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Imaging of Post Liver Transplantation Part II: Biliary Complications

Rachel Allard, Claire Smith, Jim Zhong, Maria Sheridan, Ashley Guthrie, Raneem Albazaz

Department of Clinical and Interventional Radiology

St James's University Hospital

Leeds, LS9 7TF, United Kingdom.

Abstract

Biliary complications post liver transplantation are a significant source of morbidity and mortality and early recognition is paramount to the long-term success of the liver graft. *Part II* of this series will focus on liver transplant biliary anatomy, including the blood supply to the biliary system and potential problems if it is interrupted. The imaging rationale for investigating suspected biliary complications, potential pitfalls and treatment options will be discussed. The various biliary complications will be illustrated using a collection of cases.

Introduction

Biliary complications post liver transplantation are a significant source of morbidity and mortality in the early and late postoperative phase with incidence ranging from 5-25% (1-5). With improved surgical techniques and organ selection, these complications have reduced but mortality remains significant at up to 10% (6). Early complications include bile leaks and obstruction, whilst late complications can occur several months or even years after transplant and include recurrence of primary biliary pathologies, evolution of an ischaemic biliopathy and recurrent cholangitis (7).

In *part II* of this series, we will focus on post-transplant biliary anatomy, the optimal imaging modalities for assessment of suspected biliary complications, specific imaging features of the various complications and the potential pitfalls to avoid.

Liver Transplant Biliary Anatomy and Biliary Blood Supply

Liver transplantation can be achieved with either cadaveric (orthotopic) or living donor grafts, discussed in greater detail in *Imaging of Complications Post Liver Transplantation Part I: Vascular*.

The most common biliary reconstructions are duct-to-duct (choledochocholedochostomy) or duct-to-jejunum (Roux-en-Y choledochojejunostomy) (**Fig 1**) (8). Both anastomoses are typically handsewn with surgical clips sometimes used for clipping the cystic ducts to remove the donor and recipient gallbladders.

The duct-to-duct anastomosis is preferred as it is a more technically simple operation and maintains endoscopic access to the biliary system post-transplantation (9-11). The

duct-to-jejunum approach is chosen instead when there is a disparity between the donor and recipient duct size or if there is underlying biliary disease involving the extrahepatic duct, such as primary sclerosing cholangitis (PSC), to reduce the risk of future complications.

In a duct-to-duct configuration, the biliary anastomosis can usually be identified by finding the cystic duct remnants of the native bile duct and of the transplanted extrahepatic bile duct, the anastomosis will be located in between. Sometimes, only one cystic duct remnant will be visible if the donor bile duct needs to be trimmed to make the biliary anastomosis. There may also be a slight change in duct calibre at the anastomosis, which can be a further clue to its location sometimes best seen in the sagittal plane.

The bile ducts receive their blood supply from the hepatic artery via the peri-biliary vascular plexus, with approximately 50% of hepatic arterial blood flow used for vascularisation of the biliary tree (12). The biliary tree is therefore susceptible to damage from any interruption in the hepatic arterial blood supply, which can lead to epithelial damage and stricture formation.

Choice of Imaging Modality

Biliary complications may be detected incidentally in asymptomatic patients with abnormal LFTs or symptomatically with signs of obstruction or biliary sepsis. There is however overlap in the pattern of LFT derangement with various other post-transplant complications including graft rejection and vascular problems. Imaging is therefore the

first step to assess the graft vasculature and biliary tree before considering the need for a liver biopsy to look for other causes of graft derangement.

Ultrasound

Ultrasound is very useful as an initial screening tool (13). It has a high positive predictive value for biliary complications, especially in those with dilated bile ducts, however it does not have a high sensitivity, particularly for detecting a cholangiopathy or low grade but functionally significant biliary anastomotic strictures. In practice, ultrasound is most useful for excluding vascular complications, which can present in a similar way (see *part I* of this series).

MRCP

The next non-invasive test for a suspected biliary complication is usually magnetic resonance cholangiopancreatography (MRCP), which has excellent sensitivity in detecting and characterising biliary strictures and in guiding management (14, 15). MRCP techniques vary widely but typically a combination of 2D and 3D sequences are acquired. The addition of an unenhanced T1 weighted sequence (in both the axial and coronal planes) is often very useful for detection of biliary stones, sludge and casts as discussed later on.

Functional MRCP with the use of hepatobiliary specific contrast agents (such as gadoxetic acid) in the delayed phase can be useful in selected cases if the more conventional MRCP sequences are equivocal (16). The hepatobiliary contrast is excreted via the biliary tree at a predictable time point (within 20 minutes for gadoxetic acid) appearing hyperintense on 3D T1-weighted fat saturated GRE. The speed of passage of contrast through the anastomosis can give functional information of any suspected

anastomotic biliary stricture. This technique can also help confirm and precisely locate a suspected bile leak by demonstrating the point of leakage of contrast outside the affected bile duct.

Hepatobiliary Scintigraphy

Functional information regarding the biliary tree can also be obtained by using scintigraphy with liver specific radiotracers. Most radiotracers for hepatobiliary scintigraphy are metal complexes of iminodiacetic acid (IDA) combined with a radionuclide, usually technetium-99m (Tc99m). After intravenous injection, Tc99m-IDA radiotracers follow the bilirubin metabolic pathway and are excreted into the bile ducts so any bile leaks or sites of obstruction can be detected. Images can in some instances be obtained up to 24 hours post injection to look for very small suspected bile leaks not apparent on earlier images. This technique is limited by its relatively poor spatial resolution and has been superseded by the added diagnostic value of functional MRCP techniques.

Invasive Techniques

Endoscopic retrograde cholangiopancreatography (ERCP) can be performed as a therapeutic measure once a biliary complication has been detected with imaging. Not all biliary strictures are suitable for intervention and this will depend on the site, number and aetiology of strictures identified. As it is a dynamic test, the severity of anastomotic strictures can also be assessed at the initial cholangiogram. ERCP may not be an option in patients who have a duct-to-jejunum anastomosis where it may not be possible to access the biliary tree. ERCP also has the disadvantage of not being able to evaluate the

ducts above the anastomosis if there is a very tight stricture or a significant bile leak as they will not fill with contrast.

Percutaneous transhepatic cholangiography (PTC) is an alternative therapeutic technique for treating biliary strictures and can be attempted when ERCP has failed although the major complication rates, including haemorrhage, are as high as 15% in nondilated bile ducts (17).

Overall, both techniques are invasive and carry associated risks so there must be a clear indication and anticipated therapeutic benefit of any proposed intervention.

Biliary Complications

Appearances and Pitfalls in the Early Post-Operative Period

The appearance of the biliary tree early in the post-operative period can appear falsely pathological. Mimics of anastomotic strictures include mismatch of the donor and recipient common duct (**Fig 2**) and post-operative oedema causing extrinsic pressure at the anastomosis falsely appearing as an anastomotic stricture. On MRCP, this often gives a tapered “hour-glass” appearance at the anastomosis rather than the abrupt change in duct calibre that is seen with a true stricture.

If a duct-to-jejunum anastomosis has been performed, then it is normal to see pneumobilia from refluxed bowel gas. This is particularly important to be aware of when reviewing MRCPs as pneumobilia will cause signal loss and mimic strictures on MIP reconstructed images (**Fig 3**).

Another potential pitfall on MRCP is susceptibility artefact caused by nearby surgical clips or by the presence of vascular stents. This can obscure views of the biliary anastomosis again mimicking a biliary stricture. Review of the source images alongside MIP reconstructions is essential and will help avoid this.

Bile Leaks

Incidence of bile leaks is quoted between 8 and 46% of all biliary complications post transplantation (18, 19). Presentation of a bile leak varies from asymptomatic patients with incidental localised fluid collections (bilomas), to more generalised free fluid and irritative peritonitis. In the early postoperative period, the volume and colour of surgical drain fluid is helpful in identifying leaks. Bile does not have a specific appearance on imaging although it can cause peritoneal enhancement on CT as it is an irritant to the peritoneum (**Fig 4**). If there is any doubt on the composition of fluid then an ultrasound guided aspirate can be performed for clarification.

Early bile leaks usually occur at the biliary anastomosis and can be secondary to downstream obstruction or ischaemia (**Fig 5**) (20). Distal obstruction increases pressure on the biliary anastomosis and can be due to stones, biliary sludge or strictures. Less commonly, leaks can occur at the cut liver edge as a result of injury during surgery or with the use of split donor livers (**Fig 6**).

Management of bile leaks involves diversion of bile to allow the leak to heal, either endoscopically with biliary stenting +/- sphincterotomy or percutaneously in patients

where the ducts cannot be accessed via ERCP (ie. those with a duct-to-jejunum anastomosis). PTC can be technically challenging as the ducts tend not to be dilated due to the leak. If distal obstruction is secondary to stones then an endoscopic sphincterotomy can be performed with duct clearance to relieve the obstruction. A combination of biliary stenting and sphincterotomy have high success rates (21).

Biliary Strictures

Biliary strictures have a reported incidence of 5-15% after deceased donor liver transplants and 28-32% after living donor transplants (13). In living donor transplants, the anastomosis is more complex due to the smaller graft size and smaller calibre bile duct used to fashion the biliary anastomosis, thereby accounting for the higher incidence of stricture formation. Strictures can be either anastomotic or non-anastomotic and have different aetiology, clinical course and management.

- *Anastomotic Strictures*

Anastomotic strictures usually present in the early post-operative period. Contributing factors include poor healing of the opposing biliary mucosa by early ischaemia or due to a previous bile leak at the anastomotic site; however, they often occur de novo (21).

Ultrasound is usually the initial investigation with dilatation of the intrahepatic ducts and common hepatic duct suggesting the presence of a stricture. However overall sensitivity is relatively low, quoted as only 24% (13), as the donor ducts do not display the same degree of proportional dilatation when compared to native livers (due to denervation of the implanted liver). A low threshold for performing further imaging is important if there is significant clinical concern (22).

MRCP is the imaging modality of choice, where strictures appear as a short focal abrupt narrowing at the level of the anastomosis (**Fig 7**). Formation of biliary sludge or stones proximal to the narrowed bile duct due to slow transit of bile can be a further clue to the presence of a stricture.

In selected cases with suspicion of a stricture on imaging but minimal upstream biliary dilatation, functional MRCP or hepatobiliary scintigraphy maybe helpful (choice of technique will depend on local expertise and availability) (**Fig 8**). Where the presence of a stricture remains equivocal but the clinical picture or liver biopsy results indicate biliary obstruction it may be beneficial to proceed to ERCP where a true anastomotic stricture can prove to be very tight despite minimal upstream dilatation.

Management of anastomotic strictures is primarily with endoscopic intervention, with surgical revision of the anastomosis or re-transplantation reserved when endoscopy fails (23). Repeated ERCP comes with its own risks including post-ERCP pancreatitis, haemorrhage, perforation and liver abscess.

- *Non-Anastomotic Strictures*

Non-anastomotic strictures account for 10-25% of all stricture complications with an incidence of 1-19% (24). They are more likely to be long segment, multiple and invariably affect ducts above the anastomosis. Early non-anastomotic strictures are the most common and are usually a consequence of ischaemia (25).

As previously discussed, the biliary tree is supplied by the hepatic artery and this supply can be interrupted if there is a problem with the hepatic artery post-transplantation. It may also occur in the setting of a DCD (donation after cardiac death) transplant where there is an inherent ischaemic period suffered by the liver graft (26). Ischaemic biliary strictures should be suspected in patients with this kind of transplant with imaging findings of irregularity of the biliary tree. The risk of ischaemic biliary stricture formation has been reported to be as high as 13.7% in DCD transplants compared to 1% in DBD (donation after brain death) livers (27).

In non-DCD livers, careful evaluation of the hepatic artery on Doppler ultrasound should be undertaken to look for vascular complications as a cause of non-anastomotic strictures (see *Part I* of this series).

Any part of the biliary tree can be affected and the extent of ischaemic strictures can be variable and may progress over time, sometimes months (**Fig 6c, 9, 10 and 11**) (28). The extrahepatic bile duct above the biliary anastomosis is reported to have the poorest vascularisation and therefore at most risk of ischaemic injury. The perihilar ducts are also commonly affected.

MRCP is the optimal imaging modality as it shows the full extent of abnormality. In the early phase of ischaemic injury, the affected bile ducts breakdown and intrahepatic bilomas or bile lakes can develop with a characteristic appearance (29). As well as strictures and bile lakes, biliary casts from ischaemic sloughed epithelium can also be present appearing as linear areas of high T1 signal within the affected bile duct lumen.

Late non-anastomotic strictures can be as a consequence of primary biliary pathology recurrence, chronic rejection or secondary sclerosing cholangitis from chronic reflux and cholangitis through a duct-to-jejunum anastomosis.

Non-anastomotic strictures are much more difficult to manage than anastomotic strictures as they are usually widespread and involve the intrahepatic ducts to some degree. ERCP and PTC have only a very limited role in their management and re-transplantation is often needed for the more advanced cases.

Bile Duct Stones/Sludge/Cast

Biliary stones, sludge or cast appear as filling defects on ERCP and usually have high T1 signal on MRCP, with a variable degree of associated upstream biliary dilatation (**Fig 9 and 10**). Casts from ischaemic sloughed epithelium are linear and can adhere to the duct wall or be more free floating in the duct lumen; stones are usually rounded or angulated filling defects (**Fig 2**) and sludge causes layering. Stones and sludge can occur at any time post transplantation with sludge more likely to be problematic within the first year and stones occurring later on. Anything that reduces the free movement of bile can cause formation of sludge and stones and they are frequently caused by an underlying stricture (30). Duct clearance can be performed if the affected area is localised and accessible.

Recurrence of Primary Biliary Disease

Liver transplantation is a treatment choice for patients with end stage biliary disease including PSC and primary biliary cirrhosis (PBC). Recurrence of these primary biliary

diseases in the late post-operative period is common, being reported as 45.8% and 14-35% at 10 years post transplantation for PSC and PBC respectively (**Fig 12**) (31, 32). Symptoms can be non-specific and sometimes even absent. Recurrent disease is detected with a combination of routine biochemical blood tests, imaging features and exclusion of vascular complications that can lead to similar imaging appearances in the setting of recurrent PSC.

Secondary Sclerosing Cholangitis

Secondary sclerosing cholangitis is a chronic biliary disease characterised by inflammation and fibrosis of the bile ducts leading to stricture formation and eventual destruction of the biliary tree. It can be caused by reflux through a duct-to-jejunum anastomosis and patients typically present with features of recurrent cholangitis. Reflux can be diagnosed with a barium follow-through examination where contrast is seen to reflux from the Roux loop into the biliary tree (**Fig 13**). Treatment options include conservative management of the cholangitic episodes and possible long-term antibiotic prophylaxis. If episodes become recurrent or if there is breakthrough cholangitis despite the use of prophylactic antibiotics, then surgical revision of the anastomosis with the formation of an extended jejunal loop has been shown to improve outcomes (33).

Infection

More localised infection including infected bilomas and focal parenchymal abscesses can occur either as a consequence of invasive intervention or from ascending cholangitis. If treatment with IV antibiotics is unsuccessful, percutaneous ultrasound guided drainage is a therapeutic option.

Post Transplantation Lymphoproliferative Disorder (PTLD)

PTLD is an uncommon complication that can occur any time post transplantation, most frequently within the first year, and can involve any organ system. In cases of post liver transplant PTLD, the liver is the most frequently involved solid abdominal organ seen in 30-45% of cases (34). The spectrum of imaging findings includes multiple hypovascular masses, non-specific oedema or diffuse infiltration (35). It can spread to involve the biliary system leading to biliary obstruction and hepatomegaly. Confident diagnosis can be difficult as there is overlap between more common complications such as infection. Serological markers and biopsy results can help aid diagnosis.

Conclusion

Biliary complications post liver transplantation can present in a variable way and although ultrasound is useful as an initial screening tool, a low threshold for performing MRCP is needed when a biliary problem is suspected. Long term damage to the liver graft can be avoided by early detection and appropriate treatment (usually endoscopic or surgical) of some but not all complications, with widespread biliary ischaemia and recurrence of primary biliary disease often requiring a re-graft.

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Figures:

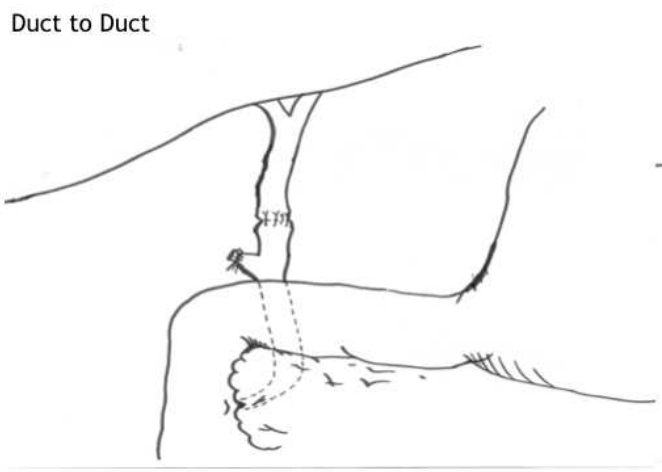


Figure 1a

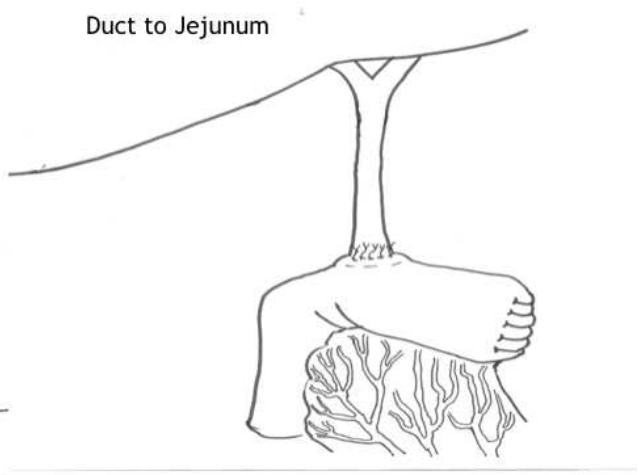


Figure 1b

Fig 1 - Types of biliary anastomosis in a liver transplant. (A) Duct-to-duct anastomosis with the cystic duct remnant of the recipient bile duct in situ. The cystic duct remnant of the donor liver has been removed along with that part of the donor duct to form the anastomosis (sometimes the donor cystic duct remnant is also left in situ and this will depend on the length of the ducts needed to form the anastomosis). (B) Duct-to-jejunum anastomosis where a Roux loop is brought up to form the biliary anastomosis.

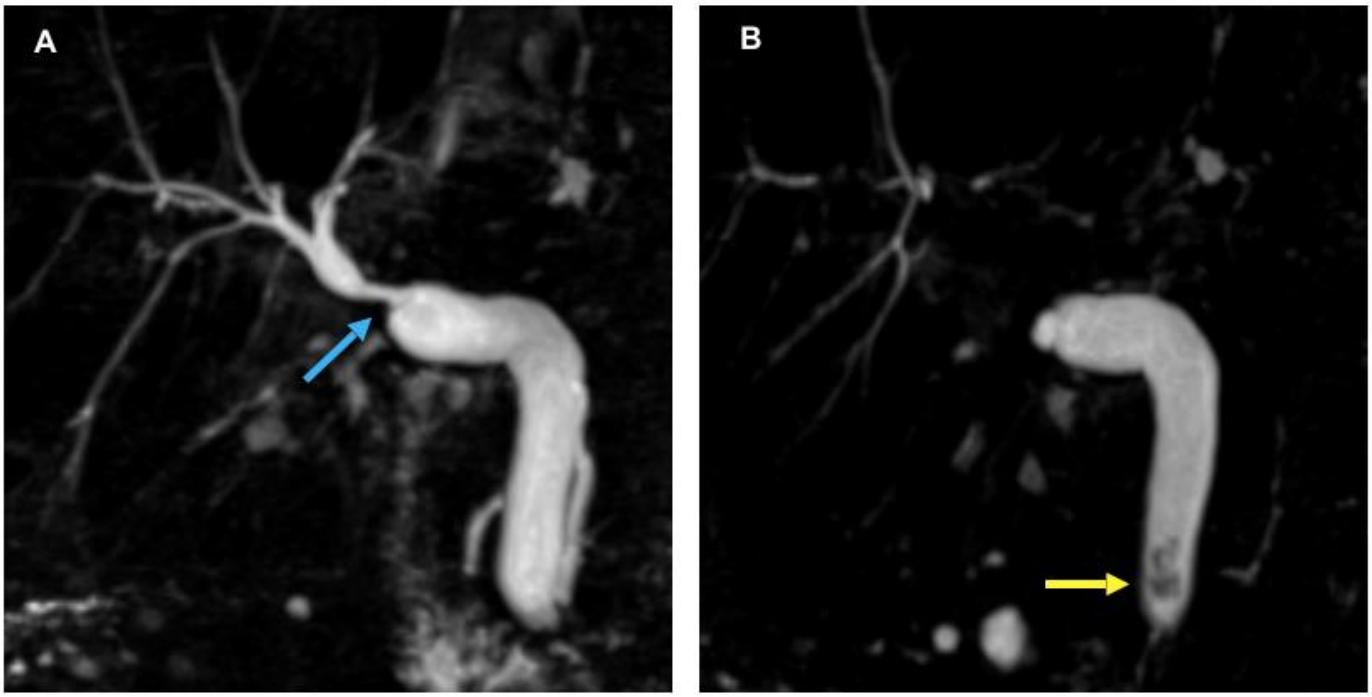


Fig 2 – 69-year-old female underwent liver transplant for primary biliary cirrhosis. A duct-to-duct biliary anastomosis was performed and a donor-to-recipient size mismatch was noted at surgery. Developed rising alkaline phosphatase 3 weeks post transplant and ultrasound showed mild intrahepatic duct dilatation. (A) Subsequent MRCP demonstrates donor-to-recipient duct discrepancy with patent lumen at the anastomosis (blue arrow). (B) Filling defects were present within the distal CBD at the level of the ampulla (yellow arrow) that proved to be stones at ERCP. Liver function improved to normal after biliary clearance.

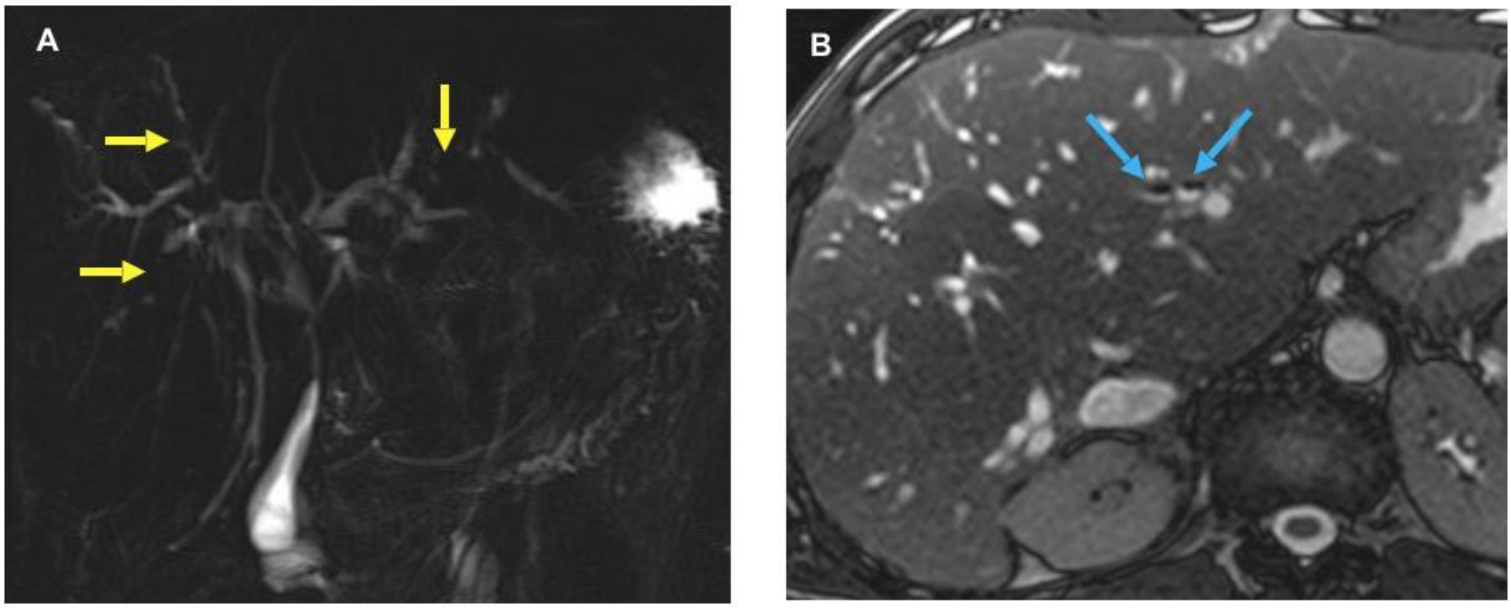


Fig 3 – 43 year old male underwent liver transplant for primary sclerosing cholangitis with duct-to-jejunum biliary anastomosis. Developed deranged LFTs 4 weeks post transplantation. (A) MRCP MIP image shows multiple “pseudo-strictures” throughout the intrahepatic bile ducts. (B) Review of the axial T2* images shows non-dependent gas within the intrahepatic ducts as the cause of the signal loss and “pseudo-stricture” appearance on the MIP images. Liver biopsy subsequently performed demonstrating features of rejection with no evidence of biliary abnormality.

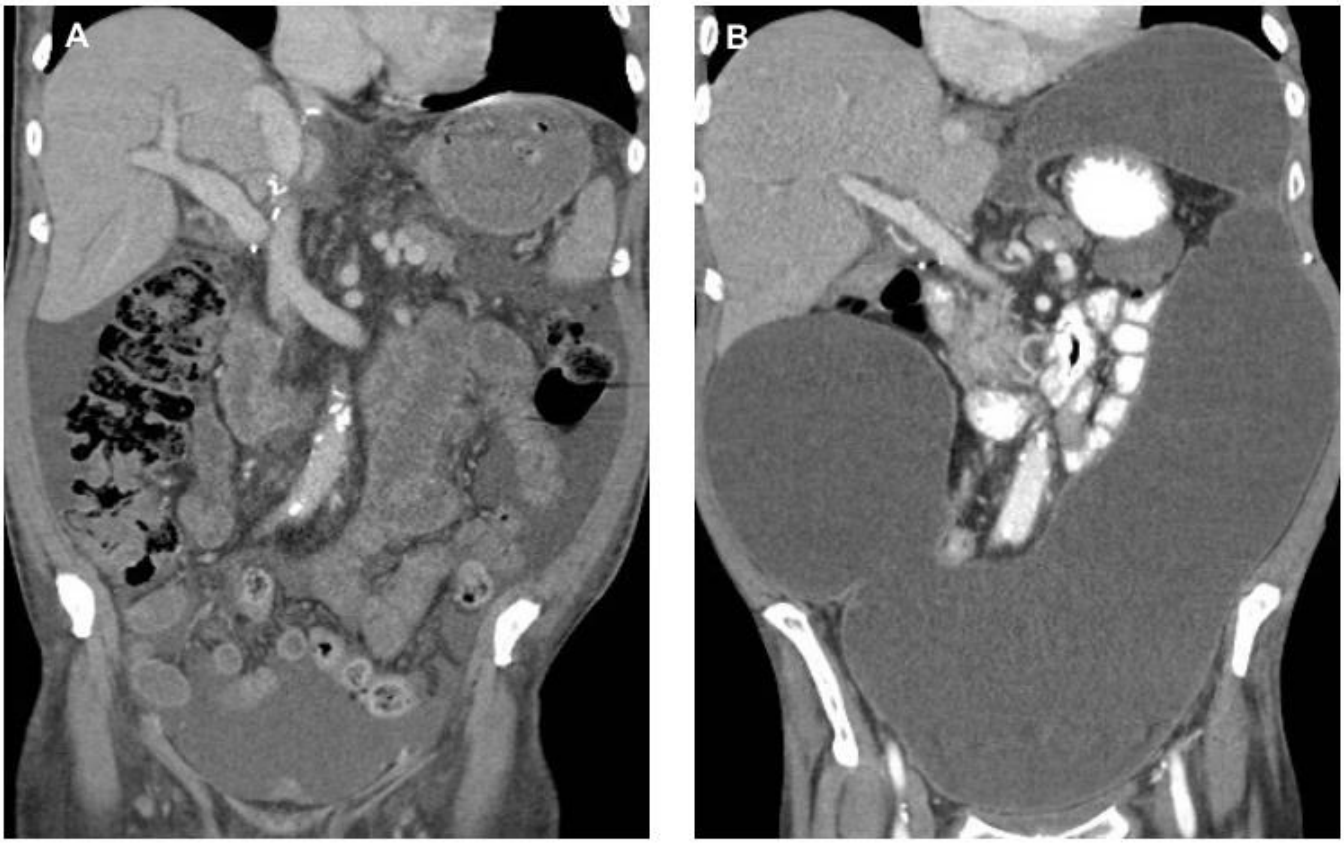


Fig 4 – 32 year old female underwent super-urgent liver transplant for acute liver failure with formation of a duct-to-duct anastomosis. (A) CT performed at day 2 for deranged LFTs demonstrates large volume free fluid. (B) Repeat CT at day 4 now shows associated peritoneal enhancement. The fluid was drained and confirmed to be bile secondary to a bile leak. This was successfully treated endoscopically with a biliary stent.

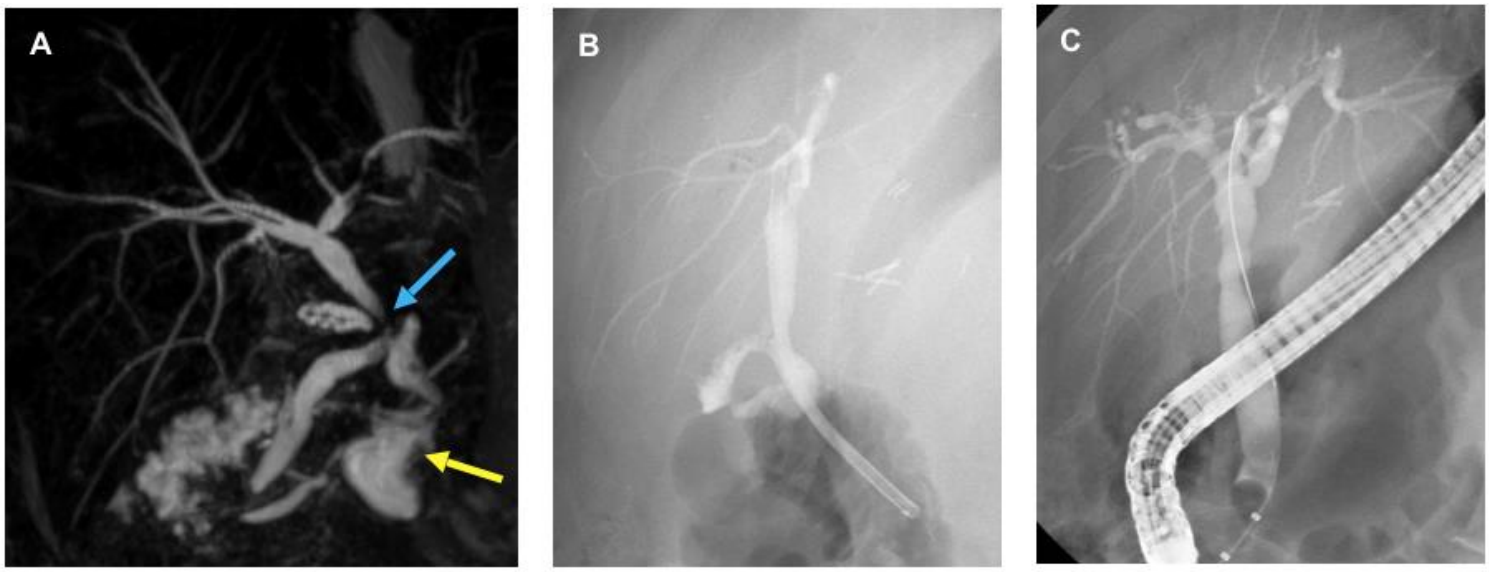


Fig 5 - 62-year-old female underwent liver transplant for hepatitis C related cirrhosis and hepatocellular carcinoma with duct-to-duct biliary anastomosis. Presented 2 months after transplant with bile leaking through an abdominal wound. (A) MRCP showed an anastomotic stricture (blue arrow) with an associated leak (yellow arrow). (B) This was treated via ERCP with a sphincterotomy and plastic stent. (C) Repeat ERCP at 4 months shows resolution of the stricture and leak.

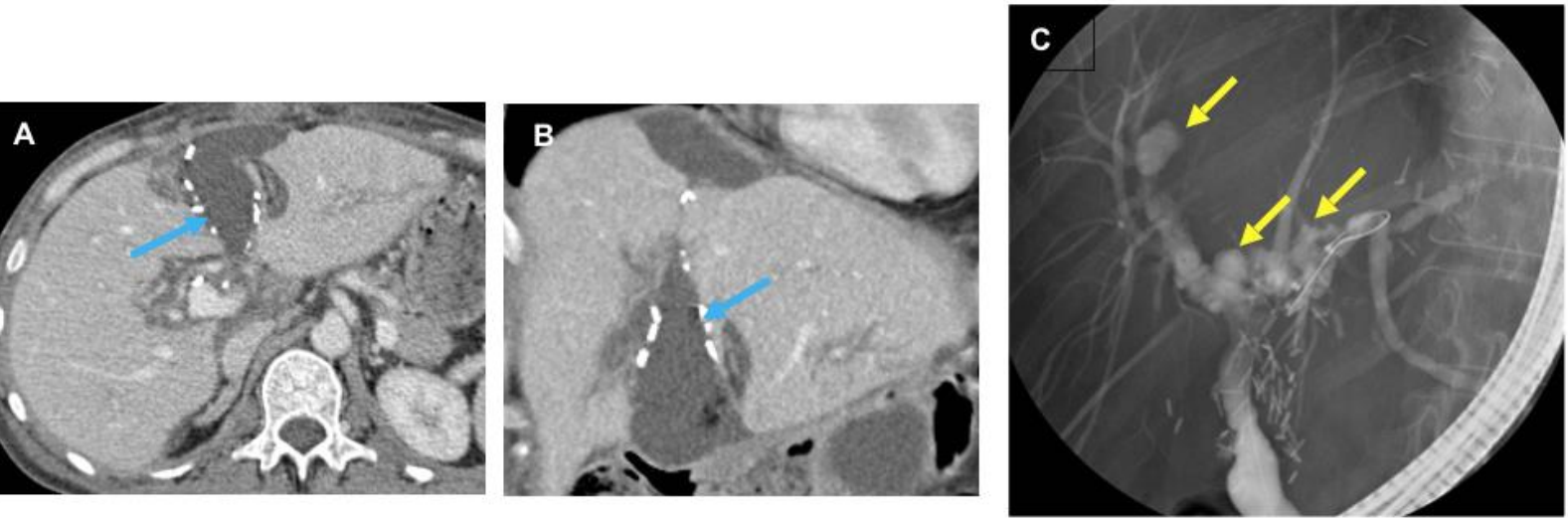


Fig 6 – 49 year old female underwent a liver transplant for primary biliary cirrhosis. Initial split liver converted to whole graft secondary to variant arterial anatomy. (A, B) Developed large biloma (blue arrows) at the site of the cut liver surface as seen on axial and coronal CT. Further complicated by ischaemic cholangiopathy secondary to hepatic arterial anastomotic stenoses seen on post operative doppler ultrasound and contrast enhanced CT. (C) Ischaemic cholangiopathy is demonstrated by central duct irregularity and multiple bilomas around the right and left hepatic ducts at ERCP communicating with the cholangiopathic ductal system (yellow arrows).

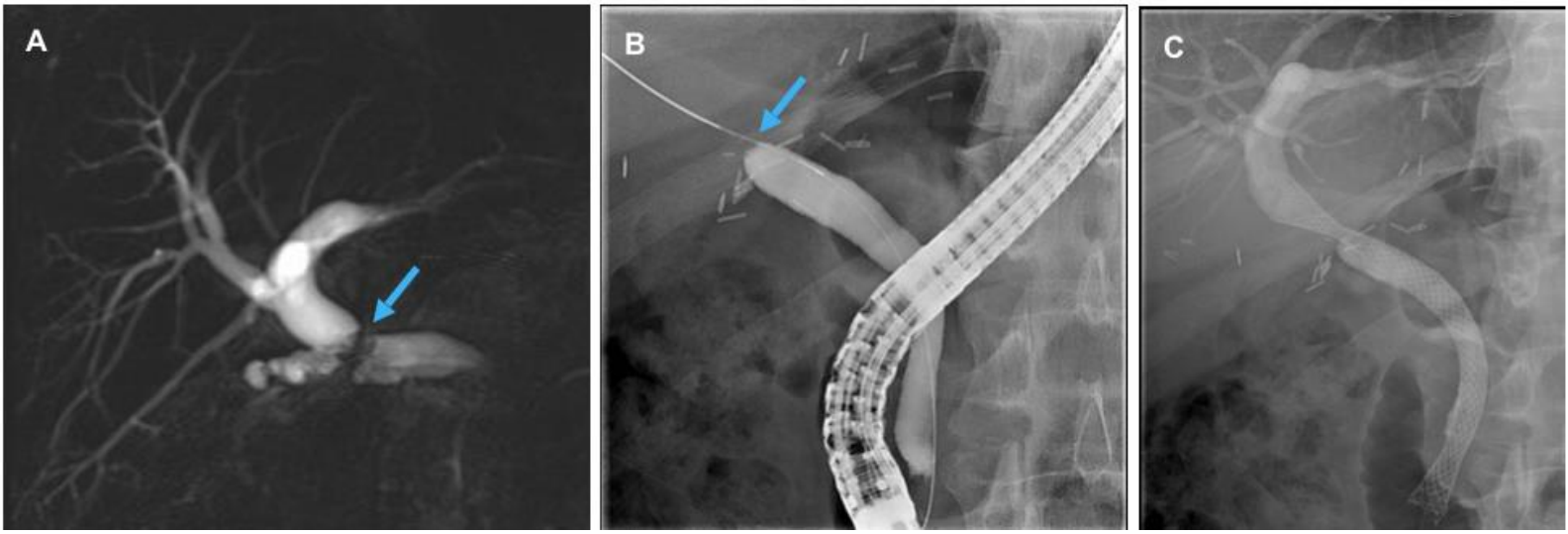


Fig 7 – 34 year old female underwent super urgent liver transplant for acute liver failure with duct-to-duct biliary anastomosis. Presented 6 months later with deranged LFTs. (A) MRCP shows a focal biliary anastomotic stricture (blue arrow) with no visible lumen on any of the other sequences performed and moderate upstream biliary dilatation. Note the cystic duct remnants either side of the stricture indicating the site of anastomosis. (B) The stricture was very tight on subsequent ERCP with no flow of contrast seen above the stricture initially (blue arrow). (C) Stricture crossed and a fully covered metal stent inserted (later removed).

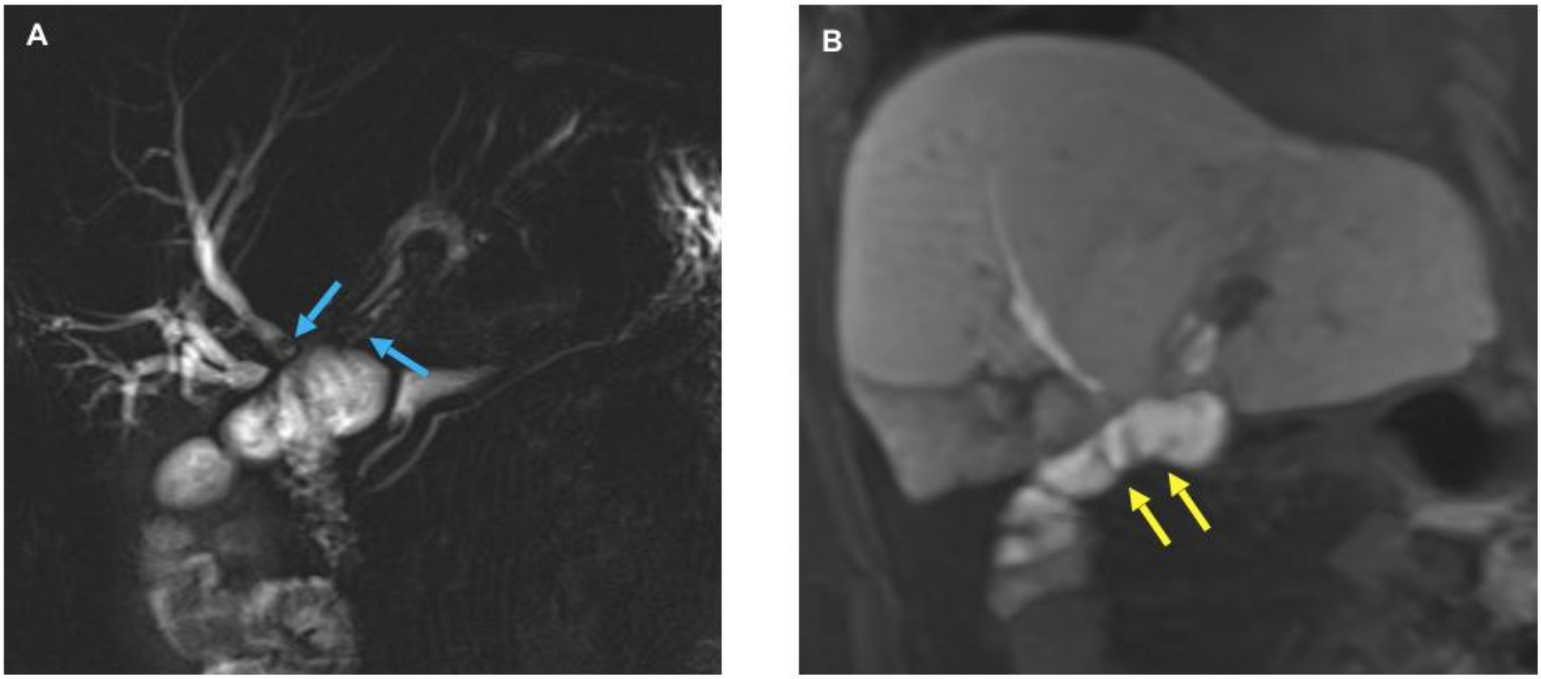


Fig 8 – 42 year old male underwent liver transplant for primary sclerosing cholangitis with duct-to-jejunum anastomosis. Developed mildly deranged LFTs 7 months post-op. (A) MRCP demonstrates mild intrahepatic duct dilatation above the anastomosis. Intraductal filling defects immediately above the anastomosis (blue arrows) were difficult to characterise as refluxed gas or stones/sludge above a stricture. (B) Functional MRCP therefore performed with gadoxetic acid, which shows normal prompt passage of contrast (appearing as high T1 signal within ducts) through the anastomosis and beyond into the jejunal Roux loop (yellow arrows) within 20 mins post injection with no evidence of a stricture.

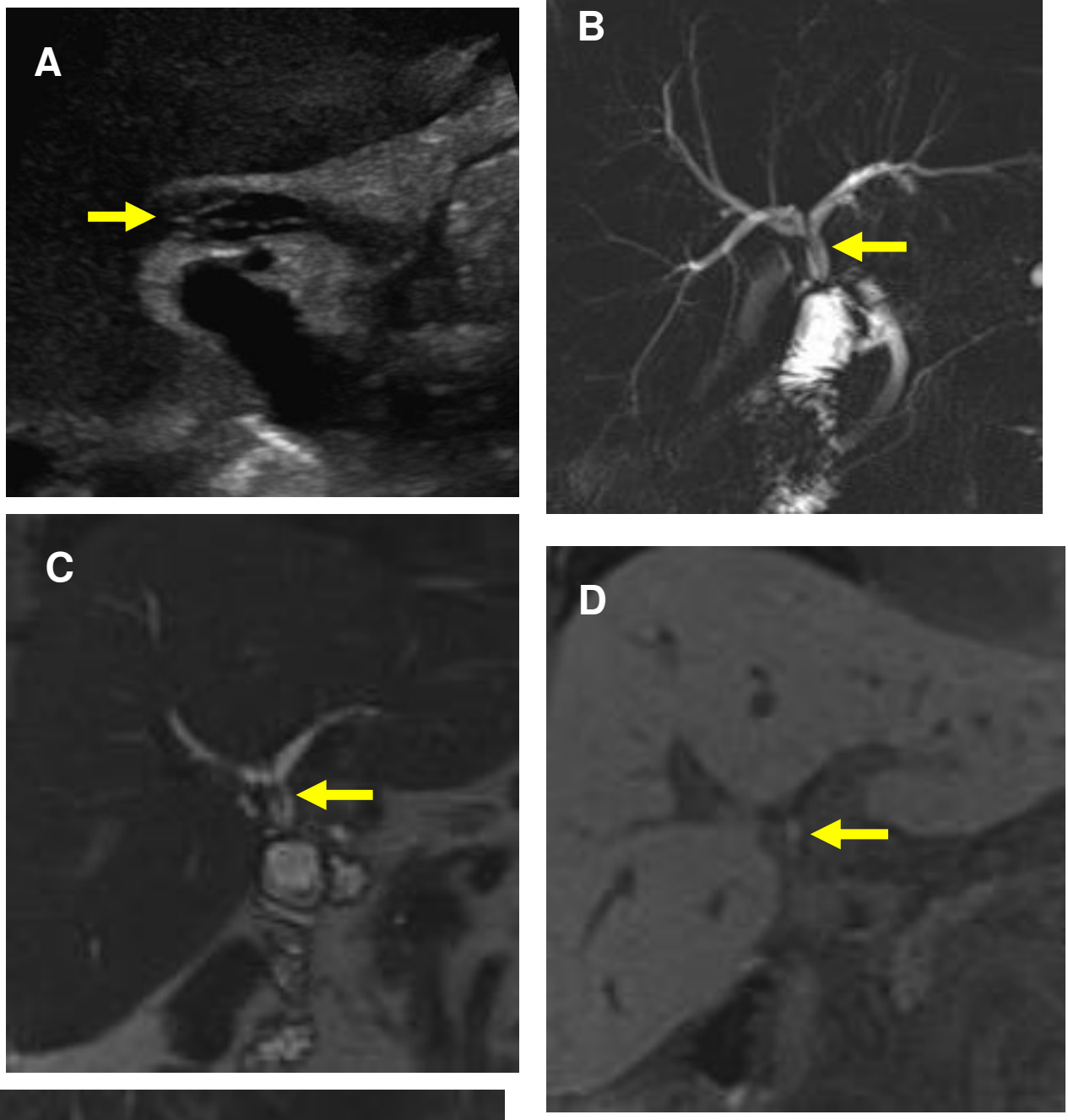
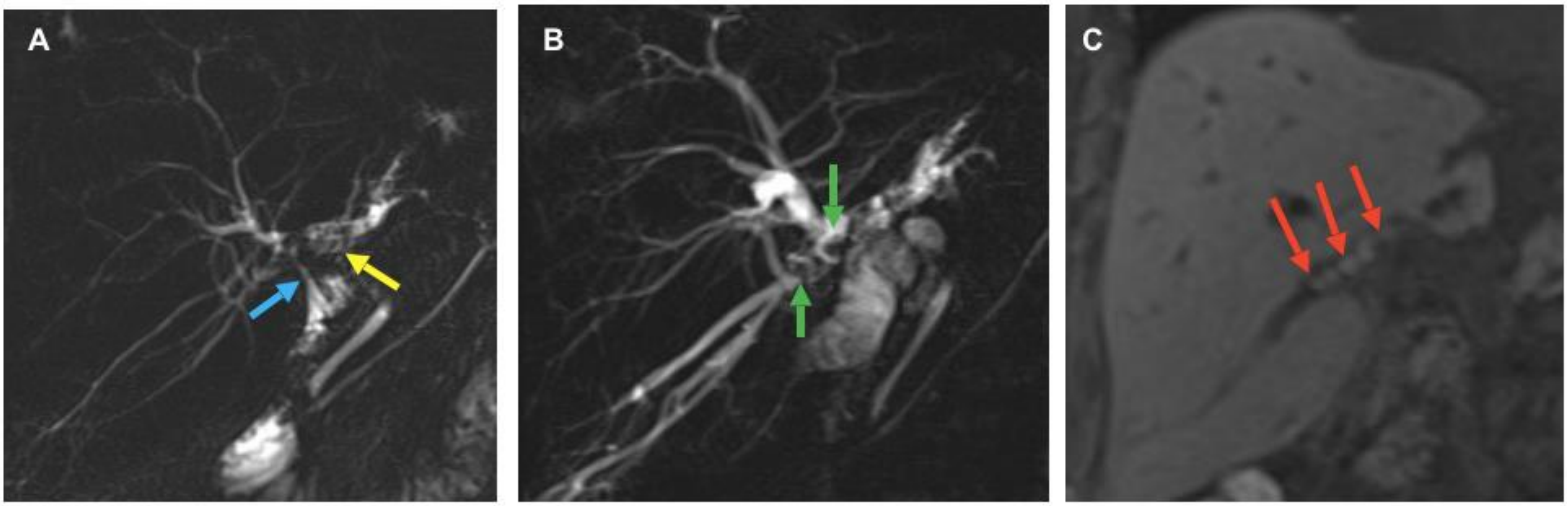


Fig 9 - 57 year old male underwent DCD liver transplant for hepatitis C related cirrhosis and hepatocellular carcinoma with duct-to-jejunum anastomosis. LFTs found to be mildly deranged 5 months post-op. (A) Ultrasound shows thickening of the bile duct above the anastomosis with intraluminal linear echogenic material (yellow arrow). (B) Subsequent MRCP also shows linear filling defect within the extrahepatic bile duct above the level of the biliary anastomosis consistent with sloughed biliary epithelium from biliary ischaemia forming a cast. The cast is low signal on T2



weighted images (C) lying centrally within the duct lumen on the axial series (E) and is of high T1 signal (D) distinguishing it from refluxed gas, which would appear of low T1 signal.

Fig 10 - 64 year old male underwent liver transplant for acute intermittent porphyria with duct-to-jejunum anastomosis. Presented with cholangitis 11 years post transplantation. (A) MRCP shows no significant duct dilatation and a patent biliary anastomosis (blue arrow). Gas seen in the ducts (yellow arrow) reduces the sensitivity for the presence of stones or sludge. (B) Re-presented 2 years later with recurrent cholangitis and deranged LFTs. MRCP performed again and shows new intrahepatic duct dilatation with stones and sludge proximal to the anastomosis (green arrows) indicative of biliary stasis and an anastomotic stricture. (C) T1 weighted image shows the high signal biliary stones (red arrows). This was treated with PTC and balloon trawl of the affected ducts containing stones.

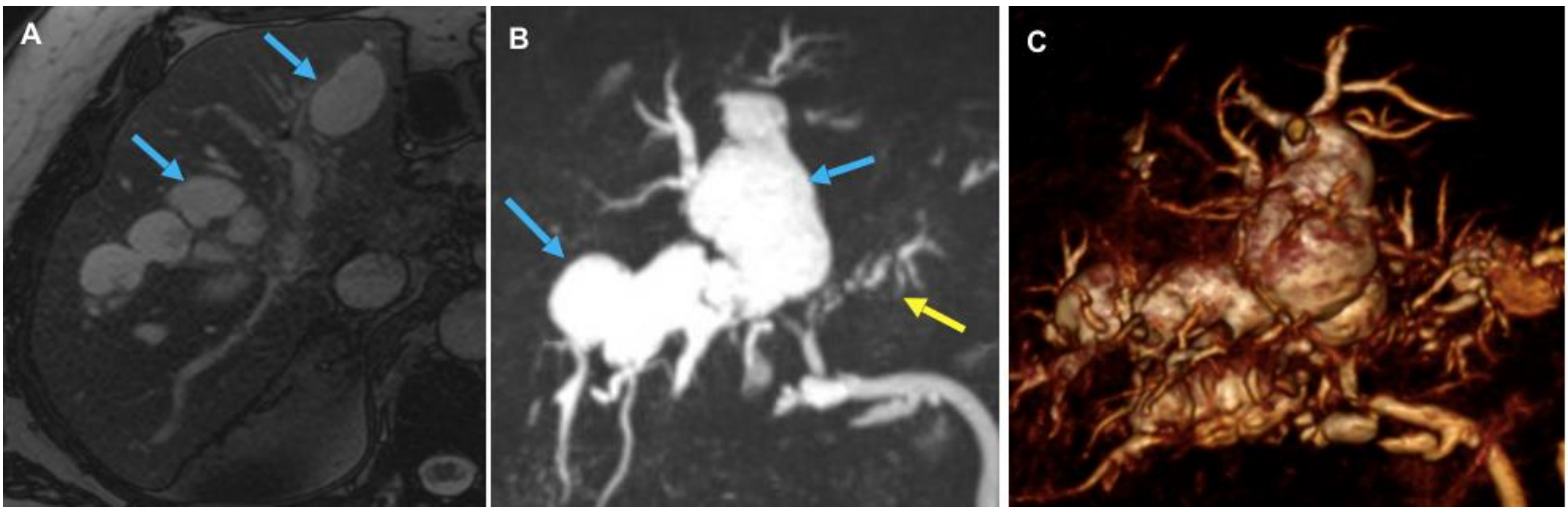


Fig 11 - 58-year-old male underwent a liver transplant for hepatic sarcoid. Noticed to have worsening LFTs at 6 weeks post-op. Initially investigated with ultrasound, which showed areas of cystic change within the liver. (A, B, C) MRCP T2* and MIP reconstructions shows cystic dilatation of the intrahepatic bile ducts (blue arrows) with relative sparing of the peripheral ducts. Findings are of multiple intrahepatic bilomas and larger bile lakes secondary to an ischaemic cholangiopathy causing breakdown of the affected ducts. Note the irregular left sided intrahepatic bile ducts (yellow arrows). The hepatic artery was found to be thrombosed and a re-graft was required.

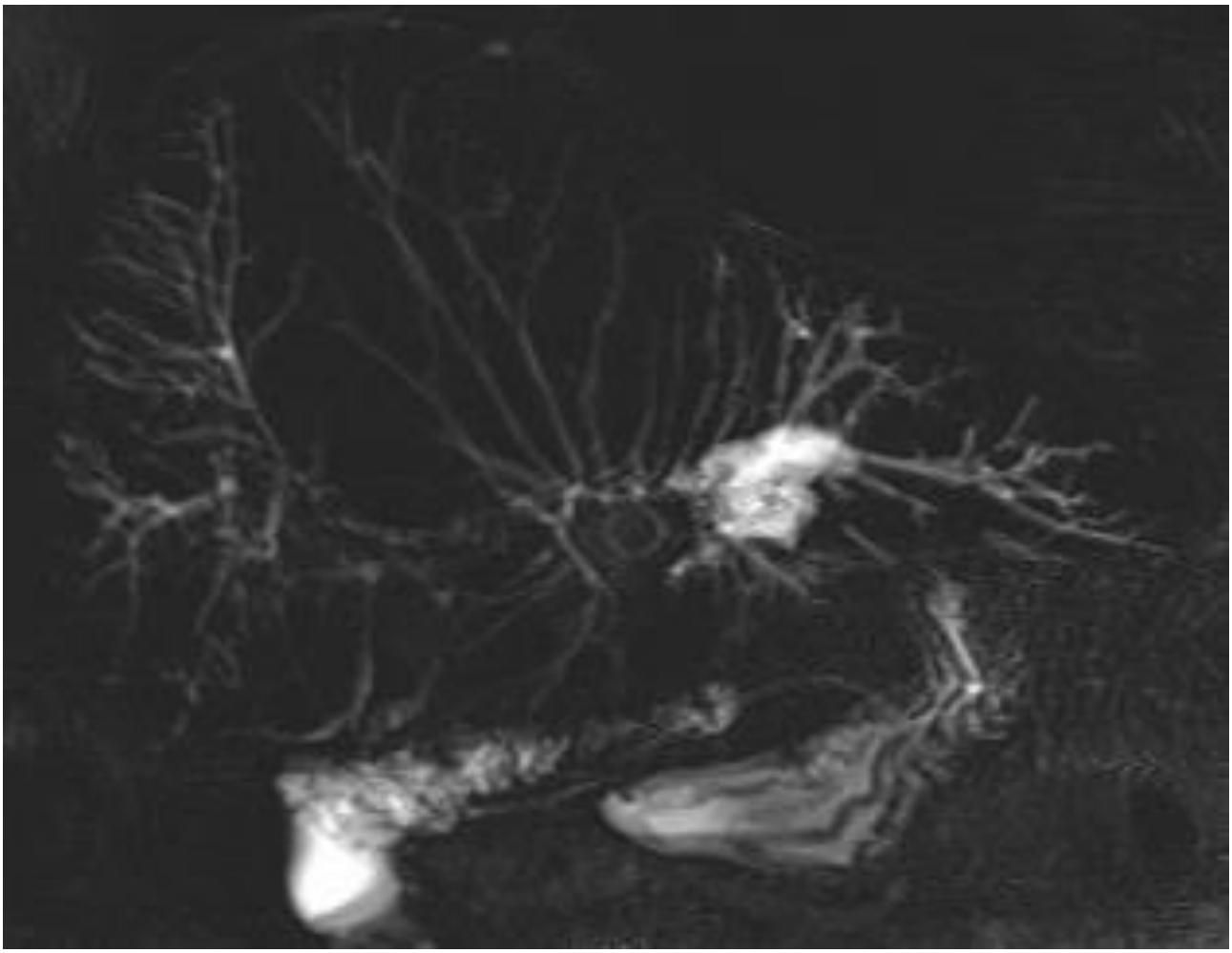


Fig 12 - 63 year old male with recurrent primary sclerosing cholangitis 9 years post liver transplant. MRCP shows multiple intrahepatic duct strictures. The graft vessels were all patent with no evidence of vascular complication.