

Response Letter

We would like to thank the editors and reviewers for their valuable comments to our submitted manuscript. We have carefully read each observation and suggestion and have answered each query as follows:

Reviewer #1

Specific comments to authors: Cervantes-Alvarez and co-others in this manuscript report on the value of liver transplantation is regardless of cirrhosis stage or acute-on-chronic liver failure grade. Congratulations upon completing such an important and complex study. The manuscript is properly written and of academic and clinical interest. The authors need to address some more points as follows. - The definition the authors adopted to classify patients into CC and DC needs a reference.

RESPONSE: We thank the reviewer for its appraisal of our manuscript. With regard to the definition used to define each cirrhosis group (CC, DC, and ACLF) within our cohort of transplanted patients, we used the same criteria as in a recent article we just published. This citation is now provided in the manuscript's methodology section (Cervantes-Alvarez et al. Liver International. 2022)

- Please mention if the patients had any other pre-transplant comorbidity (e.g. heart disease, DM, HTN, renal disease, ...) and their effect on the outcome.

RESPONSE: Table 1 includes now a comorbidities section with diabetes and hypertension being the most frequent ones. As mentioned in the results section, no statistical differences were observed between cirrhosis groups for frequencies of either type 2 diabetes mellitus or primary hypertension ($p=0.44$ and $p=0.06$, respectively). Therefore, an effect of comorbidities on posttransplant survival or mortality is unlikely.

- Did any of your patients experience recurrence of their original disease, especially patients with autoimmune conditions that may have a recurrence risk that can reach up to 30% of the cases? Thanks

RESPONSE: Thanks for this interesting question. Indeed, we are working on another manuscript precisely to evaluate the recurrence of autoimmune diseases in these patients, and preliminary we have observed that there is a 21% recurrence.

Reviewer #2

I read with great interest the article about the results of LT in ACLF patients. It is a very interesting argument. However some major concerns exist about aims, methodology, and results. In the title, I would specify that you only refer to HCC patients.

RESPONSE: We thank the reviewer for its interest in our manuscript. We apologize for this misunderstanding and respectfully, we would like to clarify that in this study we are not referring only to patients with HCC as the reviewer pointed out. The study was performed in all those patients receiving a liver transplant at our center during the period between

2015 and 2019 excluding certain patients as detailed in the methodology section and now in a flow chart we just included as per your suggestion. The main purpose was to report our transplant center's experience to assess the benefit of liver transplantation (LT) even in ACLF patients. Therefore, our population comprised patients stratified by disease severity ranging from compensated cirrhosis (CC), which are the only ones with HCC, Decompensated cirrhosis (DC) and acute on chronic liver failure (ACLF).

It is important to note that LT is reserved only for those with severe disease, usually with a MELD score greater than 15. Thus, our patients with compensated cirrhosis (CC) n=11, were patients with HCC who had no other treatment option than LT.

Therefore, for the reasons described, we believe the title of the manuscript does not have to refer to HCC.

In the abstract, as well as in the article, the aims are not clear. If you want to assess postoperative outcomes and short terms survival, you shouldn't mention long term survival. To compare the long-term survival of patients transplanted for HCC, tumoral characteristics are needed (tumor number, characteristics, pathologic results), and a multivariable analysis should be carried out to compare survivals (that maybe could explain the higher survival for stage 2 compared with 1 and 3). Thus the primary outcome must be stated univocally in the methods and treated consequently (in the results 1-yr and 6-ys OS can be presented after a multivariable analysis if you want to compare them), and you can deal with secondary outcomes properly within the abstract and the text.

RESPONSE: We understand that the previous misunderstanding about including only patients with HCC, might have led the reviewer to suggesting including the tumoral characteristics. We hope that with the explanation we provided in where only 11 patients that had compensated cirrhosis (CC) out of the 235 patients we included, had HCC, could explain why we did not include this information.

In regard to the aims of the article question from the reviewer, we would like to emphasize that the aim of our study was as we stated in our abstract *"To assess immediate posttransplant outcomes and compare the short (1 year) and long-term (6 years) posttransplant survival among cirrhotic patients stratified by disease severity"*.

We have now reintroduced the aims again in the last paragraph of the manuscript's introduction, before methodology for better clarity.

In the introduction, I would not say that the outcomes of LT for ACLF patients are debated, since all last report clearly its effectiveness. Another important problem linked to both results and organ shortage should be mentioned, that is a correct patients selection, in order to not waste organs for too advanced patients.

RESPONSE: The intention with the introduction of this manuscript was to show that there are discrepancies in the literature about transplantation in ACLF patients. Unfortunately, despite more and more articles showing the effectiveness, there is not as of now a uniform position on the benefit of this procedure. For example, a recent study by Agbim et al (Transplant Direct, 2020), disapprove transplanting ACLF patients. Since our study focuses on analyzing liver transplant benefit between the different cirrhosis severity groups, we did not elaborate in the manuscript's introduction on current problems linked to the difficulty of undergoing this procedure such as organ shortage and a still imperfect

system of organ allocation. We hope that our manuscript will contribute to the existing literature to generate a positive consensus about the transplant benefit in patients with ACLF.

About methodology, as already said, you should clearly state the primary and secondary outcomes, and correct the methodology for survival analysis, by adding tumor characteristics. A flow chart figure should be added to explain the enrollment of patients.

RESPONSE: As mentioned in the previous responses, we aimed at analyzing immediate posttransplant outcomes and compare the short (1 year) and long-term (6 years) posttransplant survival among cirrhotic patients stratified by disease severity". As per your suggestion we have included a flow chart, which illustrates the patients included and excluded in this study. We understand that the previous misunderstanding led to the reviewer's suggestion about adding tumor characteristics, which we hope we have clarified appropriately.

The title of second paragraph of the results should be shortened. The results paragraph should be shortened, since less important data are shown in the tables.

RESPONSE: A shorter title for the second paragraph of the manuscript's results is now given and information that can be visualized in the corresponding tables of this paragraph has been removed.

In the discussion you should try to underline the clinical importance of your study, and discuss it considering that LT is the ONLY effective treatment option for ACLF. You should also mention among the limitations the lacking of tumoral characteristics for long term survival analysis.

RESPONSE: Emphasis on the importance of LT as the only effective treatment option in ACLF was further made in the manuscript's discussion, emphasizing especially the importance of transplanting these patients which despite a more complicated posttransplant clinical course, had no survival differences when compared to patients with less advanced cirrhosis. Tumoral characteristics should not be a limitation in this study as we did not focus on analyzing HCC patients only.

Reviewer #3

1 Title. Title reflects the objective of the study 2 Abstract. Abstract is written very well and contains all the key data presented in the study 3 Key words. Key words reflect the focus of the study 4 Background. Introduction design is very good. Especially ACLF 2-3 patients are very controversial subject in liver transplantation. 5 Methods. The methods section is generally very good. Please add the transplant technique in brief. Information regarding immunosuppression is required (modifications during renal failure and infection should be stated)

RESPONSE: We thank the reviewer for its assessment and interest in our manuscript. We have now included a brief description of the transplant technique followed in the majority of our patients in the first part of the methodology section:

Liver transplants were carried out in their majority with classic technique. Briefly, recipient hepatectomy involved a bilateral subcostal incision with or without midline extension. Then dissection and clamping of the portal vein, hepatic artery, bile duct, superior and inferior vena cava were done. Implantation of the donor's liver was attained by anastomosing first the superior vena cava from the donor with that of the recipient, followed by the inferior vena cava, and portal vein, after which reperfusion of the donor liver was begun. Total reperfusion was then obtained by anastomosing the hepatic artery of the graft with the junction of the gastroduodenal artery and the common hepatic artery of the recipient. The procedure was completed after performing cholecystectomy and duct to duct anastomosis.

Information on immunosuppression was further detailed in this section also.

6 Results. The results are presented very well 7 Discussion. The organization of the discussion is very good, and the up-to-date references are used regarding the subject 8 Illustrations and tables. Tables are detailed but too much. Revision and reduction inn number may be considered 9 Biostatistics. The article meets the biostatistics requirements 10 Units. The manuscript uses SI units 11 References. The citations are appropriate 12 Quality of manuscript organization and presentation. Generally the quality and organization of the manuscript is very good. 13 Research methods and reporting. Strobe statement has been followed 14 Ethics statements. Ethics statement has been included. The authors should present the registration number of the ethics committee

RESPONSE: The registration number of this manuscript with the ethics committee of our institution is now provided (GAS-2368-17-20).