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Comments 1:

- Title – Overstated is not backed up by the content of the article. Would suggest to edit or show results to back up this statement.

Reply 1: We totally agree with the reviewer that the title is in hyperbole. We were provided this title by the editors. The manuscript being a review article, with an intention to provide an overview of the donor/recipient selection protocols, we feel it may not be the right to showcase our results. We would be happy to change the title to something subtler. We suggest “Patient and Donor Selection in Living Donor Liver Transplantation”, however are happy with what the reviewers/editors feel would be a suitable one.

Changes in the text: We have edited the title. “Patient and Donor Selection in Living Donor Liver Transplantation” However, we would be happy for the editor/reviewer to change it as they deem suitable.

Comments 2:

- The author talks about doing ABO incompatible liver transplants with comparable outcomes to ABO identical liver transplant using optimized immunosuppression protocols. Would recommend commenting how often are ABO incompatible transplants are performed compared to ABO compatible ones and what the outcomes are in more detail.

Reply 2: Since the section was on donor selection criteria and algorithm, we did not delve deeper into ABOi LT. Further to the reviewer’s suggestion, we have now added details of the proportion of ABOi transplants with a note on their outcomes along with appropriate references.

Changes in the text:

“...With a better understanding of transplant immunology and these optimised immunosuppressive protocols, outcomes of ABOi LT are now comparable to ABO

identical LT (12,22–24). Currently, ABOi LT account for 5-20% of the total LDLTs performed. One of the largest meta-analysis comparing ABOi LT with ABO compatible (ABOc) LT of nine high-quality studies conducted between 2015 and 2018 included a total of 3,858 patients (ABOi = 639 and ABOc = 3,219) (25). Desensitisation process with rituximab was used in all the ABOi patients. Incidences of postoperative complications were comparable between both groups. However, ABOi LT had higher incidences of CMV infection, antibody mediated rejection (AMR), overall biliary complications, and biliary stricture than adult ABOc. Despite this and in contrast to earlier studies, there was no significant difference between the ABOi and ABOc LT groups in terms of 1-, 3-, and 5-year graft survival and overall survival (25–27)…”

Comments 3:

- Author comments on the relationship of the donor and recipient and mentions that altruistic donation is allowed in Canada. I think it would be important to mention that it is also allowed in the US and that there been a few reports on this.

Reply 3:

We thank the reviewer for this comment. Following further literature search, we have added details in the manuscript and the references as well.

Changes in the text:

“...Relationship: Most state authorities across the world stipulate that the prospective donor and recipient be related. There are however, certain countries like USA, Canada, the UK, Iran, Saudi Arabia, Israel, the Netherlands, Switzerland and Hong Kong which allow for anonymous altruistic donation (31–34). Any donor from outside the country is considered “unrelated” for this purpose, even if he/she happens to be a primarily “related” donor. If the donor and recipient are foreigners, a clearance has to be obtained from the relevant embassy regarding the genuine relationship between donor and recipient...”

Comment 4:

- The author discussed age as one selection criteria for liver donors and the

declining rate of hepatic regeneration with advancing age. Would recommend discussing the evidence behind this statement and defining better what is the definition of an elderly donor? In the authors acceptability criteria the donor age needs to be 50 or below. What is the evidence behind this age cut off. Our program regularly looks at donor over the age of 50, if they are overall healthy.

Reply 4:

We totally agree with the reviewer and are in concurrence with age being a relative number. At our unit as well, we often choose donors who are above 50 years of age, if their physiological status is suitable enough to safely withstand the donor operation. The fact that liver regeneration is adversely affected by age remains an undisputed fact. However, as literature evidence suggests, because numerous factors are at play, it difficult to put an exact numerical value on what age constitutes an elderly donor. Our program, given the ethnicity of our large percentage of donor, uses 50 years as an arbitrary marker for a closer evaluation of comorbidities. This however isn't a ceiling which we would think twice of breaching. We have highlighted the modified portions of the text to reflex the same.

Changes in the text:

"...The upper limit however varies, and is more dependent on their physiological age. Most LDLT units across the globe use an arbitrary cut-off number for age, this varies between centres from 50-65 years (36). Graft volumes must also be taken into consideration; it is preferable to avoid a low graft weight to recipient's body weight ratio (GRWR expressed as %) liver from an older donor. Despite reports of successful right lobe donations from septuagenarian live-donors, extreme caution must be exercised in the selecting elderly donors and cannot be recommended as a routine (37)."

Comment 4:

- Author states that the ideal BMI for donors should be below 25, is there any literature to back this up? BMI can be falsely elevated in very muscular donors. How does BMI correlate with amount of steatosis on imaging?

Reply 4:

We thank the reviewer for this insightful question. Large cohort studies have

unequivocally shown that an increased BMI is an independent risk factor for steatosis. There is a 7 times higher risk among obese individuals to have steatosis. We do concede that the correlation between BMI and steatosis is non-linear and there are numerous other factors which could falsely elevate a BMI. These factors would include among other factors ethnicity and as astutely stated by the reviewer, muscle mass. These would however be more an exception to the rule than the other way around. The other end of the spectrum is also true, especially in the south-asian population where in prospective donors with normal range BMI have unexpectedly shown fatty livers on their imaging, a subset of individuals, known to have 'lean NAFLD' or 'non-obese NAFLD'. We have rewritten the entire section to reflect our thought process, which we find echoes with that of the reviewer.

Changes in the text:

Weight and Body Mass Index(BMI):

“...Large cohort studies and meta-analyses have shown that compared with normal BMI, the risk of fatty liver increased approximately 4.1 to 14-fold in higher BMI individuals (37,38). Dose-response analyses also show that the risk increases in a nonlinear fashion (approximate J-shaped fashion) indicating higher BMI is an independent, dose-dependent risk factor for fatty liver (37,39)...”

“...As shown by several regional studies, Asians as compared to the western population have a higher percentage of body fat for a specified BMI (40–42). Therefore, a more stringent BMI cut-off of 27.5kg/m² is recommended for prospective donors of Asian ethnicity. A BMI of over 30 kg/m² is generally considered a relative contraindication for living donation. However, in certain situations donors with a higher BMI may be considered. One such example is when the BMI is falsely elevated in very muscular donor. Another example being where there are no other suitable donors, and the donor's BMI is between 30 and 35 kg/m²...”

“...It must nevertheless be kept in mind that BMI is not an infallible marker of steatosis. This is true especially in the south-Asian population where individuals within normal-range BMI have unexpectedly shown fatty livers on imaging. This subset, which is becoming increasingly prevalent, is diagnosed to have 'lean non-alcoholic fatty liver

disease (NAFLD)' or 'non-obese NAFLD', (43–45). These prospective donors are offered a diet/exercise regime, and re-evaluated with a follow-up imaging after 6 weeks to ascertain their suitability for donation...”

Comment 4:

- Donor cardiac evaluation includes an echocardiogram and a stress test. Is the recommendation to complete in every donor? What is the reasoning for this if a donor that is otherwise healthy without any preexisting comorbidities or risk factors? Any evidence to show that this reduces cardiac events in the donor?

Reply 4:

The recommendation is to have structural, electrical and functional assessment of the heart. As aptly pointed out by the reviewer, most centres in the west, when assessing an otherwise healthy, risk-factor free individual do an EKG and echocardiogram to assess a prospective donor's cardiac fitness. However, given the previously described high incidence of metabolic syndrome in the young population, centers especially in the Indian subcontinent including ours, also add a treadmill test as a routine. We have edited the text, and added references to reflect the difference in protocols across centres.

Changes in the text:

“All donors undergo an initial cardiac evaluation with an ECG, and echocardiogram. Subsequent tests include a treadmill test or Dobutamine Stress echocardiogram. Protocols across the globe differ slightly in this regard. Transplant centres in the west assess an otherwise healthy prospective donor's cardiac status based on an ECG and echocardiogram (59–61). Given the above described high prevalence metabolic syndrome in the younger population in the Indian sub-continent, centres including ours routinely add a treadmill test to cardiac evaluation (38,41,43–45). Conventional coronary angiograms and more recently CT-coronary angiograms are selectively performed in those prospective donors who have an abnormal result in either of the above tests.”