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Title: DNA and RNA oxidative damage in patients with hepatocellular carcinoma and mortality during the first year of liver transplantation

Response to Editor:

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. We enclosed the answer to editors and reviewers, and the new version of the manuscript. The points that we have added according to the suggestion of reviewers are written in red in the new manuscript.

Response to Reviewer 06107956:

First, I think this is a new approach to find out the prognostic factors for mortality in the first year after liver transplantation. Therefore, the new findings of their study could motivate the research to clarify the potential role of oxidative damage in the prognosis of LT patients due to HCC and to explore the use of antioxidants agents to reduce oxidative stress in those patients. However, I have some comments and questions for this manuscript. 1.Q1 Greater DNA oxidative damage (assessed by concentration of 8-OHdG in liver biopsy samples) has been found in patients with chronic hepatic disease with HCC than without it public on 2001 and 2008. The patient had received LT for a long time (20 years ago). So, at the beginning, did the author ask a research question on this issue about DNA and RNA oxidative damage (serum OGS levels)??

As was suggested by the reviewer, we have clarified in method section that the study was retrospective, that we had serum samples obtained before LT and frozen at -80ºC, and that serum concentrations of 8-OhdG were determined in those samples.

2. Q2 In an article published by the author in 2019 about the relationship of caspase-3 with 1-year survival prognosis (stage 1996 - 2017, 139 patients - 16 died, 123 lived) - In this article, the author mentions OGS serumm, 114 patients (2001 - 2017), 13 deaths, 101 rivers. - So the question arises: do these patients overlap? Why not include caspase-3 in multivariate analysis??

As was suggested by the reviewer, we have clarified in method section that we had previously determined serum caspase-3 levels in some of these patients [26].

We did not include caspase-3 in the first version of the manuscript because it is a biomarker of apoptosis and OGS is a biomarker of oxidation and we wanted to reflect two different aspects that are associated with mortality. However, also as was suggested by the reviewer, we have

included caspase-3 in multivariate analysis in the new version of the manuscript. And both biomarkers are associated with mortality.

3. Q3 Most of the documents are not up to date related to the topic of the research author. There can be 2 reasons: 1. This is a very new topic 2. Researched and it doesn't really make sense in clinical practice The author needs to explain this issue?

As was suggested by the reviewer, we have added the following paragraph in discussion section: "Serum OGS levels have scarcely studied and its association with mortality has recently been found by our team in patients with sepsis [17], brain infarction [18], traumatic brain injury [19] and spontaneous intracerebral hemorrhage [20]."

Response to Reviewer 05095017:

This is a manuscript about DNA and RNA oxidative damage in patients with hepatocellular carcinoma and the authors showed that mortality during the first year of liver transplantation is associated with serum 8-OHdG concentration prior to LT. Overall, this story is interesting, however, there are some concerns that need to be addressed and I cannot recommend it for publication in the present form.
1) Although 8-OH-dG is a commonly used marker for oxidative DNA and RNA damage, there are several other markers that represent oxidative stress for nucleic acid, such as AP sites and 8-nitro-cGMP. Were they tested?

As was suggested by the reviewer, we have added this point as other limitation of our study.

2) Did serum 8-OH-dG correlate with the oxidative stress in the liver or HCC tissue?

As was suggested by the reviewer, we have added this point as other limitation of our study.

3) How was the level of serum 8-OH-dG in healthy control or chronic liver patients without HCC?

As was suggested by the reviewer, we have added this point as other limitation of our study.

4) Does serum 8-OH-dG change after LT? Which is better serum marker for prognosis, before or after LT?

As was suggested by the reviewer, we have added this point as other limitation of our study.

5) What was the cause of death after LT ? Graft rejection, HCC recurrence or others? Were there any differences among them in terms of serum 8-OH-dG?

As was suggested by the reviewer, we have added the following information in results section: "Significant differences were no found (p=0.20) in serum OGS concentrations according the cause of death (8 (61.5%) sepsis, 3 (23.1%) multiple organ failure, 1 (7.7%) HCC recurrence, and 1 (7.7%) recurrence of hepatitis C virus infection)."