Peer Review File

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Reviewer A

The work 'Development of a simple nonalcoholic fatty liver disease scoring system indicative of metabolic risks and insulin resistance' developed a simplified NAFLD score applicable to general population and health examination datasets, compared with preexisting scoring systems for estimation of NAFLD, and testified its impact on the estimation of metabolic syndrome, metabolic risk factors, obesity, and the homeostatic model assessment for insulin resistance (HOMA-IR). A wide cohort was used and numerous parameters were evaluated. The K-NAFLD score showed a significant estimative impact on metabolic syndrome, metabolic risk factors, obesity, and insulin resistance. The manuscript can be recommend for publication. Some minor remarks are below.

Comment 1: Introduction. It could be helpful to describe potential links between NAFLD and the metabolic syndrome, obesity and insulin resistance.

Reply 1: We appreciate for the helpful comment. NAFLD has been regarded as the liver manifestation of the metabolic syndrome by some researchers considering its close associations with obesity, insulin resistance, hypertension, and dyslipidemia. NASH was present in more than 60% of patients with obesity undergoing gastric bypass surgery as found by histological examination, and suggested that insulin resistance is highly predictive of NASH. In addition, it was noticed that NASH also enhances insulin resistance leading to a vicious cycle, supporting close associations between NAFLD, metabolic syndrome, obesity, and insulin resistance. We have added above contents in the Introduction section as advised.

Changes in the text:

[Page 5, line 11] NAFLD has been regarded as the liver manifestation of the metabolic syndrome by some researchers considering its close associations with obesity, insulin resistance, hypertension, and dyslipidemia. [7] Boza et al. [8] showed that NASH is present in more than 60% of patients with obesity undergoing gastric bypass surgery as found by histological examination, and suggested that insulin resistance is highly predictive of NASH. In addition, it was noticed that NASH also enhances insulin resistance leading to a vicious cycle, supporting close associations between NAFLD, metabolic syndrome, obesity, and insulin resistance. [9]

[Reference] 3 references are added.

7. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: Executive Summary. *Crit Pathw Cardiol*. 2005;4(4):198-203.
8. Boza C, Riquelme A, Ibañez L, et al. Predictors of nonalcoholic steatohepatitis (NASH) in obese patients undergoing gastric bypass. *Obes Surg*. 2005;15(8):1148-1153.
9. Dietrich P, Hellerbrand C. Non-alcoholic fatty liver disease, obesity and the metabolic syndrome. *Best Pract Res Clin Gastroenterol*. 2014;28(4):637-653.

Comment 2: Univariate analysis. Could you explain the lack of correlation with the glycosylated hemoglobin type A1C?

Reply 2: Thank you very much for the comment. Unlike other covariates, such as fasting serum glucose, we found no significant association of hemoglobin type A1C with NAFLD. From our point of view, it may be related to the study concept that the severity of NAFLD is not considered but only presence of NAFLD was considered. In a recent study (Cai et al. Correlation between serum 25-OH vitamin D expression and non-alcoholic fatty liver disease. Exp Ther Med 2020;19(3):1681-1686.) that compared HbA1c levels between control, mild NAFLD, moderate NAFLD, and severe NAFLD groups (mild, moderate, and severe NAFLD were defined by liver/spleen ratio in their study), HbA1c levels were similar between control and mild NAFLD groups (5.21 vs. 5.27; P value not significant), but moderate (7.45) and severe (8.64) NAFLD groups demonstrated higher HbA1c levels compared to the control

group. Therefore, HbA1c level may be associated with severity of NAFLD but no significant association was found in our study between HbA1c and the presence of NAFLD, potentially neutralized by light NAFLD (mild NAFLD). However, we do think that HbA1c may be highly important when consider the severity of NAFLD or progression of NAFLD to advanced liver diseases, which awaits future studies to confirm.

Changes in the text:

[Page 14, line 19] Furthermore, glycosylated hemoglobin type A1C was found not to be significantly associated with the presence of NAFLD. A previous study from China has reported that glycosylated hemoglobin level is not significantly different between healthy and mild NAFLD groups, but it significantly increased in moderate and severe NAFLD groups, suggesting that the glycosylated hemoglobin is still important in terms of NAFLD and needs to be considered especially when evaluating the severity of NAFLD. [27]

[Reference] 1 reference is added.

27. Cai J, Zhang Z, Liu J, et al. Correlation between serum 25-OH vitamin D expression and non-alcoholic fatty liver disease. *Exp Ther Med*. 2020;19(3):1681-1686.

Comment 3: Was the severity of the disease or NASH considered in the data set further evaluation?

Reply 3: Thank you for the comment. The derived score represents probability of NAFLD that higher score does not represent more severe NAFLD but higher probability of NAFLD. The severity of NAFLD or NASH was not considered in the Korean National Health and Nutrition Examination Survey dataset. We also wanted to further evaluate factors associated with the severity of NAFLD but it could not be performed due to data availability. However, we believe that operational definition on the severity of NAFLD may potentially be possible after defining NAFLD in the dataset, which we would like to proceed in the future.

Comment 4: The authors hypothesize that the higher risk of NAFLD in female can be related to lifestyle disparities, extend or fat consumption or body fat distribution. However, physiological factors could

also be involved. Is the prevalence and severity of NAFLD comparable in women during the reproductive age and/or post menopause compared to males?

Reply 4: We deeply appreciate for the important comment, and we agree with the reviewer that the prevalence of NAFLD may be associated with reproductive age and/or menopause in women. We had calculated the prevalence of NAFLD and found that it was comparable between women non-reproductive age (≥50 years) and men, but women during reproductive age (<50 years) had low prevalence of NAFLD (7.4%), as defined by the NAFLD liver fat score. Therefore, meaning of sex in multivariate adjustments in the derivation of the K-NAFLD score is likely to be reflected by women with non-reproductive age along with covariate interaction within the model.

Changes in the text:

[Page 15, Line 13] However, the prevalence of NAFLD was dependent to the reproductive age among women that those within the reproductive age showed a low prevalence of NAFLD, thus interaction between sex and other covariates needs to be considered when interpreting structure of the derived model.

Reviewer B

Comment 1: This is a study wherein the authors have derived a score that predicts NAFLD using routine laboratory and clinical parameters in a large population database. An important prerequisite in such a study is derivation of a score using parameters against an established method of diagnosis e.g. establishing a diagnosis of NAFLD in the population using standard diagnostic tests like Ultrasonography of the liver, Magnetic resonance proton density fat fraction in liver, Fibroscan with controlled attenuation parameter or liver biopsy and then to do a regression analysis of various parameters for derivation of a score. Such a methodology is not evident in this manuscript. We would like the authors to clarify as to which diagnostic test was used as a standard in this study against which the score was derived.

Reply 1: We deeply appreciate for the comments. We derived a score from the NAFLD liver fat score that was developed using proton magnetic resonance spectroscopy. According to the nature of the Korean National Health and Nutrition Examination Survey (KNHANES) dataset that does not involve results of a standard diagnostic test, we could only use a previously derived and validated NAFLD liver fat score conducted using proton magnetic resonance spectroscopy, which is a major limitation of our study. In the revised manuscript, we have now added a standard procedure that was used against which the score was derived, and the major limitation of our study is emphasized as follows:

Changes in the text:

[Page 4, Line 20] Future studies that compare the derived score with standard diagnostic tests-validated data, such as ultrasonography of the liver, are needed.

[Page 7, Line 4] Due to unavailability of a diagnostic test results within the dataset, the NAFLD liver fat score, which is derived and validated using proton magnetic resonance spectroscopy, was used to operationally define NAFLD for the analyses. [13]

[Page 17, Line 4] Future studies comparing the derived score with a standard diagnostic test-proven data, such as ultrasonography of the liver, magnetic resonance proton density fat fraction in the liver, Fibroscan with controlled attenuation parameter, and liver biopsy, are necessary for the derived score to be implemented.

Comment 2: The score derived has most of the components of metabolic syndrome in its formula-waist circumference, systolic blood pressure, fasting serum glucose and triglycerides. Hence it is obviously expected to be estimative of metabolic syndrome. The authors have derived a score which they have labelled K-NAFLD score however this is not acceptable in the absence of any comparison with existing modalities to diagnose NAFLD. The article hence cannot be accepted for publication.

Reply 2: Thank you very much for the comment. The components of metabolic syndrome were involved as covariate hence it was expected to be estimative of metabolic syndrome when we developed the score. NAFLD has been regarded as the liver manifestation of the metabolic syndrome considering its close associations with obesity, insulin resistance, hypertension, and dyslipidemia. [Grundy et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: Executive Summary. *Crit Pathw Cardiol*. 2005;4(4):198-203.] Therefore, involving the components of metabolic syndrome was indispensable in derivation of our model. In addition, we agree with the reviewer that the absence of comparison with existing modalities to diagnose NAFLD is a major limitation of our study. The present study used the Korean National Health and Nutrition Examination Survey (KNHANES) dataset and results of existing modalities to diagnose NAFLD is not involved in the dataset. Future studies comparing the derived score with existing modalities is definitely required to use in diagnosis of NAFLD. In the revised manuscript, we have emphasized this limitation and suggested future studies to compare the derived score with existing modalities to diagnose NAFLD in the Abstract and Discussion section.

Changes in the text:

[Page 4, Line 20] Future studies that compare the derived score with standard diagnostic tests-validated data, such as ultrasonography of the liver, are needed.

[Page 5, Line 11] NAFLD has been regarded as the liver manifestation of the metabolic syndrome by some researchers considering its close associations with obesity, insulin resistance, hypertension, and dyslipidemia. [7]

[Page 17, Line 4] Future studies comparing the derived score with a standard diagnostic test-proven data, such as ultrasonography of the liver, magnetic resonance proton density fat fraction in the liver, Fibroscan with controlled attenuation parameter, and liver biopsy, are necessary for the derived score to be implemented.

[Reference] 1 reference is added.

7. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: Executive Summary. *Crit Pathw Cardiol*. 2005;4(4):198-203.

Reviewer C

Comment 1: I read with great interest the article by Jeong et al, "Development of a simple nonalcoholic fatty liver disease scoring system indicative of metabolic risks and insulin resistance". This article is an interesting concept that has some clinical impact by excluding the fasting insulin level The article develops a scoring system that is of near equal efficacy to the NAFLD liver fat score. While the liver fat score is not perfect with 0.87 and 0.86 area under curve (AUC) values respectively it is a validate tool.

Reply 1: Thank you very much for the comments. We deeply appreciate it.

Comment 2: What i find interesting in this paper is the low BMI in the group. There is no scoring system at this point for patients with "lean NAFLD". Could this score be of help in lower BMI patients to identify higher risk patients?

Reply 2: We appreciate the comment. According to our data, the derived score was not only applicable for those with obesity (BMI≥25 kg/m^2; OR, 2.681; 95% CI, 2.374-3.027; P<0.001) but also applicable for those without obesity (BMI<25 kg/m^2; OR, 2.712; 95% CI, 2.445-3.008; P<0.001). If our score gets validation by future studies comparing the derived score with standard diagnostic modalities in diagnosis of NAFLD, we do believe that it would be of help in lower BMI patients to identify higher risk patients.

Changes in the text:

[Page 12, Line 13] Furthermore, the derived score was estimative of NAFLD in both BMI<25 kg/m^2 (OR, 2.712; 95% CI, 2.445-3.008; P<0.001) and BMI≥25 kg/m^2 (OR, 2.681; 95% CI, 2.374-3.027; P<0.001) subgroups (Supplementary Table 3).

[Supplementary Table 3]

Supplementary Table 3. Subgroup analysis on association of the K-NAFLD score with the NAFLD liver fat score-defined NAFLD

	Percent concordant	Percent discordant	OR (95% CI)	P value

Body mass index<25 kg/m^2	91.9	8.1	2.712 (2.445-3.008)	<0.001
Body mass index≥25 kg/m^2	89.1	10.9	2.681 (2.374-3.027)	<0.001

OR calculated using the logistic regression. Acronyms: K-NAFLD, Korea National Health and Nutrition Examination Survey-derived non-alcoholic fatty liver disease; OR, odd ratio; CI, confidence interval.

Comment 3: Is this score applicable to a western population? While the score is validated again existing tools I think external validation against either a smaller cohort of imaging/biopsy proven NAFLD would strengthen the paper.

Reply 3: We thank the reviewer for important concerns. From our point of view, whether this score is applicable to a western population requires future studies validating the score by standard modalities-diagnosed NAFLD patients or comparing the score with standard modalities to diagnose NAFLD. Therefore, we stated that external validation is necessary for the K-NAFLD score to be applied in other countries at the end of the second paragraph in the Discussion section. We also agree with the reviewer that external validation against imaging/biopsy proven NAFLD would strengthen the paper, which is a major limitation of our study. The present study used the Korean National Health and Nutrition Examination Survey (KNHANES) dataset and results of existing modalities to diagnose NAFLD is not involved in the dataset. Future studies comparing the derived score with existing modalities is necessary. In addition, we are also planning to externally validate the derived score in near future.

In the revised manuscript, we have emphasized this limitation and suggested future studies to compare the derived score with existing modalities to diagnose NAFLD as follows:

Changes in the text:

[Page 4, Line 20] Future studies that compare the derived score with standard diagnostic tests-validated data, such as ultrasonography of the liver, are needed.

[Page 17, Line 4] Future studies comparing the derived score with a standard diagnostic test-proven data, such as ultrasonography of the liver, magnetic resonance proton density fat fraction in the liver, Fibroscan with controlled attenuation parameter, and liver biopsy, are necessary for the derived score to be implemented.

Editorial Comments

Please follow the attached "Submission Checklist for Authors" and revise your paper if needed. Here are some additional points:

Comment 1: The article should follow STROBE Checklist for reporting standards. We attached an article explaining the reason of such a reporting guideline. We also attached a template for your reference.

Reply 1: Thank you very much for the comment. We have followed the STROBE checklist and provided the STROBE Checklist.

Comment 2: "Data Sharing Statement" is a statement made by authors to confirm their willingness of sharing raw data/patient information related to the article with others. We attached a template for your reference.

Reply 2: We appreciate the comment. We do not own the dataset, but it can be accessed at http://knhanes.cdc.go.kr. "Data Sharing Statement" file is now provided.

Comment 3: We are using the checklist to double-check your manuscript, place "Y" on blank space if you confirm your manuscript has followed the requirement. Place "N/A" if not applicable. If further explanation is needed on a certain item, you can copy the Item and write explanations down below.

Reply 3: We appreciate for the concern. We have checked and confirmed that our manuscript has followed the requirement. "Submission Checklist" file is now provided.