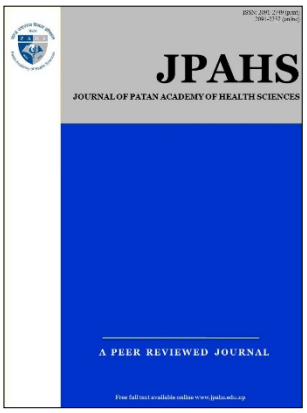

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Recent controversies in liver transplantation

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Abstract

The chronicle backdrop of liver transplantation (LT) is an intricate story to reveal- it is an adventure of extraordinary achievement and catastrophic disappointments. Historically, controversies and LT seems to be synonymous.

Despite the improvements in results, LT is still facing lots of challenges and controversies, whereby demand is high but the resources, primarily concerned to donor, are very limited.

We have focused our perspective on LT for HCV-related cirrhosis and nutritional support for cachectic patients awaiting LT.

Keywords: cachectic patients, hepatitis C virus (HCV), liver transplant, nutritional support, sarcopenia

Introduction

Liver transplantation (LT) is the gold standard and only cure for end-stage liver diseases. Demand of the organ, and low available donor pool have been marginally improved through innovations such as a living donor liver transplant, donation after circulatory death, split liver transplantation, auxiliary liver transplant, extended criteria for donors, extended criteria of LT for HCC, and ABO incompatible LT.[1-3] Nonetheless, there are lots of controversies that are needed to be discussed among the transplant community, like selection of patients in need of LT, best use of new drugs, and new advancements, Figure 1. To discuss all the controversies in LT in detail will require separate extensive review, and is beyond the scope of this article with concise viewpoint we have put here for further debate. Here we have especially focused on LT for HCV-related cirrhosis and nutritional support for cachectic patients awaiting LT.

Figure 1. Recent controversies in liver transplantation[1-5,7,9]

Note: ABOi: ABO incompatible; ABOc: ABO Compatible; ALF: Acute Liver Failure; ACLF: Acute on Chronic Liver Failure; ALD: Alcoholic Liver Disease; DBD: Donation after Brain Death; DCD: Donation after Circulatory Death; HCV: Hepatitis C Virus; LT: Liver Transplantation

Liver transplant and hepatitis C virus (HCV)- Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease and the third most common indications for LT in the United States.[6] However, since the introduction of direct-acting antiviral (DAA) therapy the number of cases has declined in recent years. It is recommended that patients with HCV infection be treated ahead of LT as there is a high chance of HCV reinfection and graft failure after LT.

It is yet unsettled whether HCV-positive patients with Child grade C on the LT waiting list should be treated with DDA before transplant and practices differ in different regions and centers.

At the time of organ shortage, donor pool can be increased by utilizing HCV-positive livers. In regions where HCV-positive livers are common, the accentuation will probably be not to treat HCV infected patients who are on the LT waiting list as HCV-positive livers can be available for such patients. However, in the regions where HCV-positive livers are not as common, the focus will be towards treating HCV-positive patients before the LT. Study shows large variations in the centers using HCV-positive liver, ranging between 0-40%.[7] Concurrently, a recent study shows transplantation of HCV-viremic livers into non-viremic recipients had acceptable short-term outcomes and all the recipients achieved sustained virologic response (SVR) at 12 weeks post-treatments with DAA-based regimens.[8] The debate continue on utilization of HCV-positive livers and choice of treating the patients with HCV before the LT.

Another factor is the Model for End-Stage Liver Disease (MELD) score at the time of the LT. In the centers where the MELD score of the patients is especially low, the emphasis will again be toward antiviral treatment prior to the LT. Such patients if treated with DDA can be virus-free with a SVR and then can be transplanted at generally lower MELD scores less than 25. However, in the centers where patients MELD scores are over 30, physicians are less likely to focus on treatment with DDA for those patients to render them virus-free and put them in the state called “MELD purgatory.” There is ongoing debate concerning why patients should not be treated when they are not too sick to undergo transplant, yet not in a good health to function satisfactorily.

Last but not the least, patient's capacity to medication adherence and to complete the normal 12 weeks course of the DDA should be considered as patients with decompensated liver fails to complete their course due to repeated hospitalization. Therefore, the patients with decompensated liver are found to have a lower SVR rate contrasted with less sick patients.

Despite the controversies, most physicians would presumably agree that patients with MELD scores of 20 or above are likely not a great contender for HCV treatment. Nevertheless, this issue largely varies among centers and geographical regions based upon physician’s understanding, the accessibility of HCV-positive organs, and the MELD score.

Nutritional support for cachectic patients awaiting liver transplant - Frailty and sarcopenia have shown to pose an increased risk of morbidity and mortality for the patient on the waiting list and after LT. Frailty is impartially evaluated through performance based, for example, grasp strength and gait speed, chair stands, and balance, though sarcopenia is formally evaluated by estimation of the psoas muscle zone on cross-sectional imaging or using whole-body bioelectrical impedance. There are more ongoing studies to characterize these patients and assess them for potential treatments more readily.

Malnourished and sarcopenic patients waiting for LT have longer ICU/hospital stay, higher incidence of infections and a lower 1-year survival.[9] Generally, 20%-60% of patients with cirrhosis develop malnutrition and sarcopenia.[9] Preoperative immunonutrition like omega-3 fatty acids, arginine and nucleotides fortified with oral nutritional supplements are recommended for the patients waiting for LT.[9] A meta-analysis investigating various peri-operative immunonutrition like glutamine or omega-3 fatty acids, arginine, and ribonucleic acids found significant reduction in infectious complications and improvement in liver function post LT; however, there was no significant difference in overall survival.[10] Likewise, Kaido et. al., reported fewer postoperative infectious complications after LT for patients who received preoperative oral

immunonutrition. Surprisingly, preoperative branched chain amino acid only showed better survival outcome for patients with sarcopenic on the waiting list; however, it failed to improve survival in non-sarcopenic patients.[11] In contrast, the randomized trial didn't find any significant benefits of perioperative immunonutrition in patients undergoing LT in terms of preoperative nutritional status or postoperative outcome compared to standard oral nutritional intervention.[12]

Together with recent understanding of sarcopenia, the issue of overweight and corpulence in cirrhotic patients warrants further investigation. Some advantages of physical activity are observed in cirrhotic patients and requires further studies.[9]

To conclude, liver glycogen is exhausted in patients with cirrhosis. Thus, it is prudent to minimize the interval without nutrient consumption to dodge gluconeogenesis from muscle protein in a previously protein depleted patients. The interest to characterize and treat frailty and sarcopenia in the patient waiting for LT is rapidly increasing. There is need for large, well-powered long-term observational studies of homogeneous groups of patients that can provide the ideal treatment for anticipation or reversal of frailty and sarcopenia.

Future perspectives- In general, LT is an exhilarating field of research. Current knowledge in the field is mostly based on retrospective, single-center studies, and we should aim to for larger, multi-center prospective studies. LT leaves a wealth of opportunities for doctors to learn not only about the liver, but also about immunology, pharmacology, oncology, psychology, infectious diseases, and cardiovascular diseases to name a few.

Conflict of Interest

Authors declare no competing interests.

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Author Contribution

Study Design: DKY, BXL, LT; Preparation of the manuscript: DKY, QZ; All authors reviewed and approved final draft.

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