Reviewer’s report

Title: Elevated plasma copeptin levels identify the presence and severity of non-alcoholic fatty liver disease in obesity.

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Reviewer: Stephan Bakker

Reviewer's report:

The study by Barchetta entitled "Elevated plasma copeptin levels identify the presence and severity of non-alcoholic fatty liver disease in obesity" has been reviewed. The study investigates the correlation of copeptin with non-alcoholic fatty liver disease in obesity.

Overall, the study design is well described and structured. The manuscript is well written and easy to understand.

1. My first concern is that the authors support their conclusions based on statistical analysis that may not be the appropriate to approach such complex disease. T-tests and correlation tests could not be enough robust to assess an clinically relevant association between copeptin and NAFLD.

1.1 As it is showed in table 1b there is a significant difference of copeptin concentrations between NAFLD and NAFLD, but it seems that there is also a big difference in terms of percentage of metabolic syndrome. Given the importance of this component I would recommend the authors to perform a separated analyses in both groups with and without metabolic syndrome.

1.2 Table 3 shows a comparison of clinical characteristics of participants belonging to quartile 1 versus quartile 4 of plasma copeptin concentration. The 4 quartile exhibited a greater percentage of participants with NAFLD (42% vs 15%); nonetheless the authors fail to show if this difference is not due to a sex difference. Given the importance of this component I would urge the authors to perform an analysis in sex-stratified quartiles.
1.3 Moreover, it also calls the attention the results showed in table 4, where the association of Metabolic syndrome (B 3.46 and 95% C.I. O.R. 1.11 - 909.1) seems more significant than copeptin (B 0.5 and 95% C.I. O.R. 1.02-2.93). Once again, given the importance of this comportment I would recommend the authors to perform the same association test using several models with the related variables (perhaps in an additive fashion considering the sample limitations). I would also suggest the authors to present the results as standardized betas coefficients.

2. Even though the correlation described in this manuscript is novel, I would recommend the authors to give mention to previous studies that have explored the association of copeptin with advanced liver disease and contextualize such findings with their own results. i.e. Plasma copeptin as biomarker of disease progression and prognosis in cirrhosis. J Hepatol. 2016;65:914-20.; Copeptin as an indicator of hemodynamic derangement and prognosis in liver cirrhosis. PLoS One. 2015;10:e0138264.; Plasma copeptin, a possible prognostic marker in cirrhosis. Liver Int. 2013;33:843-51.

3. Previous works have studied the association of copeptin with certain scores of liver disease such as the Child-Pugh score. Therefore, I highly recommend the authors to conduct and extra analysis and evaluate the association of copeptin with a NAFLD score such as the one described by Angulo 2007 (Hepatology. 2007 Apr;45(4):846-54.)

4. My last recommendation to the authors is to properly replace the term gender for sex, as I suspect it is the case.

So, overall I am positive about this study, but I would urge the authors to accommodate the recommended changes.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
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Yes
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