Editorial

Developments in diagnosis and management of post-liver transplantation biliary complications: the radiologist's perspective

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Comment on: Magro B, Tacelli M, Mazzola A, *et al.* Biliary complications after liver transplantation: current perspectives and future strategies. Hepatobiliary Surg Nutr 2021;10:76-92.

Submitted Apr 13, 2022. Accepted for publication May 06, 2022.
doi: 10.21037/hbsn-22-141
View this article at: https://dx.doi.org/10.21037/hbsn-22-141_

Biliary complications are the most common source of morbidity after liver transplantation as they may occur in up to 45% of patients (1). The review by Magro *et al.* (2) provides comprehensive insights on this topic and offers a cue for in-depth remarks form a radiological perspective regarding both diagnostic and interventional aspects.

Ultrasound (US)-based techniques, including B-mode and color-Doppler, are the milestone of post-transplant follow-up. The assessment of graft vascularization is crucial since many biliary complications are supposed to be induced by arterial ischemia. To this regard, however, it must be emphasized that US imaging is hampered by a limited panoramic view, especially in difficult abdomens, therefore it is not possible to rely exclusively on this technique. Moreover, complex vascular surgical reconstructions with multiple arterial anastomoses are often performed and US may not always be able to assess the whole liver complexity, due to limited acoustic window. Thanks to technological advances, lower radiation dose and the possibility of using lower doses of contrast medium, an early and preemptive use of computed tomography (CT) should not be disregarded, even at the first clinical suspicion of a vascular problem. This is especially true in whole liver transplantation or in the right split where the acoustic window may be very limited; conversely, in pediatric split transplantation the epigastric acoustic window generally allows a complete evaluation of the left split graft.

An important aspect to consider is the wide spread of US contrast agents that may increase the operator's confidence in the interpretation of US findings. Although US contrast agents have not been yet approved in Europe for the intravenous administration in pediatric patients, their application in urgent situations has been described (3) and an increase in clinical use is expected. Contrast-enhanced US (CEUS) may be performed at bedside, providing immediate information about graft vascularization and perfusion (4) (both arterial and portal) and allowing to distinguish small fluid collections from slow-flow pseudoaneurysms.

When biliary complications are suspected it is worth to stress the importance of the most reliable non-invasive radiological technique, which is magnetic resonance cholangiopancreatography (MRCP). In addition to the valid description of its application provided by Magro *et al.*, we highlight the utility of hepatocyte specific contrast agents (HSCA). Thanks to their uptake by normal functioning hepatocytes with consequent excretion in the biliary system, they add functional information to the morphological assessment of non-enhanced MRCP (5).

Biliary complications may be subdivided in two main

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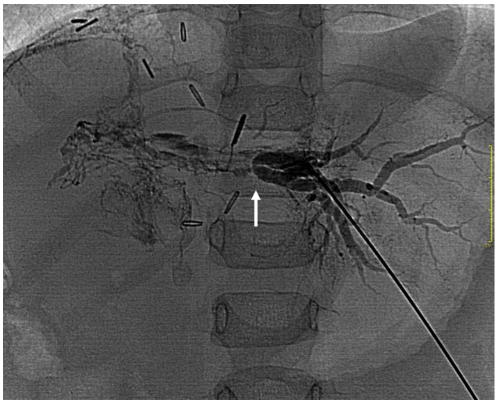

Figure 1 Intrahepatic segment 2 bile duct stenosis in a 3-year-old female after left split liver transplantation. Percutaneous transhepatic cholangiography image shows abrupt interruption of the biliary duct (arrow) with subsequent opacification of tiny lymphatic ducts draining towards the hepatico-jejunostomy at the hepatic hilum.

categories: strictures and leakages. The first are more common and hamper graft survival. Regarding biliary strictures, a first distinction between adult and pediatric liver transplantation must be made: the first is most commonly performed with a duct-duct anastomosis while the second with hepatico-jejunostomy. This implies that the prevalence of stenoses differs among categories of patients and also the treatment approach varies significantly. Indeed, pediatric patients with biliary strictures of left lateral split liver transplants with hepatico-jejunostomy are generally managed by the interventional radiologist (6), unlike most whole liver or right split liver transplants in adults and older children, which are managed endoscopically.

The role of arterial blood supply in ischemic cholangiopathy has been described, even though the mechanisms that cause biliary duct damage depend on many variables and individual factors (2). Its noteworthy that from a radiological perspective an early diagnosis (by strict follow-up US protocols after transplant) of arterial stenosis/thrombosis and timely interventional treatment are crucial. Once ischemic cholangiopathy has occurred, the typical clinical picture is usually characterized by multiple intrahepatic stenoses which are particularly hard to manage, often hesitating in retransplantation.

The suspicion and diagnosis of a biliary stricture should be clinical in the first instance, because the onset of imaging-detectable bile duct dilation may develop only in later stages or may not occur in case of fibrotic and poorly elastic liver parenchyma. Nevertheless, Sansotta *et al.* (7) observed that biliary strictures can be clinically and biochemically silent and only incidentally detected in liver biopsies performed in the routine follow-up of orthotopic liver transplantation. The mechanisms of poor clinical manifestation of biliary strictures are not clearly understood yet; a possible hypothesis, on which we are investigating, implies that biliary drainage may be compensated through lymphatic pathways (*Figure 1*). Thus, the rate of biliary strictures after orthotopic liver transplantation is likely underdiagnosed.

In this setting, the role of imaging to confirm biliary stricture is still debated. Although both US and MRCP are sensitive to bile ducts dilation, they may furnish false negative results in fibrotic livers. In case of clinico-radiological discordance, the endoscopic retrograde choledoco-pancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) still represent the gold standard techniques. At the same time these invasive tools should not be overused due to the risk of possible complications, especially infectious ones in immunosuppressed transplanted patients (8). To reduce that risk the interventional radiologist should operate in accordance with standard of practice recommendations (9).

A promising solution to the pitfalls of morphologic imaging is represented by the use of HSCA in MRCP study, providing functional information and improving the radiologist's confidence in image interpretation (10). Cholestasis is associated with reduced HSCA uptake that, in case of intrahepatic strictures, may show up as sectorial or segmental liver parenchyma hypointensity (*Figure 2*).

In particular, in the whole liver transplant, MRCP provides a panoramic view of the biliary tree, and it allows to plan the best interventional approach, especially in cases of intrahepatic stenoses. With the increasing use of HSCAs, which add functional value to MRCP, and overcoming restrictions on use in paediatric patients, we expect a further drop in the use of ERCP and PTC with only diagnostic purposes. The future perspective is that ERCP and PTC should be reserved to cases requiring therapeutic interventions.

The most important and recent developments in the interventional radiological management of benign biliary stricture after liver transplant are represented by the widespread clinical use of biodegradable biliary stents (11). To our knowledge, on the market, there are

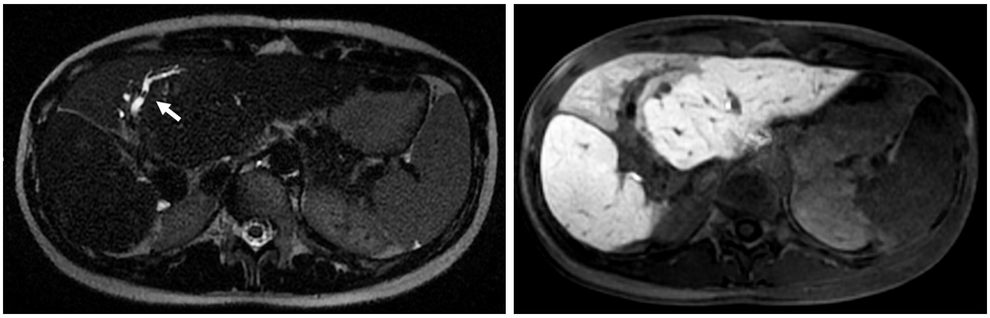

Figure 2 Segmental cholestasis with biliary stones in a 25-year-old female after left split liver transplantation. On the left, an axial T2-weighted sequence shows segmental bile duct dilation with a stone (arrow). On the right, the corresponding T1-weighted hepatobiliary phase image demonstrates relative hypointensity of liver parenchyma of the segment affected by bile ducts dilation, consistent with reduced uptake and biliary excretion of the contrast agent due to cholestasis.

currently three different devices: the firstly introduced is manufactured by ELLA CS and it is self-expandable, made of polidioxanone, with a degradation profile of 3 months; the rigid double-spiral design non-expandable Archimedes (amg International GmbH), made of polymeric compound, with a variable degradation profile up to 11 weeks, conceptually resembling a plastic endoprosthesis; and the recently introduced balloon expandable Unity-B (QualiMed) biodegradable metal stent, made of a magnesium metal alloy and a polymeric compound, with different degradation profiles (not all clinically available yet). Intuitively, expandable stents, provide more radial strength against the biliary strictures and should be preferred in case of refractory stenoses. However, also non-expandable stents can be placed in parallel, to achieve larger calipers, providing a more effective and prolonged stricture expansion. Further prospective studies are required in this field. The use of biodegradable devices has two fundamental advantages: the first is the complete reabsorption which is particularly appreciated by the interventional radiologists since it avoids the need for a delayed PTC approach for stent removal, minimizing the risk of complications; moreover, they can be used as an alternative to long-term internal-external biliary drainages, burdened by the infectious risk and device discomfort, especially in pediatric patients (12). The interventional radiological management of post-liver transplant benign biliary strictures has not been standardized yet. On the one hand this is due to the variable clinical scenarios that may present intraoperatively (single or multiple strictures; focal or lengthy stenoses); on the other, treatment response is often unpredictable. Thus, in adults, variable approaches are accepted including, multiple cycles of bilioplasty with long-term maintenance of the biliary drainage; single session bilioplasty followed by placement of a fully covered (removable) self-expandable metallic stent, that will required a new PTC for stent removal. In children, short treatment protocols to minimize drainage-related risks have been described (13). In this scenario, the use of biodegradable stents will certainly offer new therapeutic chances.

The use of biodegradable biliary stents has been also described intraoperatively, during transplantation, to spare the T-Tube (14). Theoretically, this should have a preemptive effect, reducing the risk of biliary leaks and strictures; prospective studies are to be conducted.

While the treatment of benign biliary strictures may rely on several effective strategies, refractory non anastomotic strictures are very challenging to manage, finally leading to retransplantation. Although it has not been shown to prolong graft survival, the use of uncovered metal stents in case of proved end stage biliary cirrhosis may be considered as a bridge to retransplantation. In our experience we treated several pediatric patients with refractory NAS using uncovered metallic stent and we observed a significant improvement of clinical conditions until retransplantation (unpublished data).

Diagnosis and management of biliary leaks is somewhat simpler in many cases. We remark that the hepatobiliary excretion phase of HSCAs may be used to exactly localize the source of bile extravasation with magnetic resonance imaging (15). This is crucial to guide the treatment, since anastomotic leaks should be managed with ERCP or PTC and stent or drainage implantation, while biliary leaks from the cut liver surface may resolve spontaneously, with or without percutaneous drainage, or they may require surgical revision in some cases.

In conclusion, we highlighted the pitfalls and potential solutions of imaging in the diagnosis of biliary complications after liver transplant. We remarked the utility of HSCAs that represent one of the most promising tool in magnetic resonance imaging, to overcome the limits of a static morphologic assessment. We made a brief overview of the interventional radiological treatments focusing on the most promising tool, which is represented by new biodegradable biliary stents.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Hepatobiliary Surgery and Nutrition*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-141/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Marra P, Bonaffini PA, Ippolito D, Sironi S. Developments in diagnosis and management of post-liver transplantation biliary complications: the radiologist's perspective. HepatoBiliary Surg Nutr 2022;11(3):457-461. doi: 10.21037/hbsn-22-141

