Submission Needing Revision:

Reviewer #1 comments:

1) Thanks for your hard work in reviewing endoscopic management of biliary stricture in the post-transplant setting. I think further revisions should be finished before acceptance of your manuscript.

    a. We are grateful for the reviewer's comments and have made the following the changes to the manuscript as indicated below

2) In the thorough introduction of bile duct strictures, what is your consideration in the order of possible risk factors: the rates or the reasons? I cannot figure out the logics. Only two reasons including T-tube and living/deceased donor were discussed, so what is your consideration? Biliary strictures secondary to liver transplantation have been classified as early (≤60days), middle (60days -1year), and late (≥1year) complications in some studies, and their responses to endoscopic managements differs. To include some descriptions like this may be better for the introduction of Bile Duct Strictures.

    a. We agree biliary strictures can and are classified in some studies based upon when they occur after transplantation. We have included this description under the heading "Bile duct strictures."

    b. We have made the following changes under the heading "Bile duct strictures" to elaborate on risk factors of bile duct strictures along with when they can be seen post-liver transplantation. Please see the revised introduction to bile duct strictures below.

    c. *There are several risk factors that predispose to the development of bile duct strictures including hepatic artery thrombosis, donor after cardiac death, ABO incompatibility, preservation injury (cold and warm ischemia time),*

cytomegalovirus infection, duct mismatch between donor and recipient, presence of primary sclerosing cholangitis, bile duct leaks, placement of T-tubes, and living donor transplantation (10-15). *Bile duct strictures can be noted early (< 30 days), delayed (30 – 90 days), or late (> 90 days) after LT (11, 16) (Figure 1). Early complications include hepatic artery thrombosis which can result in ductal stenosis and strictures as well as hepatic ischemia (5). Post-operative edema can also result in early ductal stenosis. Delayed and late complications can involve biliary obstruction at the anastomotic site or intrahepatic ducts due to ischemia (17). Bile leaks and recurrence of PSC are risk factors for the development of delayed/late bile duct strictures.*

3) Can you make a simple flowchart for guiding other endoscopists to manage these patients?

    a. We created a flowchart depicted in Figure 1 titled "Evaluation of suspected bile duct strictures post-liver transplantation." Please see attachment. We have also referred to figure 1 in the manuscript under the heading "Bile duct strictures."

    b. *Bile duct strictures can be noted early (< 30 days), delayed (30 – 90 days), or late (> 90 days) after LT (11, 16) (Figure 1).*

Reviewer #2 comments:

1) This is a review article reporting endoscopic management of biliary strictures post-liver transplantation. The topic is not new. There are some comments for the authors. 1. In the Introduction section, the authors reported “It is prudent to consider the potential of a malignant obstruction when evaluating strictures in the post-transplant setting (figure 1)”. This should be omitted because it has nothing to do with the liver transplantation.

    a. We appreciate the reviewer’s comments. We were fortunate to be invited to give a review regarding “Endoscopic Management of Biliary Strictures Post-Liver Transplantation” and focused on only this issue in our manuscript. We have deleted the comment regarding the potential of a malignant obstruction when evaluating strictures in the post-transplant setting along with the image. It now reads as follows:

    b. *It is important to consider non-obstructive causes of cholestasis including cellular rejection, drug induced cholestasis, or recurrence of primary disease as this may prevent a delay in therapeutic intervention. Advancements in endoscopic techniques and tools have allowed endoscopic management to be the preferred method to manage most biliary complications (8, 9)*

2) In the "Introduction and Conclusion" section, the authors emphasized that "biliary stenosis plays an important role in morbidity and mortality in patients with LT." What is the mortality rate? It is not described in the body of the manuscript.

    a. We have deleted the word “mortality” in both the introduction and conclusion and it now reads as follows:

    b. *Introduction: Biliary complications after liver transplantation (LT) is a known and significant cause of morbidity in LT recipients.*

    c. *Conclusion: Biliary strictures play a significant role in morbidity of LT recipients*

3) In page 6, the authors determined the patency of the anastomosis as “by evaluating the resistance encountered with anterograde and/or retrograde biliary balloon sweeps across the anastomosis”. Is there a definition regarding the diameter of the inflated balloon used to sweep across the anastomosis?

    a. We have edited the manuscript to reflect that there is no standardized bile duct diameter that corresponds to bile duct strictures.

    b. *There is no standardized bile duct diameter that corresponds to a clinically significant bile duct stenosis. However, cholangiogram features of a thin focal narrowing with proximal bile duct dilation along with evaluating the resistance encountered with anterograde and/or retrograde biliary balloon sweeps with an 8.5 mm or 11.5 mm biliary balloon across the anastomosis can help determine the patency of the anastomosis.*

4) In addition, figure 2 should contain two images showing: (a) AS before stenting, and (b) a waist is no longer seen after stenting.

    a. We have edited the manuscript to include three images (Figure 2a, 2b, 2c) that depict an anastomotic stricture prior to stenting that resolved with multiple biliary stents and balloon dilation.

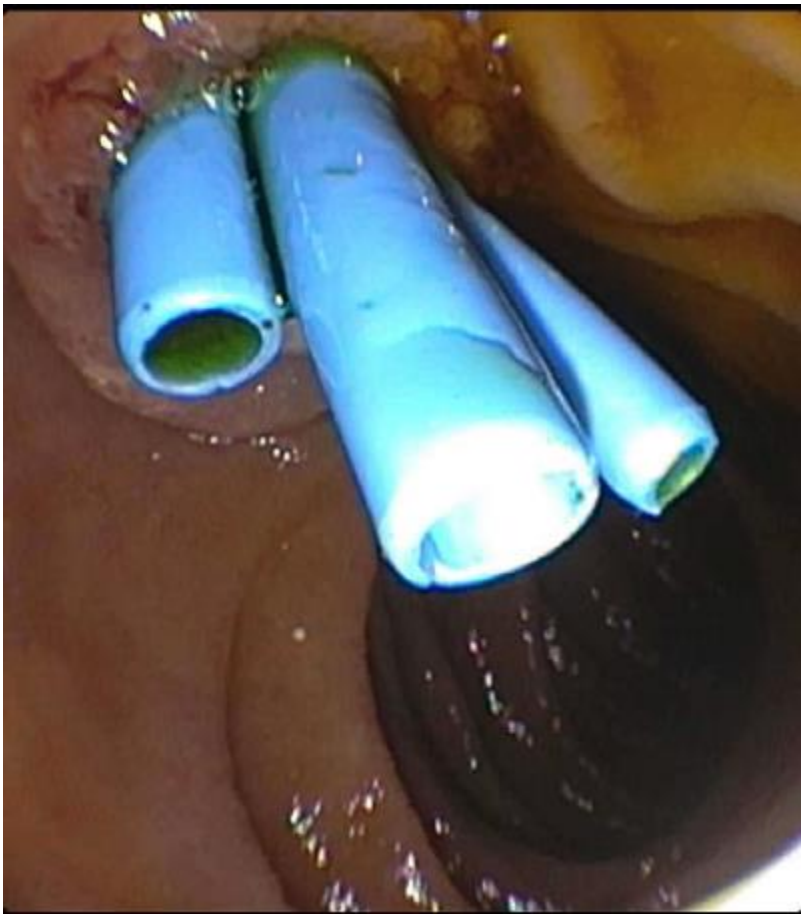
Image 2a

Anastomotic bile duct stricture managed with biliary stenting and balloon dilation

A patient less than 60 days post-liver transplantation who presented with elevated liver tests and found to have an anastomotic bile duct stricture.

Image 2b

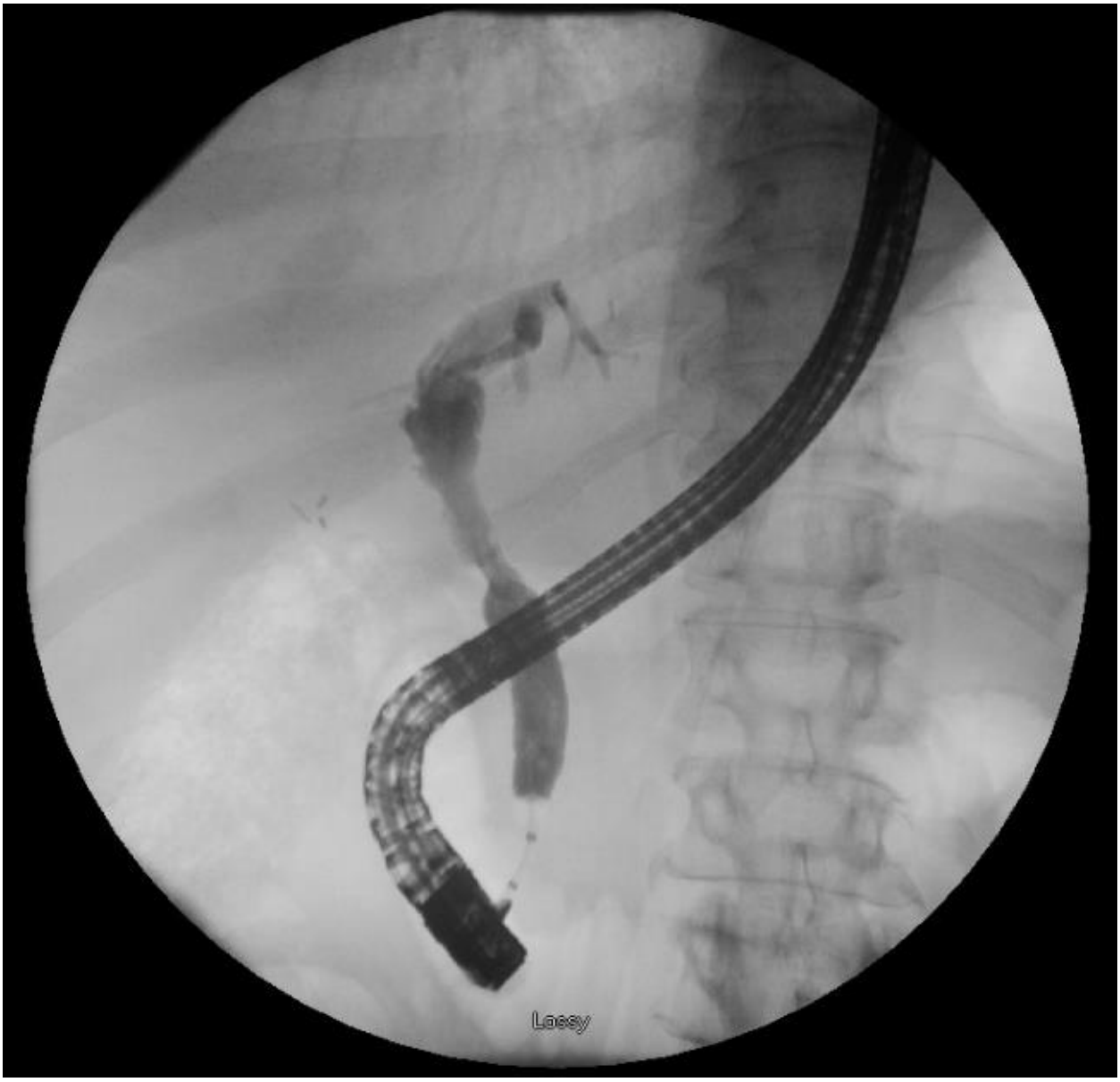
Anastomotic bile duct stricture managed with biliary stenting and balloon dilation



The patient was managed with serial balloon dilation and multiple biliary stents.

Image 2c

Anastomotic bile duct stricture managed with biliary stenting and balloon dilation



Approximately 9 months post-liver transplantation the anastomotic stricture had resolved and required no further intervention.

5) There have been many similar articles in the literature. Therefore, it would be better if the authors could report more endoscopic techniques (or in more details) to resolve difficult cases of bile duct stricture. For example: I. SpyGlass cholangioscopy-assisted guidewire placement when the guidewire passage of the strictures site is impossible by conventional methods. II. Balloon-assisted enteroscopy for surgically altered anatomy (such as hepaticojejunostomy mentioned in the Introduction section). III. Rendezvous ERC. Figure 3 should include a series of images that demonstrate the rendezvous ERC process. IV. Any other endoscopic methods to resolve difficult cases of bile duct stricture.

a. We have edited the manuscript to include additional details regarding the use of balloon assisted enteroscopy, PTC and the use of rendezvous technique, single-operator peroral cholangioscopy (SpyGlass), and described an alternative technique using magnetic compression anastomosis. In addition, we have included a series of images in reference to the rendezvous technique

b. *Endoscopic methods may not be feasible due to surgical anatomy (bilio-enteric anastomosis), tortuosity and angulation of the bile duct, or severity and location of the stricture which prevents a guidewire or dilation devices to traverse the stricture. Roux-en-Y hepaticojejunosotomy or roux-en-Y gastric bypass require deep ERCP methods such as balloon-assisted enteroscopy, endoscopic ultrasonography-directed transgastric ERCP, or percutaneous transhepatic cholangiography (PTC). A multi-center trial showed balloon assisted enteroscopy to be successful in two thirds of cases and in 88% of patients in whom the papilla is reached. Single or double balloon assisted enteroscopy may be an alternative before pursuing PTC or surgical alternatives (62).*

A rendezvous technique may also be used which combines PTC and an endoscopic transpapillary approach to access the bile duct and traverse the stricture that otherwise may have failed with conventional endoscopy (Image 3a,3b, 3c, 3d). PTC in cases of benign bilio-enteric anastomotic strictures are reported to have an overall success rate of 80% (63). It is also especially helpful in those with intractable or multiple intrahepatic strictures as internal-external stents can be placed and relieve the obstruction. In addition, the potential of swing-tip cannulas in accessing tight intrahepatic strictures have been reported and may also help achieve faster cannulation of the bile duct (64, 65).

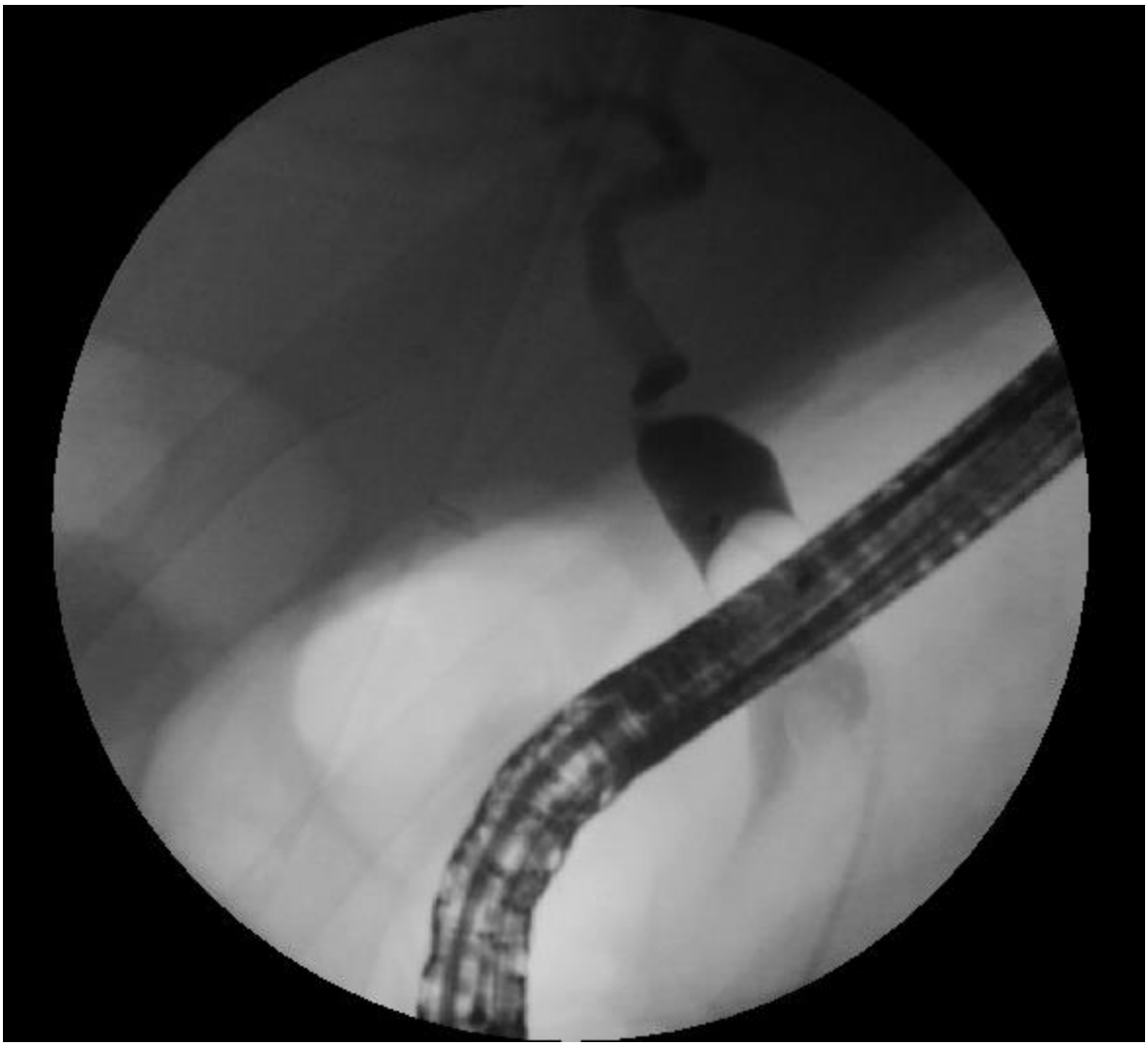
Single-operator peroral cholangioscopy can also be used in the treatment of bile duct strictures by providing direct visualization of the lumen of the bile ducts. Direct visualization of the inside of the bile duct may help predict outcomes of endoscopic therapy based upon the pattern and severity of edema and inflammation seen (66). In addition, direct visualization can also be used in conjunction with the rendezvous technique to puncture the bile duct and safely traverse a completely obstructed duct (67, 68).

Magnetic compression anastomosis (MCA) is a rescue technique used in the setting of complete biliary obstruction. A magnet is advanced to the site of the stricture via ERCP and another magnet is advanced percutaneously via PTC. Fluoroscopy is used to properly align the magnets and a hole in the center of the magnets allow a guidewire to be advanced. Recanalization can be achieved via PTC and serial biliary stenting can be performed. Magnet approximation and recanalization have been reported to be successful in 84% and

77% of patients respectively. MCA has been shown to be effective for short strictures (< 1 cm) with a low stricture recurrence rate (69, 70).

Image 3a

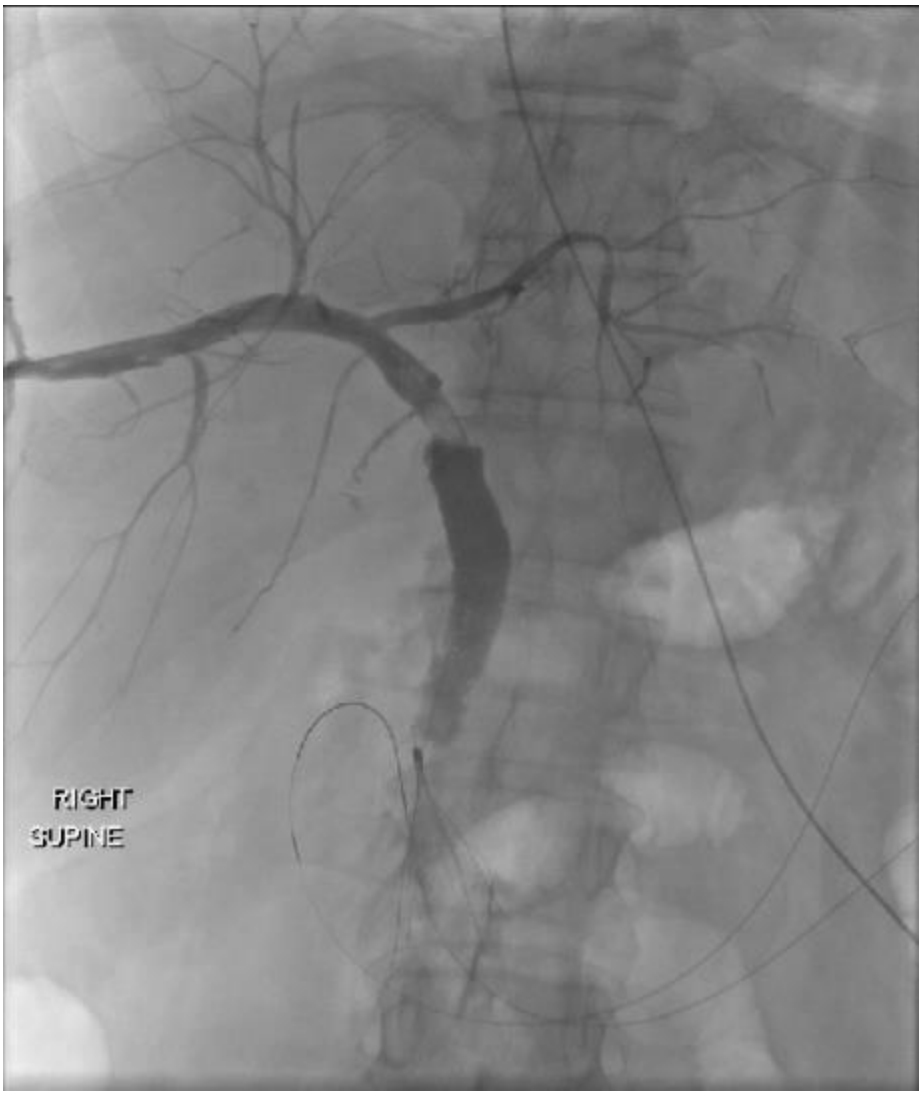
Anastomotic bile duct stricture treated with rendezvous technique



A 56-year-old patient who presented two years after transplantation with jaundice and found to have a severe anastomotic stricture which was not able to be traversed with a guidewire.

Image 3b

Anastomotic bile duct stricture treated with rendezvous technique



Percutaneous transhepatic cholangiogram showing a stricture at the anastomosis with the guidewire inserted through the transhepatic tract.

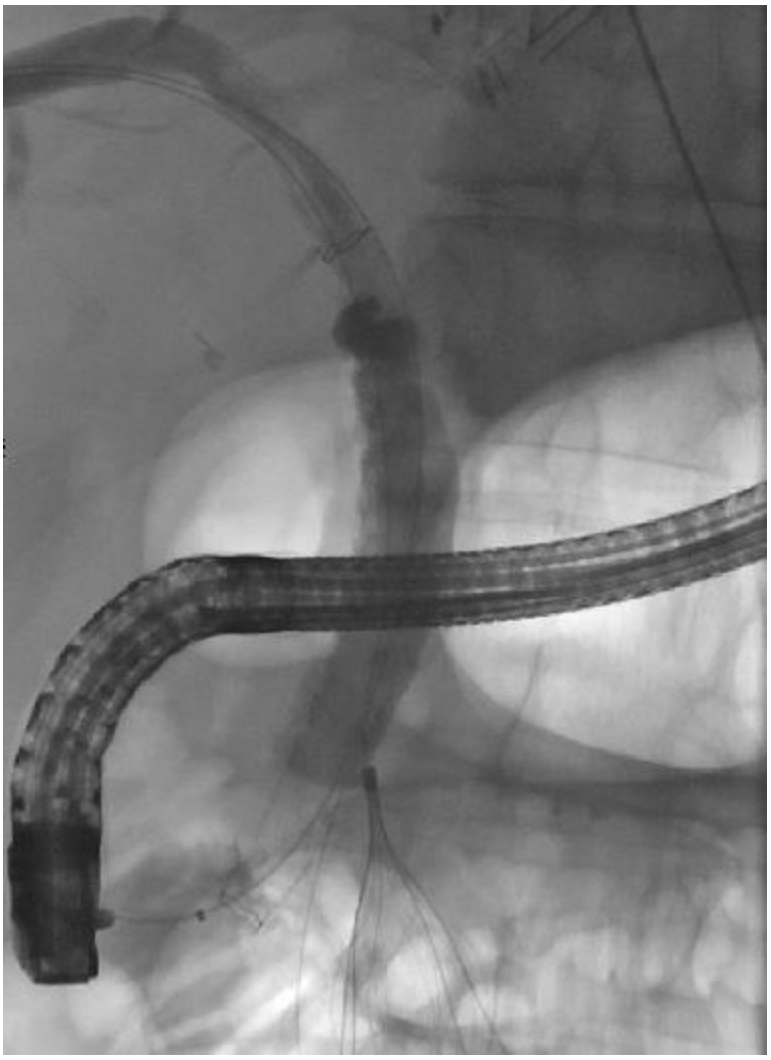
Image 3c

Anastomotic bile duct stricture treated with rendezvous technique

The rendezvous technique was used to advance the endoscopic catheter over the transhepatic guidewire and proximal to the anastomotic stricture.

Image 3d

Anastomotic bile duct stricture treated with rendezvous technique



A fully covered metal biliary stent was placed traversing the anastomosis.

Reviewer #3 comments:

1) This is a narrative review where the authors review the risk factors associated with the development of bile duct strictures in the post-transplant setting along with the efficacy and complications of current endoscopic approaches available for the management of bile duct strictures. Here are my comments on this review: 1) Well, this is an article sent by invitation and the least expected was that it follows the rules and writing guidelines of the WJGE. This needs to be adjusted. The "Guidelines for Manuscript Preparation and Submission: Review" file needs to be followed. There is an example of submission in the file "Format for Manuscript Submission: Review"

    a. We referred to the “Guidelines for Manuscript Preparation and Submission: Review” file and have made the following changes on the title page

        i. Included running title: **Akhter A**, et al. Biliary strictures post-liver transplantation.
        ii. Included Open-Access statement: **Open-Access:** This article is an open-access article which was selected byan in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
        iii. Included the copyright statement below key words listed in the abstract: © **The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.
        iv. Submitted audio core tip
        v. Edited references to include “DOI” and superscripted references in the manuscript

2) This theme is well discussed in the literature and there are numerous publications. We recently have another review, on the same theme, published in March 2019 by Lee DW et al (PMID: 30840808). I would like to know what your review adds to the literature since we already have a review published recently. What's different about your study?

    a. We appreciate the reviewer's comments and viewed the well-done publication by Lee DW, et al. We submitted our invited review on February 21, 2019 prior to the publication by Lee DW, et al on February 25, 2019.

    b. While both studies discuss endoscopic management of biliary strictures, our study focuses on both anastomotic and non-anastomotic strictures after deceased donor transplantation along with living donor transplantation. As mentioned in Lee DW, et al. they focus primarily on issues of anastomotic strictures in living donor transplantation. In addition, we also discuss alternative methods of treating bile duct strictures when conventional ERCP methods fail including the use of balloon assisted enteroscopy, per oral cholangioscopy, PTC, rendezvous technique, and magnetic compression anastomosis. Please see revisions noted in "Reviewer #2 comments: #5."

3) In the topic "Anastomotic bile duct strictures": You cite a systematic review by Kao et al 2013 and concluded: "Currently, there is substantial evidence that multiple plastic biliary stents with dilation provide adequate resolution of AS in liver transplant recipients with lower adverse events than SEMS, though, time to resolution may be longer. But this is not the result found in the last published systematic review on the subject. Visconti et al., 2018 (PMID: 30258982) performed a systematic review with meta-analysis including only RCT articles (evidence 1A) and concluded: No difference was observed between the stricture resolution rate (RD: 0.01; 95%CI [−0.08–0.10]), stricture recurrence (RD: 0.13; 95%CI [−0.03–0.28]), and adverse events (RD: −0.10; 95%CI [−0.65–0.44]) between the plastic and metallic stent groups. The metallic stent group demonstrated benefits in relation to the number of ERCPs performed (MD: −1.86; 95%CI [−3.12 to

−0.6]), duration of treatment (MD: −105.07; 95%CI [−202.38 to −7.76 days]), number of stents used (MD: −10.633; 95%CI [−20.82 to −0.44]), and cost (average $8,288.50 versus $18,580.00, P <0.001). This needs to be reviewed and your discussion updated.

a. We appreciate the reviewer's comments and bringing the publication by Visconti, et al to our attention. We have updated the manuscript to include the findings by Visconti, et al as well as the discussion of plastic biliary stents and metal stents.

b. *A systematic review of case series including 446 patients by Kao et al. did not find SEMS to have a clear advantage over multiple plastic biliary stents in LT recipients but found stricture resolution was improved in those patients whom the stent duration was longer than 3 months (52). A recent meta-analysis of four randomized controlled trials comparing plastic stents to fully covered SEMS found no difference between stricture resolution, stricture recurrence, and adverse events. However, those who received a metal stent did have fewer ERCPs performed as compared to those who had plastic stents (53). Currently, there is no standardized approach for endoscopic management of anastomotic strictures. The use of multiple plastic biliary stents with balloon dilation and fully covered SEMS can provide similar resolution rates of AS after liver transplantation with overall low risk of adverse events.*

4) Your bibliography uses old and outdated articles. Including a self-citation of 2003 where even articles are updated. Please review this.

a. We have added the following references:

i. Visconti TAC, Bernardo WM, Moura DTH, Moura ETH, Gonçalves CVT, Farias GF, et al. Metallic vs plastic stents to treat biliary stricture after liver transplantation: a systematic review and meta-analysis based on randomized trials. Endosc Int Open. 2018;6(8):E914-E23. Epub 2018/08/01. doi: 10.1055/a-0626-7048. PubMed PMID: 30258982; PubMed Central PMCID: PMCPMC6156748.

ii. Shah RJ, Smolkin M, Yen R, Ross A, Kozarek RA, Howell DA, et al. A multicenter, U.S. experience of single-balloon, double-balloon, and rotational overtube-assisted enteroscopy ERCP in patients with surgically altered pancreaticobiliary anatomy (with video). Gastrointest Endosc. 2013;77(4):593-600. Epub 2013/01/03. doi: 10.1016/j.gie.2012.10.015. PubMed PMID: 23290720

iii. Kim JH, Lee SK, Kim MH, Song MH, Park DH, Kim SY, et al. Percutaneous transhepatic cholangioscopic treatment of patients with benign bilio-enteric anastomotic strictures. Gastrointest Endosc. 2003;58(5):733-8. PubMed PMID: 14595311

iv. Uchida D, Kato H, Saragai Y, Takada S, Muro S, Tomoda T, et al. Usefulness of a Cannula with a Flexible Tip (Swing Tip) for Managing Severe Biliary Stricture. Can J Gastroenterol Hepatol. 2018;2018:7125714. Epub 2018/12/12. doi: 10.1155/2018/7125714. PubMed PMID: 30643761; PubMed Central PMCID: PMCPMC6311258.

v. Laasch HU, Tringali A, Wilbraham L, Marriott A, England RE, Mutignani M, et al. Comparison of standard and steerable catheters for bile duct cannulation in ERCP. Endoscopy. 2003;35(8):669-74. doi: 10.1055/s-2003-41515. PubMed PMID: 12929062

vi. Bukhari MA, Haito-Chavez Y, Ngamruengphong S, Brewer Gutierrez O, Chen YI, Khashab MA. Rendezvous Biliary Recanalization of Complete Biliary Obstruction With Direct Peroral and Percutaneous Transhepatic Cholangioscopy. Gastroenterology. 2018;154(1):23-5. Epub 2017/11/02. doi: 10.1053/j.gastro.2017.09.050. PubMed PMID: 29102615.

vii. Gürakar A, Wright H, Camci C, Jaboour N. The application of SpyScope® technology in evaluation of pre and post liver transplant biliary problems. Turk J Gastroenterol. 2010;21(4):428-32. PubMed PMID: 21331998.

viii. Jang SI, Kim JH, Won JY, Lee KH, Kim HW, You JW, et al. Magnetic compression anastomosis is useful in biliary anastomotic strictures after living donor liver transplantation. Gastrointest Endosc. 2011;74(5):1040-8. doi: 10.1016/j.gie.2011.06.026. PubMed PMID: 21855872.

ix. Parlak E, Koksal AS, Kucukay F, Eminler AT, Toka B, Uslan MI. A novel technique for the endoscopic treatment of complete biliary anastomosis obstructions after

liver transplantation: through-the-scope magnetic compression anastomosis. Gastrointest Endosc. 2017;85(4):841-7. Epub 2016/08/24. doi: 10.1016/j.gie.2016.07.068. PubMed PMID: 27566054