

December 18, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13640-edited.doc).



Title: Composite prognostic models across the NAFLD spectrum: clinical application in developing countries

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13640

The manuscript has been improved according to the suggestions of reviewers:

Commentary provided by Reviewer #1

1. "The revision is presented, structured, clear and updated. Congratulations to the authors"

Reviewer #1 is thanked for the positive feedback concerning the presentation, structure, clarity and novelty of the review.

Commentary provided by Reviewer #2

Major queries:

1. "Elastography and fibroscan are useful tools to define liver fibrosis...roles in case of NAFLD/NASH should be reported and discussed"

As noted in the abstract, the primary aim of this review article was to provide an overview of existing non-invasive composite prognostic models used to 1) confirm the presence of undiagnosed hepatosteatosis, 2) distinguish between simple steatosis and NASH, as well as 3) predict advanced hepatic fibrosis from the perspective of a resource-limited healthcare setting, with particular emphasis on the relationship between histological severity and cardio-metabolic risk. It is noted in the text that "Imaging modalities such as ultrasonography (US) further have limited sensitivity in moderate steatosis, while the application of more complex technologies in resource-limited environments is restricted by their expense". In the revised version of the manuscript, the incorporation of transient elastography (TE) to existing composite prognostic models as a possible means of improving their performance and predictive accuracy is discussed.

2. "NAFLD/NASH is present very often in patients presenting metabolic syndrome. In this case the only effective treatment consists in reduction of BMI and increase of physical activity with the aim to reduce cardiovascular risk, independently from NASH/NAFLD, whose presence, at the end, becomes less important: this point is to be addressed and discussed. - In case of NASH/NAFLD without metabolic syndrome no effective treatment does exist."

Reviewer #2 is thanked for helpful input concerning this matter. In the original version of the manuscript, it is noted that even uncomplicated hepatosteatosi poses independent risk for new-onset cardiovascular disease, endothelial and diastolic dysfunction, subclinical atherosclerosis and cardiovascular mortality, considered in relation to the positive association between cumulative cardio-metabolic risk and histological severity, diagnostic confirmation of NAFLD/NASH could play an important role in determining the need for more sustained and aggressive lifestyle-based intervention. As reiterated by Reviewer #2, there is however still insufficient evidence to justify the routine use of any specific tailored therapeutic interventions such as thiazelidinedione pharmacotherapy in NAFLD/NASH. In the revised version of the manuscript, greater emphasis is placed on the benefits of a multidisciplinary lifestyle-based approach incorporating a low-calorie diet and moderate physical exercise aimed at decreasing body weight by ~10% with the goal of improving metabolic and histological abnormalities in patients with NAFLD while concurrently decreasing cumulative cardiovascular risk.

3. "At the light of that the attempt to ascertain the presence or not of NAFLD/NASH in a population based screening probably is not cost-effective: this point has to be addressed and discussed."

In the revised version of the manuscript, it is stated: "Whether routine screening for hepatic steatosis in high-risk asymptomatic patients is practical or cost-effective remains subject to debate, as the vast majority are likely to present with uncomplicated and non-progressive disease."

The following aspects were also addressed in the abstract, core tip as well as conclusions and future prospects sections of the revised version of the manuscript:

1. The role of inflammatory biomarkers and iron parameters in the diagnosis of NASH and the dysmetabolic iron overload syndrome (DIOS) as a common comorbidity in patients with the metabolic syndrome and/or NAFLD is elaborated on and discussed.
2. In view of the limitations which continue to impede the more widespread clinical adoption of composite prognostic models in general medical practice, the incorporation of functional genomic markers as a means of improving the diagnostic accuracy and/or predictive performance with the goal of addressing these concerns is discussed.

In addition, formatting of the title page as well as references as requested was also addressed, and the conflict of interest statement is included in the revised version of the manuscript.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in dark ink, appearing to be 'Hilmar Klaus Luckhoff', with a long horizontal stroke extending to the right.

Hilmar Klaus LUCKHOFF, MBChB, HonsBSc

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