

## Answers to Reviewer comments

Reviewer 1/2:

1. First, hepatic injury secondary to cold organ storage or preservation is one of the major factors in graft survival after liver transplantation. I would like to see improving this manuscript in the aspect of organ preservation injury.

Thank you for this comment. We included a section into the manuscript about aspects of organ preservation injury.

2. Second, related to my first comment, IR injury of the liver is divided into two sections in liver transplantation; cold IR injury and warm IR injury. Most studies on the field focused on warm IR injury. This imbalance may be related to feasibility of warm IR models compared to cold ones. In addition, the current advancement of liver surgery is directly based on well-understanding of warm IR injury of the liver. However, differences between cold and warm IR injury of the liver should be mentioned in the manuscript.

Thank you for this comment. We included this fact in the manuscript (p. 5, second paragraph).

3. Third, in the “mechanisms of hepatic ischemia-reperfusion injury” part of manuscript, authors are described hepatic IR injury with this sentence “The hepatic ischemia-reperfusion injury is associated with an inflammatory response leading to liver tissue necrosis and release of reactive oxygen species (ROS), induction of adhesion molecules, cytokine secretion and activation of leukocytes”. Regarding to the current literature, necrosis has not been considered to the sole cell death mechanism in liver IR injury. Despite the efforts of authors regarding the description

of apoptotic cell death in liver IR injury in the following pages in manuscript, this sentence should be revised.

We revised the sentence and discarded the word “necrosis”.

4. Figures of the manuscript are very poor. Figure-1 is unelaborately prepared. I can't reach a perspective on the issue in the help of this figure. This should be revised.

We revised the figure as proposed.

5. The necessity of histopathological figure (figure-2) in this manuscript is bizarre. This figure is not including data regarding to “release of danger signals activating innate immune cells by TLR4, RAGE and TLR9 on Kupffer cells and neutrophils and CD4 Th1 effector T cells by the CD154-CD40 pathway”. If authors would like to enrich manuscript with histopathological figures, these figures should be included early and late period of warm and cold (preservation) liver injury, acute rejection or chronic rejection after liver transplantation and electron microscope images of Kupffer cells.

We included the histopathological figure from our previous research studies, but as you indicated the text and figures did not match together well.

Unfortunately, we do not have figures as suggested, so we deleted the figure from the manuscript.