

February 21, 2019

Manuscript: 45973

Manuscript Title: SYSTEMATIC REVIEW: RENIN-ANGIOTENSIN SYSTEM INHIBITORS IN CHEMOPREVENTION OF HEPATOCELLULAR CARCINOMA

Dear Editor,

Enclosed please find our manuscript, revised according to your suggestions and to the criticisms raised by the reviewers, together with a point-to-point comment on the criticisms and the changes made in the paper.

General comments

As suggested, the English has been carefully revised. In addition, we added some comments in the "Results" and "Discussion" sections.

Specific changes

Answer to the Reviewer (code 03537407)

1. At first we want to thank the reviewer for his/her suggestions on the need of a more detailed discussion regarding clinical data. To achieve this goal we added some comments in the Results (page 8, lines 13-14 and 17-19). Moreover, we completed our discussion adding some specific comments on the single clinical studies (page 18, lines 8-11 and 19-24; page 19, lines 1-14 and 19-22; page 20, lines 1-2).
2. As suggested, a possible prospective study design was added to the end of the discussion with two new references (55 and 56) (page 21, lines 13-19), to give a better explanation on data currently missing.
3. We did not perform meta-analysis of the human studies for two reasons:
  - a. prospective studies such as randomized clinical trials cannot be analyzed together with retrospective studies; in addition, since all three randomized clinical trials already demonstrated a protective effect of RAAS a meta-analysis would have not added any further information;
  - b. the six retrospective studies were heterogeneous [1 cohort study (ref. 16), 2 nested case-control studies (ref. 17,18), and 3 case-control studies (ref. 19-21)], and therefore they could not be analyzed all together; in addition, among the 3 case-control studies which could have been examined all together, one of them (ref. 19) did not report sufficient data to perform a meta-analysis.