

Answering Reviewers

Reviewer 1# 02099384: Chela et al reviewed the outcome of the use of elderly donor graft in liver transplantation. I have some comments. 1. (Introduction) Is the definition of elderly aged>60 years? If yes, what is the background of cutting off line at 60 year of age? 2. (Impact of age on the liver) The authors described that the hepatic mass and blood flow decreased by age. To what degree? 3. (Functional change) The authors described that the rate of regeneration decreased by aging. To what degree? 4. (Outcome of using elderly grafts) Other reports than ref 11 should be included.

Reviewer 2# 00503243: This is a review facing the well known problem of transplanting liver from old donors. The authors treat extensively the changes of old livers and their evaluation. I have some concerns from the practical point of view. One relevant problem is the one of transmitting malignancies. I do not think that ultrasound examination is enough to avoid the risk. In our experience many times we found at autopsy small cancers in the liver, lung or prostate. This point should be treated more extensively to give useful informations. Additionally the references are poor and they should be enriched as the practice of transplanting liver also from very old people is performed currently by many centers.

Point-to-point answers to reviewers

Reviewer#1:

1) The definition of the elderly donor s was based on the data and articles that we reviewed. Our article is a review article and the papers that we evaluated used elderly donors being those above the age of 60 years. Authors like Zhao et al, Jiménez-Romero et al as well as Dasari et al used the age cut off of 60 years to classify elderly donors as those above the age of 60 and above. The rationale behind this was not provided in all the articles that we came across as why the exact age of 60 as opposed to for example 65. Though it is clear that as the age of the liver increases the concern for complications arises due to the changes that the liver undergoes, the reasoning for the exact number of '60 years' was not mentioned.

2) Hepatic mass and blood flow can decrease by roughly 30% from the ages of 30 to 100 years as cited by Jiménez-Romero *et al*. There is a steady and progressive decline with age at a rate of 0.3-1.5% was stated by the same article.

3) The degree to which the rate of regenerative declines would be dependent on the number of hepatocytes and hence the hepatic mass remaining. The articles that we evaluated did not mention actual figures to quantify this change.

4) Another report was also referenced for the outcome as well and this includes a study conducted at a center in Birmingham, UK. They did not find that the use of elderly livers led to overall inferior outcomes and hence their study also supported the use of elderly donors for transplantation. They noted that mortality rates were comparable in the liver recipients of the two groups (elderly vs. young livers). They even found that risks of arterial complications like hepatic artery thrombosis were fewer in the recipients of elderly donors though this was not significant on the statistical level. It did show that at least such complications are not higher in the elderly liver recipient group.

The studies conducted by Rodriguez *et al.* also supported this in their study of 100 elderly donors aged > 60 years. They emphasized that elderly donors can be used as long as a comprehensive risk assessment and evaluation is performed. Factors like cold ischemia time of less than 6 hours ideally as well as macrovesicular steatosis < 30 % were very important contributors to a favorable outcome when using the elderly donors in their study.

A study conducted by Thorsen *et al.* focused on liver from deceased donors aged > 75 years and though they noted an increased rate of biliary complications, they did not see overall worse outcomes with regards to mortality rates in recipients or graft survival.

Reviewer # 2:

We definitely agree that there would be a potential risk of transmission of malignancies. Ultrasound may not be sufficient alone and hence many times liver biopsies are performed of the liver donors to assess for not only the malignant changes as well as steatosis, hepatitis, cholestasis, fibrosis. Several authors like Jiménez-Romero *et al.*, Dasari *et al.* among many others support and encourage the use of liver biopsies to further assess the liver architecture and to detect malignancy. Other measures like exploration of the abdominal cavity and exploring for any obvious masses or suspicious lesions is also performed as described by like Jiménez-Romero *et al.* Donors themselves are also extensively evaluated and hence a thorough history and physical exam would be key as well. Imaging studies can also be targeted towards a particular region if there is concern for malignancy elsewhere in the body. Further evaluation using labs tests can also be performed or biopsies of another organ if there is concern of malignancy in that organ. So if there is suspicion for an underlying malignant process in the donor though the history, the examination or pre-operative labs or imaging then accordingly

steps can be taken to evaluate. However the fear of such transmission should not deter the use of elderly donors as every procedure is involved with the risk and we have to assess the risks and benefits prior to proceeding.