Biliary Strictures After Liver Transplantation with Grafts from Donors After Cardiac Death: Narrowing Down the Etiologies

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Liver transplantation (LT) is the standard-of-care for patients with end-stage liver disease. With improving techniques, graft and patient outcomes are excellent. The number of orthotopic LTs in the USA is on the rise; since demand for livers continues to exceed supply, transplant centers are constantly expanding donor liver utilization criteria [1]. Traditionally, allografts that are obtained through donation after brain death (DBD) have been the principal source of liver allograft donor pool. Donation after cardiac death (DCD) is on the rise in the USA and is becoming a rapidly growing source of liver allografts to fill the gap in organ scarcity. Unlike DBD grafts, livers from DCD suffer from a variable form of ischemia. Hence, DCD allografts are at a higher risk of developing biliary complications (biliary strictures and ischemic cholangiopathy), with resultant graft loss and death [2]. An analysis of the national registry of LT recipients database showed that DCD allografts experienced inferior survival at 1 and 3 years as well as a higher risk of re-transplantation compared to DBD recipients [3]. Similar results were reported in a prospective multicenter study in the UK [4]. Despite recent advances in treatments for biliary strictures after LT, they continue to be of concern as they are observed in approximately in 5–15% of patients following deceased donor LT and 28–32% following living donor LTs [5].

Risk factors for post-transplant biliary strictures include hepatic artery thrombosis (HAT), primary sclerosing cholangitis (PSC), older age donors, as well as use of vasopressors in the donors [6]. Biliary strictures can be anastomotic

strictures (AS) or non-anastomotic strictures (NAS). AS are usually short segmental areas of stenosis involving the ductal anastomosis occurring early after transplantation, most frequently caused by technical issues related to the transplant surgery due to scar formation at the anastomotic site. Contrariwise, NAS, thought to be the result of ischemic injury to the duct, may be associated with obvious vascular compromise (hepatic artery or portal vein occlusion) or secondary causes injuring the vasculature (cytomegalovirus, ischemia time, blood group ABO incompatibility) and are relatively more common in cases of DCD liver transplantation [7]. An Australian cohort demonstrated that elevated bilirubin levels in the first week after transplantation are predictive of the later development of biliary strictures in DBD transplants [8]. Nevertheless, data regarding the predictors of biliary complications in DCD grafts are limited.

In this issue of *Digestive Disease and Sciences*, Kohli and his colleagues examine factors that predict the risk of biliary strictures in patients undergoing LT after DCD [9]. This retrospective study included one hundred adult patients who underwent LT after DCD in a single tertiary center over a 7-year period. Subjects were divided into two groups based on the presence of post-LT biliary strictures that were determined after reviewing endoscopic retrograde cholangiopancreatography (ERCP) reports and subdivided into AS and NAS. The authors report a 34% incidence of biliary strictures in LT after DCD. AS were more common (59%). Several clinical factors, including patient demographics, LT perioperative course, and laboratory factors were studied. Confounders, such as the cause of liver disease, were controlled for. Of clinical significance, the authors observed that consistent with prior reports, strictures were more common with grafts from older donors [9]. They also report that although a higher bilirubin level at day 0 post-LT was observed in the stricture group compared to the non-stricture group (3.5 vs. 2.6), a similar association was not perceived at day 7. Subgroup analysis designed to evaluate variances between AS and NAS did not reveal any

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differences. Similarly, they also found that a higher international normalized ratio (INR) at day 7 post-LT was also a predictor of biliary stricture formation (median INR 1.24 in patients with biliary strictures vs. 1.13 in others). Although this is a statistically significant finding, its clinical impact is minimal, considering that the absolute difference between numbers is small.

It is not entirely clear why an elevated bilirubin on day 0 would predict the incidence of biliary strictures several months after LT. In this study, the median time of onset of biliary strictures was 107 days post-LT in the AS group and 166 days in the NAS group. One can hypothesize that organ ischemia at the time of procurement, which is manifest as early post-LT hyperbilirubinemia, could be associated with NAS. Prior reports have attempted to explain the pathophysiological alteration by proposing that bilirubin elevation level post-LT is likely due to impaired bile transporter function as a consequence of the prolonged graft ischemia that commonly occurs in DCD LT [7]. Interestingly, there was no difference between the two groups regarding the duration of cold and warm ischemia, though cold ischemia would be expected to have more impact on biliary stricture in DCD LT. Cold ischemia occurs during the preservation of graft at cold temperature while warm ischemia occurs in span between removal from cold storage to establishment of reperfusion of liver graft [10]. This interesting study by Kohli and colleagues provides a snapshot about the possible etiologies and natural history of biliary strictures in DCD LT. It supports prior reports of donor age as an independent risk factor for biliary stricture formation [11].

What is the clinical significance of this finding? Perhaps DCD organs involving an older donor and recipients with bilirubin levels > 3.5 mg/dl should be more closely followed for the appearance of biliary strictures, with a low threshold for ERCP in the presence of abnormal liver enzymes and hyperbilirubinemia in the post-LT period.

Studies on post-transplant biliary strictures are challenging due to low sample size since most studies are single center. Multicenter studies are needed to better identify risk factors for post-transplant biliary strictures and quantify the impact of early post-transplant hyperbilirubinemia as a predictor of post-transplant biliary stricture formation.

The field of liver transplantation is predicted to undergo a major change with the increasing use of normothermic perfusion devices, which functions to keep a physiological environment for the liver during transportation to decrease the risk of ischemic injury as well as post-reperfusion injury [12]. If the mechanism of post-transplant biliary strictures is secondary to impaired bile transporter function, it is possible

that the incidence of biliary strictures in DCD transplantation may decrease in the future; thus, studying the incidence of post-transplant biliary strictures with the use of normothermic perfusion devices is an important area for future research.

Author's contribution Hamzeh Sarairoh drafted the article; Latha Thankam Sundaram critically revised the article; Binu V John drafted the article and critically reviewed the article.

References

1. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2016 annual data report: liver. *Am J Transplant.* 2018;18:172–253.
2. O'Neill S, Roebuck A, Khoo E, Wigmore SJ, Harrison EM. A meta-analysis and meta-regression of outcomes including biliary complications in donation after cardiac death liver transplantation. *Transpl Int.* 2014;27:1159–1174.
3. Jay C, Ladner D, Wang E, et al. A comprehensive risk assessment of mortality following donation after cardiac death liver transplant—an analysis of the national registry. *J Hepatol.* 2011;55:808–813.
4. Callaghan CJ, Charman SC, Muiesan P, et al. Outcomes of transplantation of livers from donation after circulatory death donors in the UK: a cohort study. *BMJ Open.* 2013;3:e003287.
5. Ryu CH, Lee SK. Biliary strictures after liver transplantation. *Gut Liver.* 2011;5:133–142.
6. Sharma S, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: past, present and preventive strategies. *Liver Transpl.* 2008;14:759–769.
7. Pereira P, Peixoto A. Biliary complications—the “Achilles Heel” of orthotopic liver transplantation. *GE Port J Gastroenterol.* 2017;25:1–3.
8. Forrest EA, Reiling J, Lipka G, Fawcett J. Risk factors and clinical indicators for the development of biliary strictures post liver transplant: significance of bilirubin. *World J Transplant.* 2017;7:349–358.
9. Kohli DR, Harrison ME, Adike AO, et al. Predictors of biliary strictures after liver transplantation among recipients of DCD (donation after cardiac death) grafts. *Dig Dis Sci.* (Epub ahead of print). <https://doi.org/10.1007/s10620-019-5438-0>.
10. Hong JC, Yersiz H, Kositamongkol P, et al. Liver transplantation using organ donation after cardiac death: a clinical predictive index for graft failure-free survival. *Arch Surg.* 2011;146:1017–1023.
11. Mocchegiani F, Vincenzi P, Lanari J, et al. Immunological risk factors in biliary strictures after liver transplantation. *Ann Transplant.* 2015;20:218–224.
12. Jayant K, Reccia I, Viridis F, Shapiro AMJ. The role of normothermic perfusion in liver transplantation (TRaNsIT Study): a systematic review of preliminary studies. *HPB Surg.* 2018;2018:6360423.

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