis are reported in the natural history of these patients.

The choice of biliary reconstruction can be determined by the underlying hepatic disease, the caliber of donor and recipient choledochal ducts, previous transplant or hepato-biliary surgery and the preference of the performing surgeon. However, there are no clear guidelines on the preferred type of surgical anastomosis[6].

DIAGNOSIS OF BILIARY ADVERSE EVENTS AFTER OLT

The clinical presentation of biliary adverse events varies considerably and can vary from an asymptomatic patient with moderate liver enzyme elevations to a septic patient with fever and hypotension due to ascending cholangitis[6,9].

The prompt diagnosis and appropriate management of these adverse events are important to ensure the survival of both the organ and the patient after OLT, and the diagnostic algorithm has been repeatedly revised in order to achieve the most accurate approach[2,9-11].

Whenever a biliary adverse event is suspected, diagnostic work-up usually begins with laboratory evaluation and an abdominal Doppler ultrasound (US) that allows for the evaluation of the biliary tree and the hepatic vasculature. The positive predictive value of abdominal ultrasound is very high, especially in the presence of dilated bile ducts. In the absence of dilated bile ducts, the sensitivity of the ultrasound for detecting biliary obstruction ranges from 38% to 68%[12]. Although ultrasound is a non-invasive method to assess adverse events in recipients, a normal US examination cannot exclude the presence of biliary strictures, bile leakage or widespread abnormalities of the bile ducts[2,13,14]. When US findings are indeterminate or there is persistent clinical suspicion for an abnormality, multi-detector computed tomography (MD-CT) is often performed in the period after transplantation. This imaging technique is a fast, reliable, and non-invasive mean of visualizing hepatic artery, portal vein, hepatic veins, and inferior vena cava and assessing non-vascular graft complications and extra-hepatic organs. As concerns as biliary adverse events, CT can be utilized to identify biliary obstruction or leakage, but its true role has yet to be definitely established. Recent developments in imaging technology have enabled to obtain drip infusion cholangiography with CT, that allows detailed evaluation of biliary anatomy thanks to the high resolution of images, though the availability of intravenous cholangiographic contrast media is limited to a few countries.

A more conclusive evaluation of biliary adverse events can be obtained using T-tube cholangiography or invasive procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous trans-hepatic cholangiography (PTC)[4]. In patients with a suspicion of biliary adverse events in the early phase after OLT during which the T-tube is still in place, T-tube cholangiography is the examination of choice[15]. Nevertheless, when the T-tube is removed three months after transplantation or in the case it is not utilized at all, direct visualization of the biliary tract is only possible when using invasive procedures such as PTC and ERCP, which are associated with adverse events in 3.4% of PTC and 1%-7% of ERCP[4,15]. Although a commonly effective procedure adverse events caused by ERCP are well known and mainly include pancreatitis, gastrointestinal haemorrhage, cholangitis, hemobilia, and duodenal perforation; they can be life-threatening and can delay or even diminish the chance of managing the primary disease. Furthermore, in patients with biliodigestive anastomoses ERCP may be impossible or very difficult since endoscopic approach of the biliary tract is generally precluded because technically challenging[15-17].

Endoscopic ultrasound-guided biliary drainage (EUS-BD) is a recently introduced procedure which has been quickly accepted in recent years as a possible alternative for biliary drainage in patients in whom ERCP has previously failed[18]. Though EUS-BD is rapidly gaining popularity and attraction in the endoscopic world, the methods and indications have yet to be fully standardized and this new approach cannot be considered a treatment of first instance[18].

With the introduction of magnetic resonance cholangiopancreatography (MRCP) the same level of imaging of invasive procedures can be obtained non-invasively and this approach is particularly useful in recipients in which the tube T has been removed or has never been placed.

MR CHOLANGIOGRAPHY

As a non-invasive and accurate alternative to direct cholangiography, MR cholangiography represents the next step in the event that ultrasound does not reveal evidence of bile duct abnormalities despite clinical suspicion, and actually plays a crucial role in the assessment of biliary abnormalities after surgery[19]. Although various modifications of this technique have been recently proposed, they all require the acquisition of a heavily T2-weighted sequence, which allows to visualize the structures containing stationary or slow-moving fluids as very hyperintense areas. The quality of MRC has been significantly improved with the recent introduction of multiple three-dimensional (3D) pulse sequences. After preliminary acquisition of T1- and T2-weighted sequences in the axial plane, two MR cholangiographic techniques are conventionally performed: respiratory-triggered, thin-collimation (2.4 mm thk/-1.2 mm) 3D FRFSE T2-weighted sequences in the coronal plane and breath-hold, thick-collimation (40-60 mm), single-shot fast spin-echo T2-weighted sequences utilizing coronal/coronal oblique projections[19,20].

Very encouraging results have been reported by different authors as concerns as the MRC evaluation of biliary adverse events in patients who have undergone OLT[15,20-25]. In a recent meta-analysis published by Jorgensen *et al*[26], the authors concluded that using MRCP we can obtain an excellent diagnostic accuracy for biliary obstruction in liver transplant patients, with a combined sensitivity and specificity of 96% and 94%, respectively. On the basis of their data they also suggested that MRCP may be a suitable test in recipients having low to moderate suspicion for biliary obstruction, and the employment of this non-invasive technique may prevent the unneeded possible risks of ERCP in this clinical setting[26]. Besides, in a still more recent meta-analysis by Xu *et al*[27], these authors confirmed that MRCP is a highly accurate diagnostic technique for diagnosis of biliary complications and strictures in patients who have undergone OLT.

The disadvantages of conventional MRCP[28,29] are that it lacks functional information and so, differentiation between obstructive and non-obstructive dilatation of the bile ducts is often extremely difficult. Depiction of anatomy and lesion detection can be inadequate in a non-dilated biliary system; besides, free fluid and leak in the vicinity obscures the biliary anatomy due to overlapping[30]. Hence, there is often a need for a non-invasive imaging modality, which can provide reliable anatomic as well as functional information.

T1-weighted contrast-enhanced MR cholangiography with intravenous administration of hepato-biliary contrast agents such as Mn-DPDP, Gd-BOPTA and Gd-EOB-DTPA[31] is a technique that has been recently introduced and may provide both anatomical and functional information on the biliary tract. The above mentioned contrast media are picked up by normal hepatocytes and eliminated in the biliary system (3% to 5% for Gd-BOPTA, 20% for Mn-DPDP, 50% for Gd-EOB-DTPA)[32]. Subsequent contrast-enhanced MR imaging that can include both dynamic and delayed hepato-biliary phases are acquired by utilizing 3D breath-hold fat-suppressed T1-weighted gradient-echo imaging in the axial and coronal plane.

This emerging diagnostic tool, especially when using Gd-EOB-DTPA, is particularly helpful for depicting the anatomy of biliodigestive anastomoses and identifying

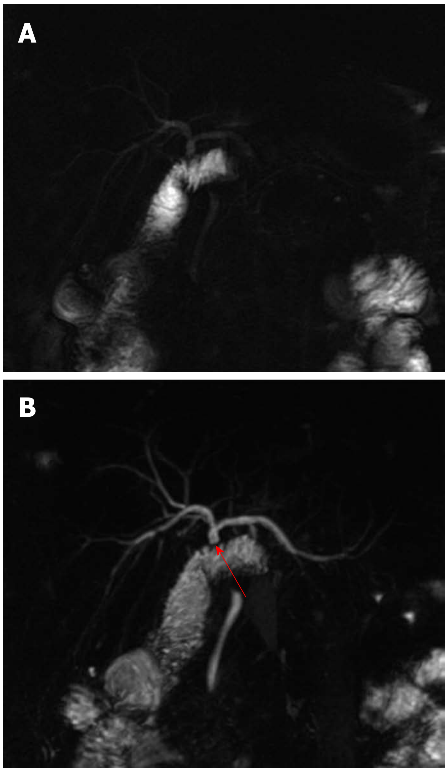

Figure 1 Bilio-enteric anastomosis. A: Single-shot thick-slab magnetic resonance cholangiogram shows a regular hepatico-jejunostomy; B: Maximum intensity projection reconstruction of 3D thin-slab fast spin-echo T2-weighted images confirms the anastomotic patency (red arrow) and better demonstrates the portion of the jejunum and the choledocho of the recipient.

adverse events such strictures of the anastomosis, bile leakages and lithiasis; besides, it can provide functional informations that are extremely promising in the grading of biliary obstruction. The drawbacks of contrast-enhanced MRC include its high cost (it is also a time-consuming technique) and its limited role in delineating the biliary tract in patients with liver dysfunction[32].

In a preliminary experience on 13 patients with hepaticojejunostomy, Hottat *et al*[29] concluded that contrast-enhanced T1-weighted MRC with intravenous administration of Mn-DPDP provides useful anatomic and functional information in patients suspected of having biliary obstruction on conventional T2-weighted MR cholangiography.

Hepatic excretion of hepato-biliary contrast agents results in enhancement of biliary structures and it is likely to have a great impact on better visualization of biliary system; on the basis of these characteristics it may potentially increase reliability of the MR examination or decrease the occurrence of a non diagnostic or equivocal interpretation[32].

BILIARY ANATOMY

In complex biliary surgical procedures, such as liver transplantation a non-invasive means of assessing the biliary tree after surgery is often necessary to exclude adverse events. MR cholangiography well depicts the postoperative reconstruction of the biliary system (particularly when it is dilated) and the different types of biliary anastomosis (Figures 1 and 2). Nevertheless, it can be limited in the visualization of the site of biliary-enteric anastomosis and also the possible cause of obstruction. Contrast-enhanced MRC may provide images with a higher resolution than those we can obtain using conventional T2-weighted MR cholangiography and has the advantage of contrast agent into the biliary system and jejunal loop, that significantly contribute to a better visualization of the anastomotic region.

BILIARY LEAKAGE

Although a series of biliary adverse events have been reported after OLT, the most frequent are leakages and strictures. The occurrence of biliary leaks is typically in the early phase after transplantation, while strictures can usually develop from several months to years[33]. Bile leaks occur in 2%-25% of cases after liver transplantation and can be classified in two categories: early bile leaks, which present within 4 wk of OLT and late bile leaks, which present beyond this time[34-37]. Early bile leaks usually occur at the anastomotic site or at the T-tube insertion site.

In liver transplant patients with both CC and a biliary-enteric anastomosis quick and correct localization of biliary leakages is helpful for guiding the more appropriate therapy. Thus, morbidity and mortality rates can be reduced significantly. The surgical reconstruction of the biliary tree and the time of onset determinate the treatment method when a biliary leakage occurs. The treatment of leaks is usually performed through endoscopic removable stenting that allows biliary drainage. Endoscopic sphincterotomy is sometime used for the removal of obstructing lithiasis or for the placement of a second stent so as to improve drainage of bile[38]. In patients in whom ERCP cannot be carried out, percutaneous transhepatic biliary drainage is usually used for diversion. In all cases in which there is a significant collection associated with a leakage, the collection must necessarily be drained in order to eliminate the risk of consequential infections and adhesions associated with the biliary fluid. In recipients with a leak shortly after transplantation or if it occurs at a hepaticojejunostomy, reintervention is generally considered[38].

US, CT, and MRC can be generally employed to identify a biliary leak[39,40]. Though imaging findings provided by these cross-sectional modalities may be suggestive of a biliary leakage in a proper clinical setting, they are frequently nonspecific (*e.g.*, fluid collection). In order to confirm the presence of an active leak, invasive procedures such as PTC or, less frequently, ERCP are generally utilized to demonstrate contrast agent extravasation from the biliary system. Nevertheless, in the current diagnostic work-up for a bile leak the first step is represented by abdominal US, and, if the findings provided by this examination are non-diagnostic, to perform conventional T2-

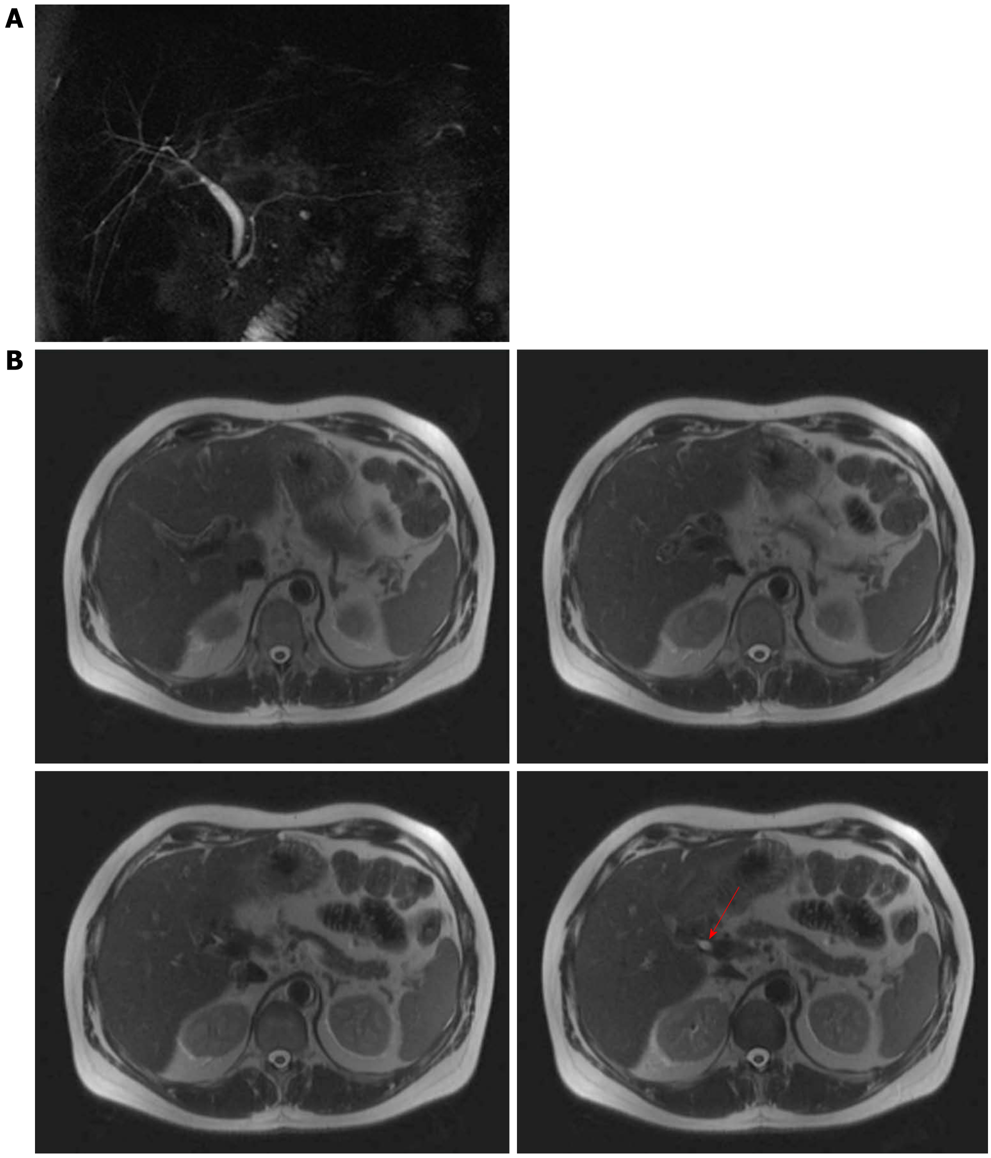

Figure 2 Duct-to-duct anastomosis. A: Single-shot thick-slab magnetic resonance cholangiogram shows a choledocho-choledocho anastomosis with a discrepancy of caliber between donor and recipient choledocho; B: Axial single-shot T2-weighted images demonstrate the anastomotic patency (red arrow).

weighted MR cholangiography. The reported accuracy of T2-weighted MRC in the detection and localization of a biliary leakage is between 70% and 74%[41].

Contrast-enhanced MRC with intravenous administration of hepato-biliary contrast agents provides functional informations as concerns as biliary excretion and may be extremely helpful in localizing the bile leak, which is not generally possible at un-enhanced T2-weighted MR cholangiography[42]. Indeed, using contrast-enhanced MRC we can demonstrate active biliary leakage by visualizing contrast media extravasation into the fluid collection and so we can also localize the anatomic site of the bile leak[43] (Figure 3).

BILIARY STRICTURES

Biliary strictures are the most frequent type of late biliary adverse events, occurring approximately 5-8 mo after OLT, and can be classified according to their location into stricture of the biliary anastomosis (AST) and non-anastomotic stricture (NAS)[44]. The incidence of the biliary strictures ranges from 5% to 34% of patients receiving liver transplant[37,45]. The prompt identification of AST and NAS is important to ensure the survival of both the organ and the patient after OLT. Moreover, the differentiation between the two types of stenosis is essential for the more appropriate therapeutic approach. Over the past few years the role of endoscopy in the management of post-OLT biliary strictures is gradually increased. Actually, the standard first-line therapy of biliary strictures is represented by endoscopic dilation with placement of single or multiple plastic stents; in most of cases and particularly in patients with anastomotic strictures this therapeutic approach avoids the need for percutaneous transhepatic therapy and surgery[46]. Non-anastomotic strictures are more difficultly treated than anastomotic

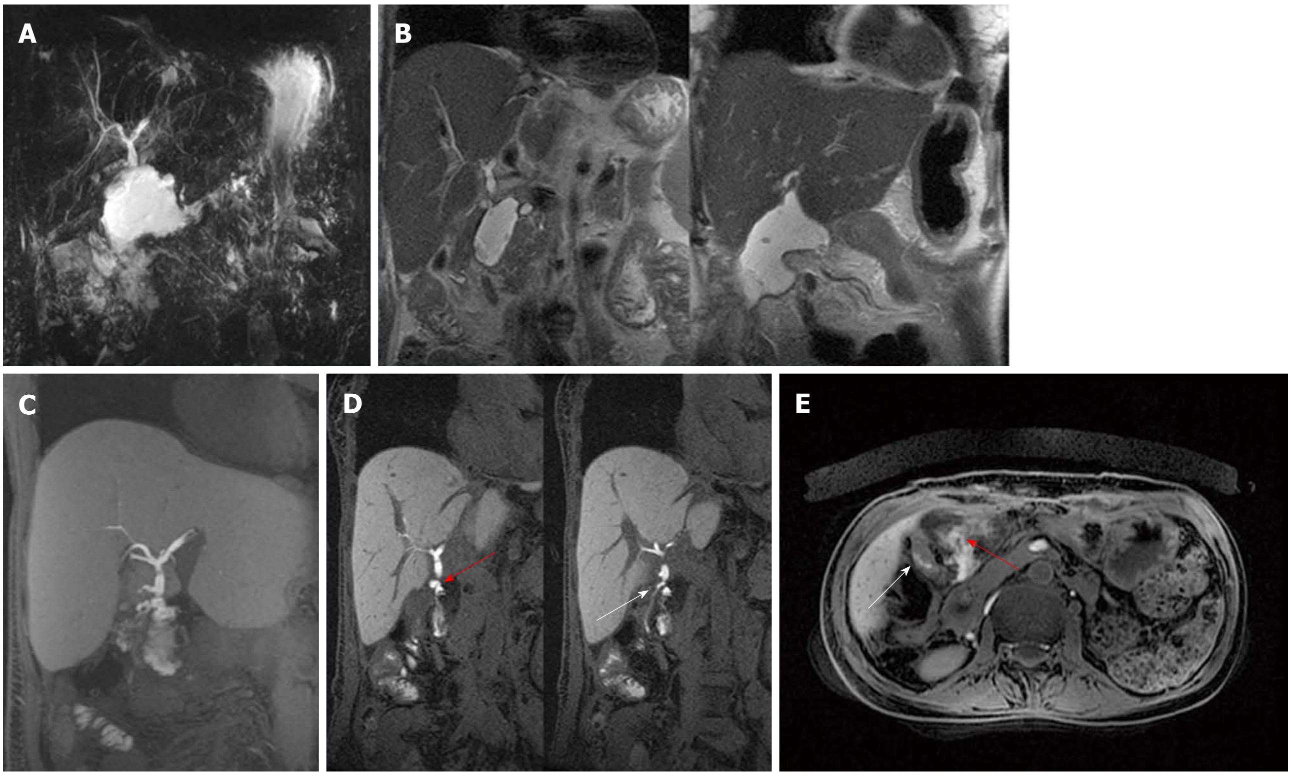

Figure 3 Anastomotic leak in a patient with hepatico-jejunostomy. A: Single-shot thick-slab magnetic resonance cholangiogram shows a fluid collection in the area of biliary-enteric anastomosis; B: Coronal T2-weighted images (at different levels) accurately depict circumscribed sub-hepatic fluid collections with thickened walls. C: Maximum intensity projection reconstruction of Gd-EOB-DTPA enhanced LAVA T1-weighted sequence well exhibits extravasation of contrast material into the peri-anastomotic space compatible with bile leak; D: Coronal Gd-EOB-DTPA enhanced LAVA T1-weighted images better identify contrast agent both extravasating from an anastomotic leak (red arrow) and filling the Roux-en-Y anastomosis (white arrow); E: On axial post-contrast LAVA image it is possible to distinguish the fluid collection (red arrow) from the jejunum (white arrow).

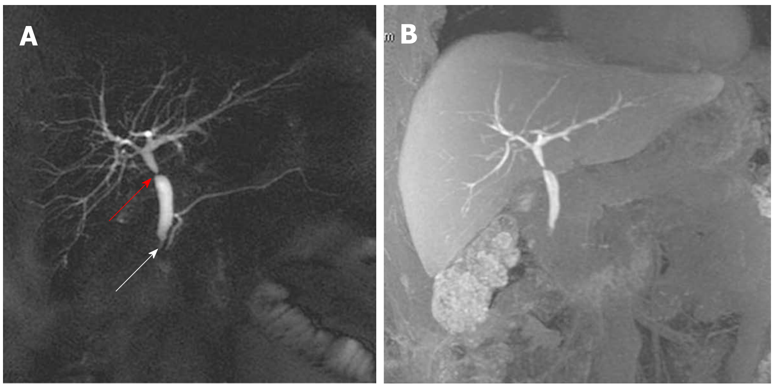

Figure 4 Anastomotic biliary stricture associated with sphincter of Oddi dysfunction. A: Single-shot thick-slab magnetic resonance cholangiogram shows stricture of both anastomotic site (red arrow) and iuxta-papillary choledocho (white arrow), with dilation of pre- and post-anastomotic biliary tract; B: Maximum intensity projection reconstruction of Gd-EOB-DTPA enhanced T1-weighted LAVA sequence demonstrates regular excretion of contrast-enhanced bile in the extra-hepatic biliary tract at 20 min, while contrast-enhanced bile excretion in the duodenum is not appreciable.

strictures, present an higher rate of episodes of cholangitis, and show a less favorable outcome in terms of graft and patient survival. A long term response to endoscopic treatment with dilatation and stent placement is reported in 50%-75% and in 70%-100% of patients with NAS and AS, respectively[46]. Percutaneous transhepatic approach and surgery including re-transplantation are currently considered for patients in whom endoscopic therapy is repeatedly failed and for those with bilio-digestive anastomosis. However, even in these latter patients, the possibilities of endoscopic treatment are expanding with the recent improvements of deep small bowel enteroscopy[46].

Anastomotic strictures at the site of biliary anastomosis can occur in both CC and CJ type of reconstruction, but they are more common after CJ than CC due to the direct bilioenteric connection[47].

In the choledochocholedochal strictures two-dimensional and 3D MR cholangiography show a circumscribed

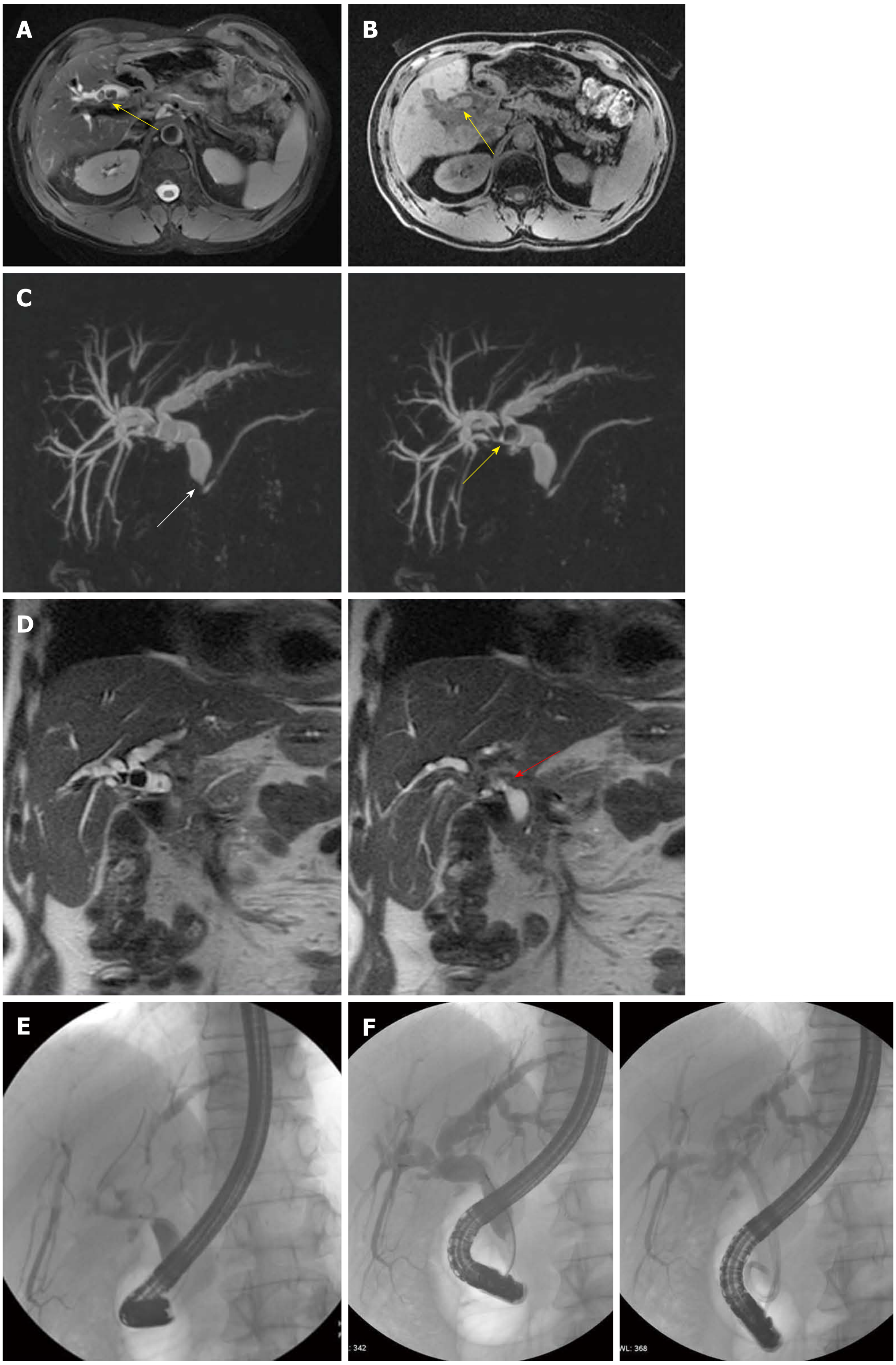

Figure 5 Anastomotic biliary stricture with lithiasis. A: Axial T2-weighted image shows dilation of the biliary system with concomitant stones (yellow arrow); B: Axial T1-weighted image confirms the presence of stones in the biliary tract (yellow arrow); C: Maximum intensity projections of 3D thin-slab fast spin-echo T2-weighted images (obtained using different thicknesses) demonstrate the dilation of the both intra- and extra-hepatic (pre- and post-anastomotic) biliary tract with a stricture of the iuxta-papillary choledocho (white arrow); the presence of two stones at the level of the hepatic bifurcation (yellow arrow) is also well appreciable; D: On coronal single-shot T2-weighted images (at different levels) is also better appreciable a stricture at the anastomotic site (red arrow); E: Endoscopic retrograde cholangiography confirms the presence of strictures and stones in the pre-anastomotic biliary tract; F: Stones were endoscopically removed and strictures were treated by stenting as shown on different projection images.

narrowing at the level of the surgical anastomosis that can be associated or not with dilatation of the pre-anastomotic biliary tract[48] (Figure 4). T1- and T2-weighted images in the axial plane show a regular thickening of

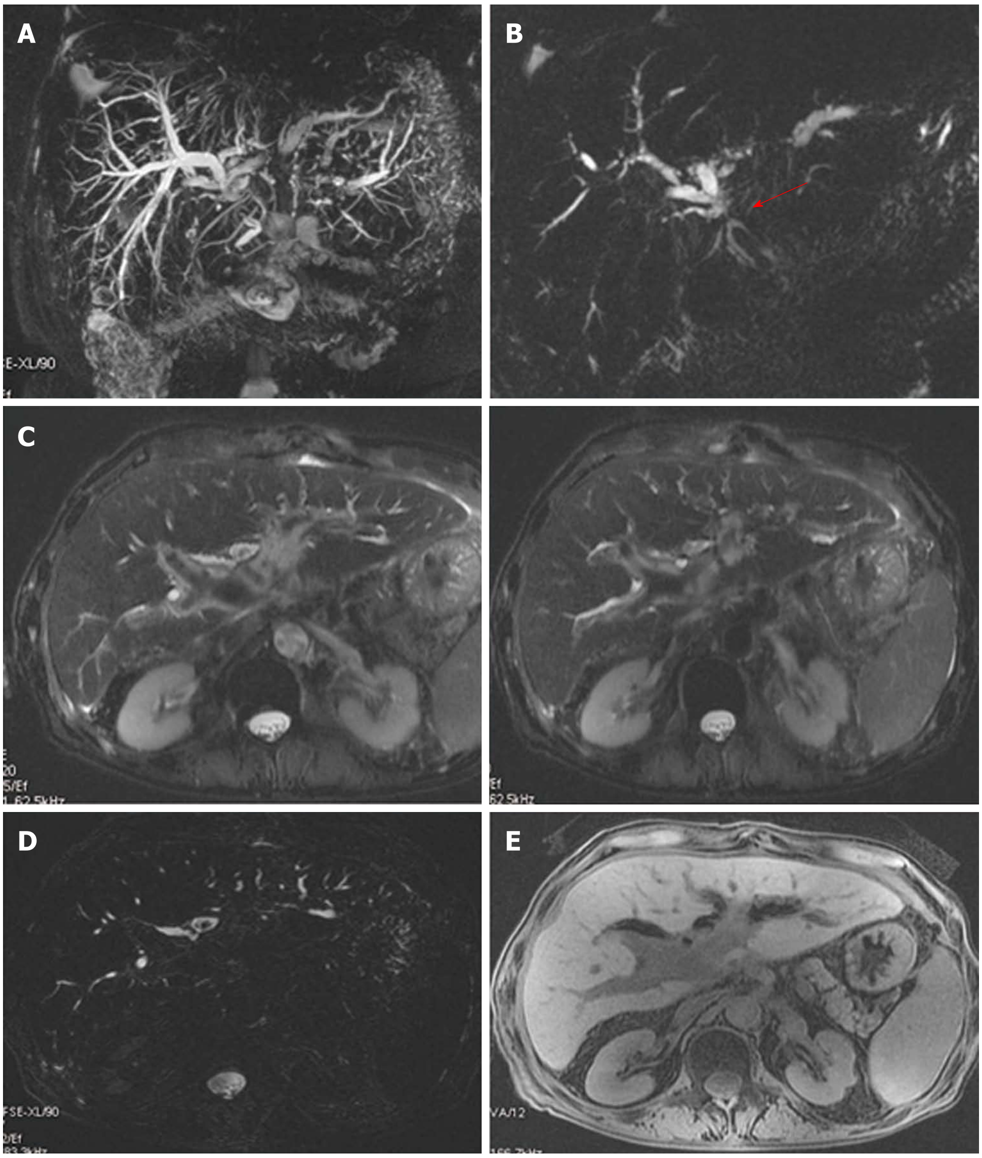

Figure 6 Anastomotic biliary stricture with lithiasis in a patient with hepatico-jejunostomy. A: Maximum intensity projection reconstruction of 3D thin-slab fast spin-echo T2-weighted images shows marked dilation of the biliary system with partial visualization of the left hepatic duct; B: Single-shot thick-slab magnetic resonance cholangiogram well depicts the stricture of the anastomotic site (red arrow); C, D: Axial single-shot T2-weighted images and axial 3D thin-slab fast spin-echo T2-weighted image demonstrate dilation of the pre-anastomotic biliary tract with the presence of pneumobilia, in particular at the level of left and common hepatic ducts with concomitant stones into the left one; E: Axial T1-weighted image better recognizes pneumobilia.

the anastomotic biliary wall with a typical ring-shaped hypointensity[48]. Besides, calculi can be appreciable in the pre-anastomotic biliary tract (Figure 5).

The surgical conformation of a biliodigestive or choledochojejunostomy make it difficult to assess with MR cholangiography. The physiological motility of the jejunal loop can cause occasional folding of the anastomotic junction with a consequent dilatation of the biliary system above the anastomosis. Besides, the bowel gas and fluid collections prevent the assessment of the anastomosis[48-50]. In a recent paper Kinner *et al*[44] concluded that post-OLT biliary stenoses can be properly identified by MRCP in recipients with CC. Nevertheless, in patients with a biliodigestive anastomosis the diagnostic performance of MRCP is reduced due to the less precise delineation of the anastomotic site (Figure 6).

Differentiation between non-obstructive *vs* obstructive dilatation of the biliary tract may be arduous on conventional T2-weighted MRC since this technique does not provide functional informations as concerns as biliary drainage[32,51]. Alternatively, high concentration of hepatobiliary contrast agents in bile ducts enables functional imaging of the biliary excretion since contrast-enhanced MRC may provide an indication of excretory function on the basis of the reference values of contrast media for biliary excretion. Furthermore, clear demonstration of the patency of the biliodigestive anastomosis can be provided by contrast agent filling of the jejunal loop on contrast-enhanced MRC (Figure 7).

Among biliary adverse events, the most troublesome are the so-called "ischemic-type biliary lesions" (ITBL), that are non-anastomotic intra- or extrahepatic stenoses

Figure 7 Patent anastomosis in a patient with hepatico-jejunostomy. A: Coronal T2-weighted magnetic resonance cholangiography reveals a moderate dilation of the intrahepatic biliary system, but does not visualize the site of the biliary-enteric anastomosis; B, C: Coronal Gd-EOB-DTPA-enhanced T1-weighted magnetic resonance cholangiogram, obtained 20 min after contrast injection, shows contrast excretion into the intrahepatic biliary system, the site of biliary-enteric anastomosis (red arrow) and anastomotic jejunal loop, demonstrating the patency of the biliary-enteric anastomosis.

and dilatations involving electively the biliary system of the transplant occurring in the absence of hepatic artery thrombosis, ABO incompatibility, or other known causes of bile duct damage. These non-anastomotic strictures have been known since the early liver transplants[52]. The appearance of these lesions suggests that microcirculatory problems related to graft preservation factors or immunogenic injury are the main pathogenic mechanisms.

Using MRC, most of ITBL show a lengthy stricture that frequently involves the right and left hepatic ducts and the hepatic bifurcation, which is a prevalent localization for ischemic injures after OLT. These stenoses more commonly start at the biliary confluence and then extend to the peripheral bile ducts, but the biliary involvement can also be intrahepatic and of various bile ducts[15]. Another characteristic feature of ITBL is represented by wall thickening of the graft common bile duct, that is generally well demonstrated on MR imaging; this findings can be sometimes associated to biliary sludge, stones or casts[15,25] (Figures 8-10). Based on MRI findings transplant surgeon can accurately assess the extension of bile ducts involvement in order to plan the more appropriate therapy and utilize ERCP only for therapeutic purposes[15].

Preliminary experiences suggest that contrast-enhanced MRC using Gd-EOB-DTPA may provide both anatomical and functional information of ITBLs in liver transplant recipients. In fact, times of contrast agent excretion seem to be in correlation with different degrees of biliary obstruction.

Several trials have evaluated the diagnostic accuracy of MRCP for the depiction of anastomotic and non-anastomotic biliary strictures. In a study by Aufort *et al*[53] twenty-seven liver transplant patients underwent MRCP using direct cholangiography as the gold standard technique. A good or excellent visualization of 80% of all biliary segments was demonstrated by MRCP. Sensitivity and specificity of MRCP for the delineation of biliary strictures were 85% and 81%, respectively. Nevertheless, these authors did not perform a separate analysis for anastomotic or non-anastomotic stenoses. In the trial by Zoepf *et al*[45] fifty liver transplant patients both with AST and NAS were examined by means of MRCP utilizing ERCP as the standard of reference. MRCP showed a sensitivity of 71% and 89% for the delineation of AST and NAS, respectively; on the other hand, the reported values of specificity were only 25% for both types of stricture. However, neither detailed description of the MRCP technique nor on the reviewers' expertise was provided in this study. Sensitivity and specificity values over 90% were reported by Boraschi *et al*[20] in a series of patients with CC undergoing MRCP. Kinner *et al*[44] evaluated the diagnostic performance of MRCP for the detection of biliary strictures after OLT according to the type of surgical reconstruction. In this trial in recipients with biliodigestive anastomosis sensitivity and specificity values of MRCP for the depiction of anastomotic and non-anastomotic biliary stenoses were 50% and 83%, 67% and 50%, respectively. Additionally, in the cohort of patients with CC the sensitivity (AST: 100%, NAS: 100%) and specificity (AST: 100%, NAS: 88%) values of MRCP were significantly higher for both types of anastomosis. Other studies have also reported an excellent accuracy of MRCP for the delineation of biliary stenoses in a inhomogeneous cohort of recipients[54,55].

At least, patients undergoing OLT for primary sclerosing cholangitis can develop multiple biliary strictures alternating with dilation of bile ducts after liver transplantation. MRCP's sensitivity is lower than that of ERCP in the identification of early alterations, but this non-invasive technique is helpful for detecting typical signs of biliary involvement in patients with a known diagnosis, in order to monitor the progress of these changes. MRCP shows beaded bile ducts or we can observe a "pruned tree" appearance of the biliary system with multiple stenoses alternating with normal or slightly dilated ducts (Figure 11).

BILIARY STONES, SLUDGE AND CASTS

Endoluminal bile duct obstruction, in the form of biliary stones, sludge and casts, can virtually occur at any time

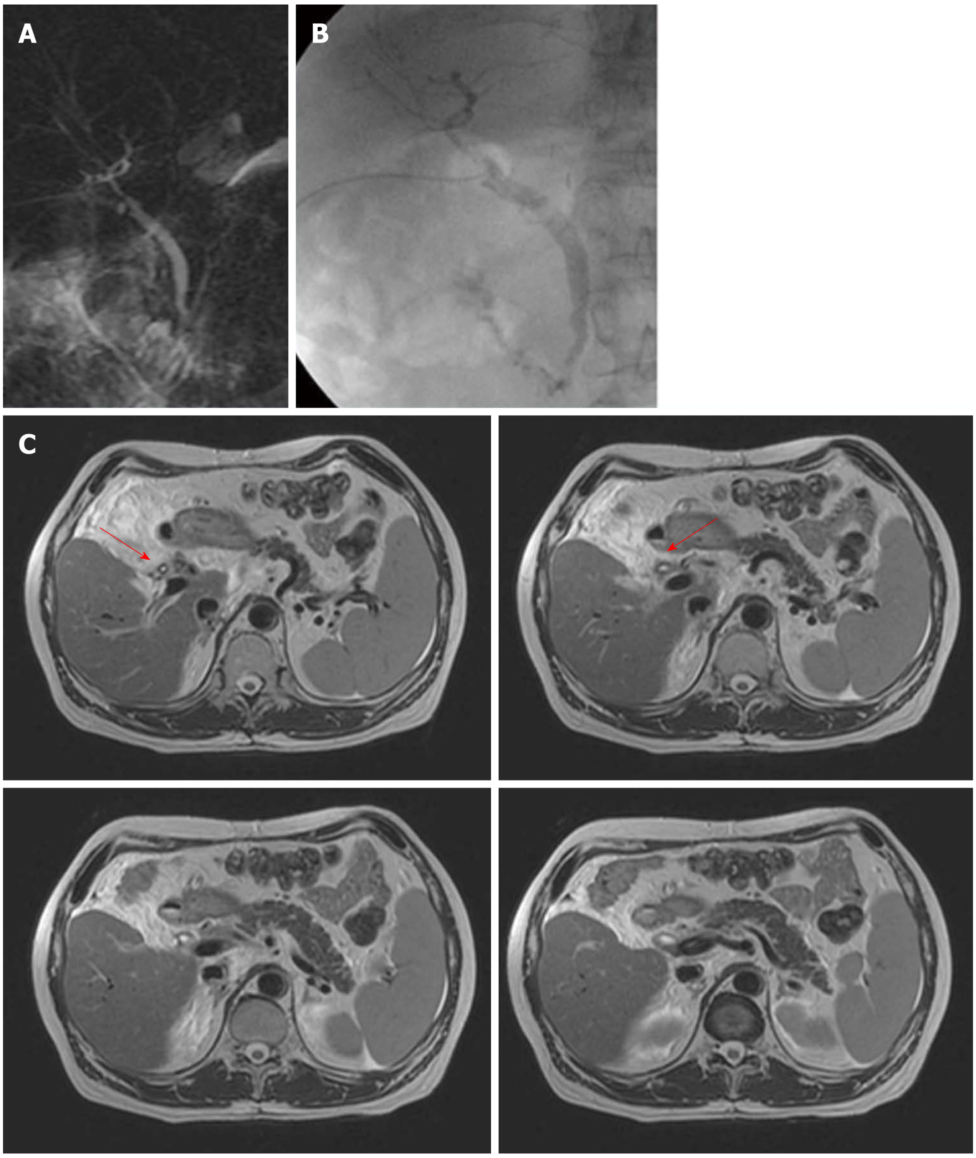

Figure 8 Non-anastomotic biliary stricture: Early ischemic type biliary lesion. A: Single-shot thick-slab magnetic resonance cholangiogram demonstrates discrepancy of caliber between donor and recipient extrahepatic biliary tract without dilation of intrahepatic biliary system; B: T-tube cholangiography confirms the presence of the mild stenosis; C: Axial T2-weighted images well exhibit the presence of circumferential wall thickening of the extrahepatic biliary tree of the graft (red arrows).

after OLT. Sludge is described as a mixture of mucous, calcium bicarbonate and crystals of cholesterol, which go on to form biliary stones if not treated. Biliary cast syndrome is characterized by an endoluminal brown, hardened material that molds to the shape of the biliary tract, leading to a "mold" or "cast" of the ductal system. The timing of onset of biliary sludge and cast syndrome is usually within the first year of transplant, while biliary stones tend to occur after. On ERCP, stones, sludge and casts are usually seen as a defect in the contrast column and described as "filling defects". Most of these latter and in particular biliary stones, are successfully treated with an endoscopic approach including sphincterotomy, lithotripsy and extraction[2].

Numerous published studies have shown that MRC is as effective as ERCP in diagnosing common bile duct stones, although the possibilities of MRI in identifying calculi of a few millimeters in size are still to be fully proven[56]. Endoscopic ultrasound (EUS) is able to provide images of high resolution since the endoscopic probe is in close proximity to the internal structures. The spatial resolution of EUS is higher than that of MRCP (0.1 mm *vs* 1.5 mm) and consequently this technique is extremely reliable for the detection of small calculi also for the advantage of providing dynamic images compared to MRCP[57]. Nevertheless, since EUS is an invasive procedure and requires sedation of the patient, the need to perform it in low risk subjects should be carefully evaluated. In fact, even a merely diagnostic EUS may cause complications such gastro-intestinal bleeding and bowel perforation[57]. In a recent paper Verma *et al*[57] compared the diagnostic performance of EUS and MRCP for the identification of common bile duct stones when using the data from published prospective comparative stud-

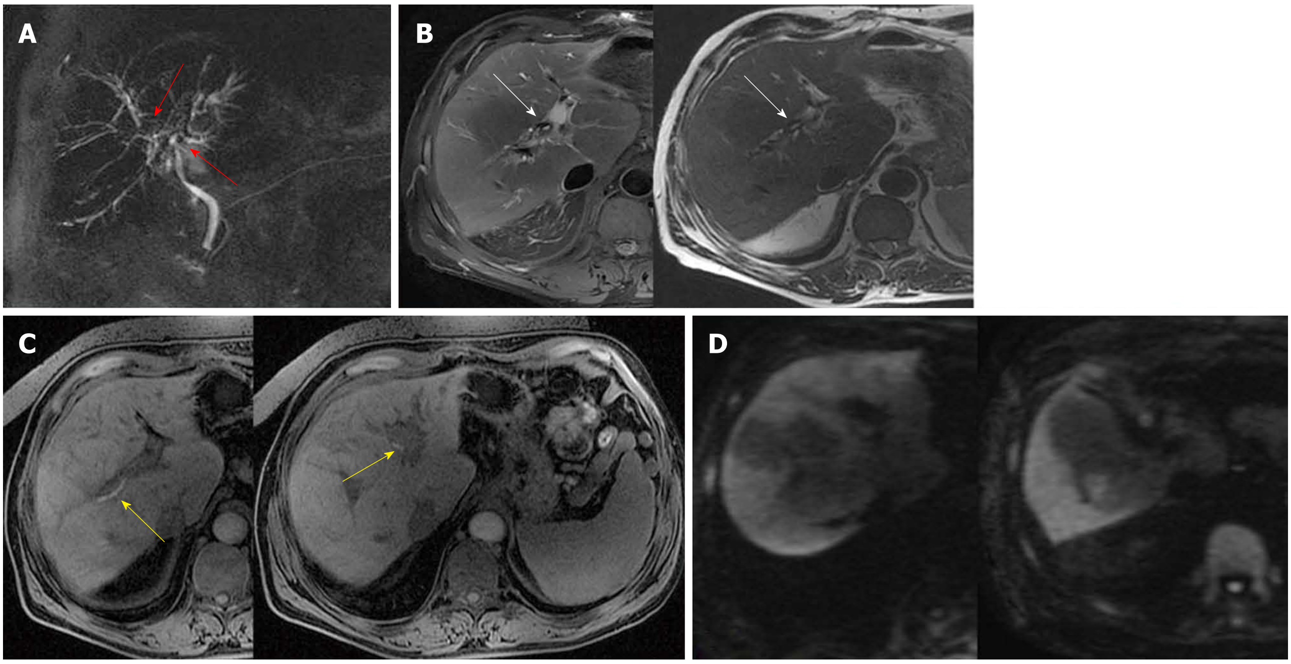

Figure 9 Non-anastomotic biliary stricture: Advanced ischemic type biliary lesion. A: Single-shot thick-slab magnetic resonance cholangiogram demonstrates a stenosis of the hepatic bifurcation and hepatic ducts (red arrows) with an irregular dilation of the intrahepatic biliary system; B, C: Axial T2- and axial T1-weighted images well exhibit the presence of circumferential wall thickening (white arrows) at the level of hepatic bifurcation and endoluminal casts (yellow arrows); D: On diffusion-weighted imaging the liver parenchyma appears inhomogeneous with multiples areas of persistent high signal intensity in highest *b*-value acquisitions.

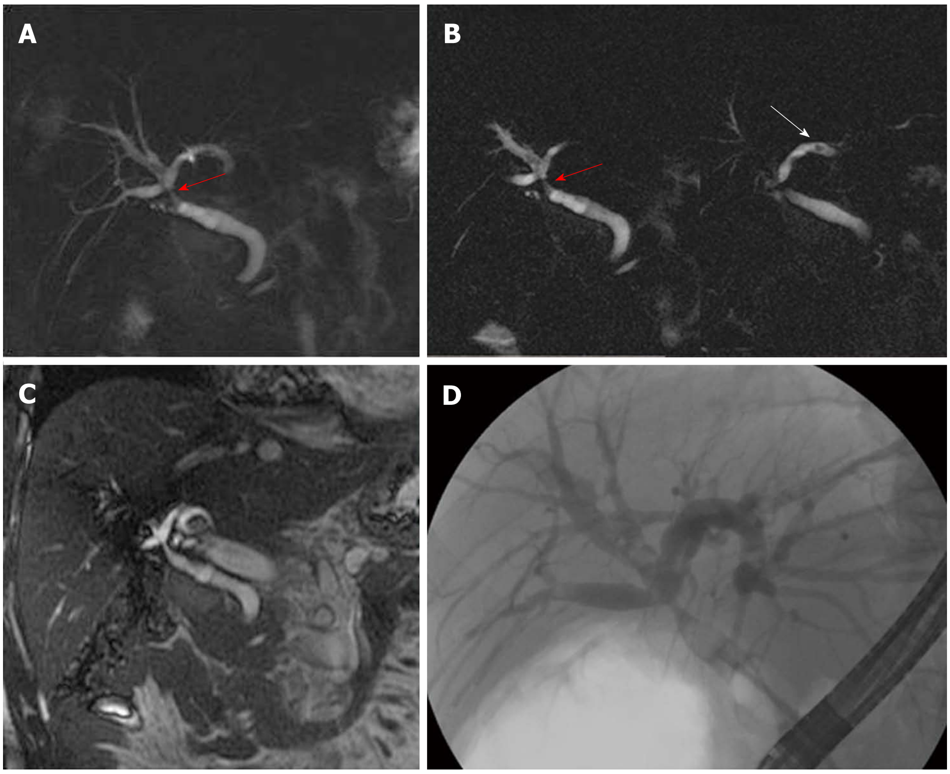

Figure 10 Non-anastomotic biliary stricture: Classic signs of ischemic type biliary lesion. A, B: Single-shot thick-slab magnetic resonance cholangiopancreatography show the stricture at the level of hepatic bifurcation (red arrow) and the presence of biliary sludge/stones (white arrow) in the dilated intrahepatic biliary system; C: On coronal T2-weighted image the wall thickening of the extrahepatic biliary tree of the graft is also well appreciable; D: Endoscopic retrograde cholangiography exhibits the optimal correlation of these features.

ies. On the whole, no significant difference was found between these two tests for the diagnosis of choledocholithiasis, though both techniques showed high diagnostic accuracy. The authors concluded that factors such as pa-

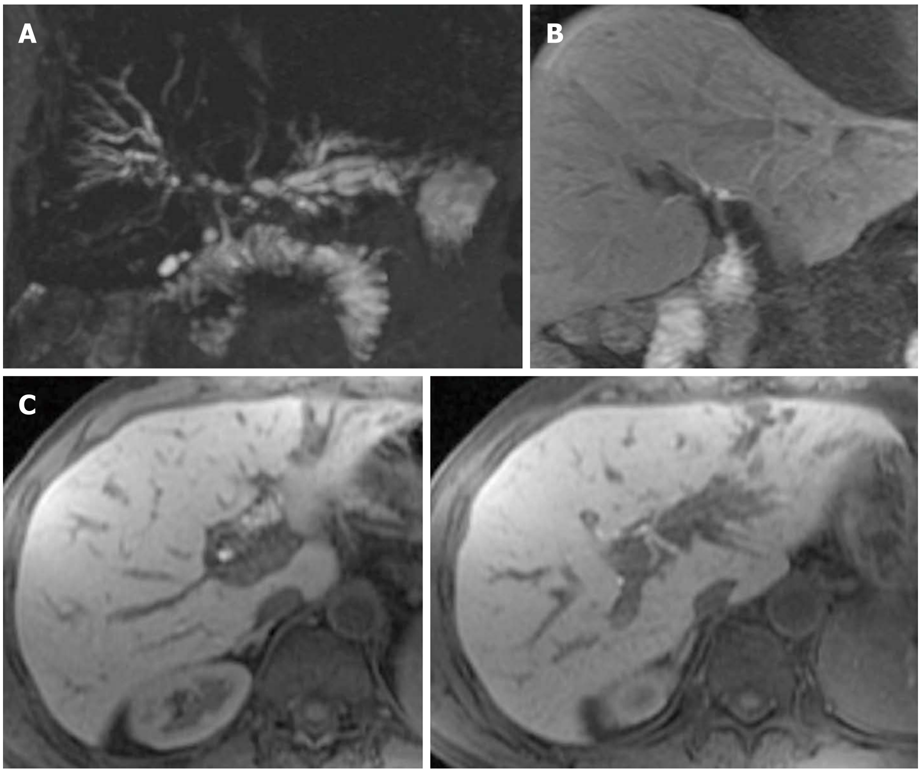

Figure 11 Recurrence of primary sclerosing cholangitis in a transplant patient with hepatico-jejunostomy. A: Maximum intensity projection (MIP) reconstruction of 3D thin-slab fast spin-echo T2-weighted images shows multifocal stenosis with intervening saccular dilation affecting the intrahepatic biliary system; B, C: On MIP reconstruction and axial Gd-EOB-DTPA enhanced LAVA T1-weighted sequences the intrahepatic biliary system is not appreciable, however the irregularities of the extrahepatic biliary tract are more accurately depicted.

tient suitability, expertise and costs should be considered when deciding between EUS and MRCP[57].

On conventional T2-weighted MR cholangiography the presence of pneumobilia is an element that can compromise the correct diagnosis of lithiasis. The differential diagnosis between stones and pneumobilia is usually performed on axial T2-weighted sequences. Calculi are generally identified as endoluminal areas of signal void surrounded by high intensity of bile in the dependent portion of the duct (Figure 5), whereas pneumobilia is typically characterized by low signal intensity in the non-dependent portion of the bile duct[19] (Figure 6). Besides, on conventional T2-weighted MRC flow artifacts are sometimes observed in the central portion of choledochal duct as thin area of low signal intensity[58]. These flow artifacts are not commonly recognized on contrast-enhanced T1-weighted MR cholangiography, that may be helpful in providing an increased diagnostic confidence in the differential diagnosis between stones and pneumobilia. Furthermore, Kinner *et al*[59] showed that adding non-enhanced T1-weighted sequences to conventional T2-weighted MRCP the diagnostic performance of MRI for the diagnosis of biliary cast syndrome after OLT is significantly improved since biliary cast is hyperintense on T1-weighted images (Figure 9).

In liver transplant patients biliary obstruction caused by lithiasis is usually associated with an anastomotic stricture. Moreover, a biliodigestive by-pass (even if patent) is a factor encouraging the development of biliary stones[19]. Clinically these patients can present typical signs of cholangitis, represented by abdominal pain, fever, and jaundice, the classic Charcot triad. If an obstruction of the biliary system is not promptly recognized, patients may develop ascending cholangitis, showing multiple intrahepatic biliary strictures that mimic the features of primary sclerosing cholangitis[19].

SPHINCTER OF ODDI DYSFUNCTION

Another common occurrence after OLT is represented by sphincter of Oddi dysfunction (SOD) that is reported to be up to 7% in liver transplant recipients. The pathogenesis of SOD is attributed to the denervation of the sphincter during liver transplantation. This leads to an increase in basal pressure, thus causing increased pressures in the choledochal duct and, as a consequence, a mild increase in the size of donor and recipient common bile ducts[60]. There have been virtually no clinical trials that demonstrate the best treatment option for SOD. In recent years, endoscopic therapy with sphincterotomy with or without stenting has been the most acceptable treatment option for SOD in liver transplant recipients.

On MRCP we can observe a significant dilatation of both recipient and donor bile duct in the absence of cholangiographic evidence of obstruction; a protrusion of the enlarged ampullary region into the duodenal lumen is sometimes associated (Figure 4). In these cases, SOD is suspected and contrast-enhanced MR imaging

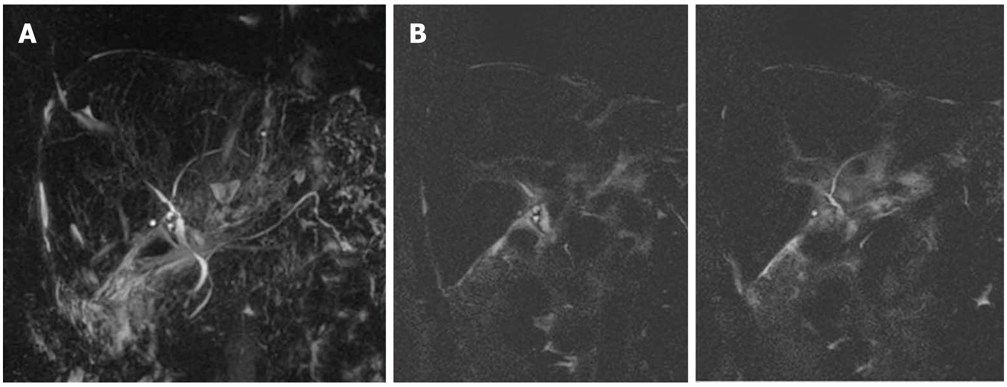

Figure 12 Vanishing bile duct syndrome. A: Maximum intensity projection reconstruction of 3D thin-slab fast spin-echo T2-weighted images shows only extrahepatic pre- and post-anastomotic biliary tract; the entire intrahepatic biliary system is missed; B: These findings are better appreciable on single-shot thin-slab magnetic resonance cholangiograms.

can be added to T2-weighted MR cholangiography in order to obtain functional information on the degree of biliary obstruction and increase the diagnostic accuracy of MR imaging, particularly in patients with biochemical abnormalities that could be treated endoscopically with or without stenting.

VANISHING BILE DUCT SYNDROME

Vanishing bile duct syndrome is characterized by progressive loss of small intrahepatic ducts caused by a variety of different diseases leading to chronic cholestasis, cirrhosis, and premature death from liver failure[61]. In post liver transplantation patients acute and chronic rejection and ischemia are the most common causes. The diagnosis is usually established by liver biopsy in the appropriate clinical setting and treatment depends mainly on the underlying etiology of the disease. On MRCP images this disease entity, also referred as ductopenia, can be suspected when we observe a paucity of small intrahepatic bile ducts (Figure 12).

CONCLUSION

Biliary adverse events following OLT are relatively common and continue to be important causes of morbidity, mortality, and transplant dysfunction or failure.

MR imaging with MRCP sequences is crucial in assessing abnormalities in the biliary system after liver surgery, including liver transplant. MR cholangiopancreatography is a safe, rapid, non-invasive, and effective diagnostic modality for the evaluation of biliary adverse events after OLT, since it plays an increasingly important role in diagnosis and management of these events. It can provide a non-invasive method of imaging surgical reconstruction of the biliary anastomoses as well as adverse events including anastomotic and non-anastomotic strictures, biliary lithiasis and sphincter of Oddi dysfunction in liver transplant recipients. Nevertheless, conventional T2-weighted MR cholangiography can be implemented with T1-weighted contrast-enhanced MR cholangiography using hepatobiliary contrast agents (in particular using Gd-EOB-DTPA) in order to improve the diagnostic accuracy in the adverse events' detection such as biliary leakage and strictures, especially in selected patients with biliary-enteric anastomosis.

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