World Journal of Clinical Cases

Manuscript ID: 82275

Manuscript Title: Patients with hepatocellular carcinoma that die during the first year of liver transplantation have high blood sFasL concentrations prior to transplantation

Response to Editor comments:

Thank you very much for offering to reconsider a revised version of our manuscript. Thank you for your comments and those from reviewers which have helped us to improve our manuscript. The points that we have modified in the manuscript are written in red We enclosed the answer to editor and reviewers, and the new version of the manuscript.

Response to Reviewer 05391966 comments:

The novelty of this manuscript was new, and the results also support their conclusions, but some information should be revised before publication.
1. The detailed patients information included in this study should be supplied and discussed in the main text.

As was suggested by the reviewer, we have included the description of basic characteristics of patients as follows: "A total of 127 patients were included in the study, 113 (89.0%) of them remain alive at one year post-LT and 14 (11.0%) dead during the first year of LT. Their mean age was 51±17 years, 109 (85.8%) were males and 18 (14.2%) were females. Of them, 121 (95.3%) were inside Milan criteria previously to LT and 107 (84.3%) after LT, 87 (68.5%) had portal hypertension, 44 (34.6%) multinodular tumor, 41 (32.3%) infiltration, 7 (5.5%) macrovascular invasion, and 29 (22.8%) microvascular invasion."

In addition, we have included this paragraph in discussion section: "The 1-year survival rate from LT in our series (89%) is similar to those reported in other series (75%-95%) [24-28]. Several factors associated with worse prognosis in HCC patients undergoing LT have been reported (tumour size, outside Milan criteria, serum AFP levels, tumour number, hepatic microinvasion, degree of differentiation, vascular infiltration and invasion) [29]; however, only higher serum sFasL levels and age of the LT donor were factors associated with worse prognosis in our series."

2. The detailed statistical method should be included in each figure legend.

As was suggested by the reviewer, we have included the statistical method in each figure legend.

3. Some new references should be included in this manuscript

As was suggested by the reviewer, we have changed the 4 first references for more recent references:
1.Tümen, D.; Heumann, P.; Gülow, K.; Demirci, C.N.; Cosma, L.S.; Müller, M.; Kandulski, A. Pathogenesis and Current Treatment Strategies of Hepatocellular Carcinoma. *Biomedicines*. **2022**, 10, 3202.

2. Ince, V.; Sahin, T.T.; Akbulut, S.; Yilmaz, S. Liver transplantation for hepatocellular carcinoma: Historical evolution of transplantation criteria. *World J Clin Cases*. **2022**, 10, 10413-10427.
3. Bzeizi, K.I.; Abdullah, M.; Vidyasagar, K.; Alqahthani, S.A.; Broering, D. Hepatocellular Carcinoma Recurrence and Mortality Rate Post Liver Transplantation: Meta-Analysis and Systematic Review of Real-World Evidence. *Cancers (Basel).* **2022**, 14, 5114.
4. Vogel, A.; Meyer, T.; Sapisochin, G.; Salem, R.; Saborowski, A. Hepatocellular carcinoma. *Lancet*. 2022, 400, 1345-1362.

Response to Reviewer 06277476 comments:

Although this study is relatively new, it also has clinical value. However, there is a big problem in the description of the manuscript. It is suggested that the team carefully revise the manuscript and add more necessary content to increase the richness of the article.
1. Lack of description of basic characteristics of patients, such as age composition, sex ratio, overall survival, etc.

As was suggested by the reviewer, we have included the description of basic characteristics of patients as follows: "A total of 127 patients were included in the study, 113 (89.0%) of them remain alive at one year post-LT and 14 (11.0%) dead during the first year of LT. Their mean age was 51±17 years, 109 (85.8%) were males and 18 (14.2%) were females. Of them, 121 (95.3%) were inside Milan criteria previously to LT and 107 (84.3%) after LT, 87 (68.5%) had portal hypertension, 44 (34.6%) multinodular tumor, 41 (32.3%) infiltration, 7 (5.5%) macrovascular invasion, and 29 (22.8%) microvascular invasion."

2. Lack of inclusion criteria and exclusion criteria.

As was suggested by the reviewer, we have clarified those points as follows: "Inclusion criteria were the following: Patients undergoing donor LT in brain death at the Hospital Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife, Spain) from January 1996 to May 2017 by HCC. No exclusion criteria were considered."

3. The discussion part did not highlight the value of this study.

As was suggested by the reviewer, we have added the following paragraph in discussion section about this point: "We think that the findings from our study with patients undergoing HT due to HCC could encourage research to clarify the potential role of serum sFasL levels in estimating the prognosis of HT patients in a larger series.".

4. The variables recorded in this study recorded many indicators. Although most of them were not different from the 1-year survival and death of patients, were these indicators related to the serum sFasL level?

As was suggested by the reviewer, we have included the analysis about serum sFasL related to the different variables as follows: "We found an association between serum levels of sFasL and AFP (rho= 0.73; p <0.001). However, no statistically significant differences were found in

serum sFasL levels related to LT recipient age (p= 0.36), sex (p= 0.27), MELD score (p= 0.12), Child–Pugh score (p= 0.48), portal hypertension (p= 0.82), multinodular tumor (p= 0.16), microvascular invasion (p= 0.19), macrovascular invasion (p = 0.48), degree of tumor differentiation (p= 0.22), serun protein concentration (p= 0.67), serum albumin concentration (p= 0.07) and serum creatinine concentration (p= 0.96)."

In addition, we have included this paragraph in discussion section: "In addition, we also found a positive association between serum levels of sFasL and AFP, and that association is according to the findings of one previous study [30]; however, we did not found an association between serum sFasL levels and other variables."

Thus, we have included a new reference number 30: Song, le H.; Binh, V.Q.; Duy, D.N.; Bock, T.C.; Kremsner, P.G.; Luty, A.J.; Mavoungou, E. Variations in the serum concentrations of soluble Fas and soluble Fas ligand in Vietnamese patients infected with hepatitis B virus. *J Med Virol*. 2004, 73, 244-249.

5. In this study, only 13 patients died in one year, and there may be deviation in survival analysis. So I think we can increase the analysis between survival and death.

As was suggested by the reviewer, we have included the relatively low sample size of our study to include more variables in the regression model as another limitation. In addition, we have added the following paragraph in discussion section about this point: "We think that the findings from our study with patients undergoing HT due to HCC could encourage research to clarify the potential role of serum sFasL levels in estimating the prognosis of HT patients in a larger series.".