JOURNAL
OF HEPATOLOGY

[2]Division of Gastroenterology and Hepatology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02115, USA

*Corresponding author. Address: Division of Gastroenterology and Hepatology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02115, USA.
E-mail address: zgjiang@bidmc.harvard.edu (Z.G. Jiang)

Reply to: "A good step toward low-cost prognostication of liver-related outcome awaits more validation"

To the Editor:

We are sincerely grateful to Drs. Song and Jiang for externally validating the Chronic Liver Disease (CLivD) risk score in a representative US general population cohort (NHANES III).[1] As shown by their survival curves, the CLivD score performed well in risk stratifying the US population with regard to liver mortality. The lower absolute risk estimates in their validation study compared to our original study are expected since the US data only included liver mortality, not hospitalization or incident liver cancer outcomes. A few points raised by the authors deserve clarification.

The relatively low performance of the CLivD score in African Americans makes sense for a couple of reasons. First, among African Americans, cirrhosis is more often driven by viral hepatitis[2] which is highly relevant since the NHANES III cohort was conducted in 1988-1994, before the advent of current effective antiviral drugs. Viral hepatitis was an exclusion criterion in the original CLivD publication.

Secondly, it has been previously reported that Africans are protected from non-alcoholic fatty liver disease relative to the degree of their metabolic disturbance, which might be attributed to genetic disparity.[3] For example, Africans have a low prevalence of the *PNPLA3* I148M polymorphism. This calls for recalibration of CLivD components, especially the waist-hip ratio (WHR), in different ethnic groups, similar to what has been done with risk prediction scores for cardiovascular diseases.

Regarding the choice of WHR over BMI in the CLivD score, evidence is now accumulating that WHR better reflects metabolic unhealthy obesity than BMI (Fig. 1).[4] Hip circumference mirrors lower-body subcutaneous fat mass, which is metabolically beneficial and counteracts harm from abdominal/visceral obesity.[4] Hip circumference has been shown to modify the association between waist circumference and liver disease, and this seems to be largely captured in the WHR.[5] WHR was the superior anthropometric predictor of liver-related outcomes both in our CLivD study and in a previous study,[6] where it was further shown that BMI provided no added prognostic value.[6]

Although WHR may be less accessible than BMI in many study cohorts and current clinical practice, valid (self-)measurement of WHR requires only a simple measuring tape. Moreover, novel digital video/photography-based mobile applications[7] could contribute to making WHR even more accessible. The lack of requirement for absolute circumference measures makes such digital applications potentially even more feasible.

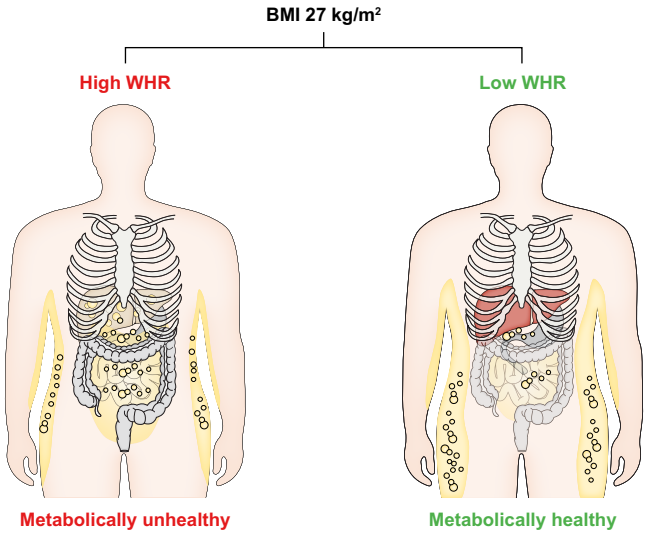

Fig. 1. The WHR reflects the distribution of metabolically harmful visceral fat in the abdominal compartment to metabolically beneficial subcutaneous fat in the gluteofemoral region. Epidemiological evidence points to the critical value of the WHR in predicting incident severe liver disease, regardless of the BMI. WHR, waist-to-hip ratio. (This figure appears in color on the web.)

Regarding the choice of GGT over ALT or AST in the CLivD score, our analyses in the derivation cohort corroborated previous findings that GGT is a more powerful predictor of liver-related outcomes in the population than ALT or AST.[8,9] As a well-established and inexpensive biomarker of future disease risk, GGT should keep its place in routine primary care[8] and in the CLivD score. We agree that more validation studies in different populations with different baseline risks of liver diseases are needed, as well as studies on the use of the CLivD score as a first-line step to identify a high-risk population warranting further screening for liver fibrosis.

Received 23 May 2022; accepted 31 May 2022; available online 9 June 2022
https://doi.org/10.1016/j.jhep.2022.05.034

Financial support

Dr. Åberg was supported by the Mary and Georg Ehrnrooth Foundation, Medicinska Understödsföreningen Liv och Hälsa, Finska Läkaresällskapet, Academy of Finland (#338544), and Sigrid Jusélius Foundation. Dr. Luukkonen was supported by the

Novo Nordisk, Sigrid Jusélius, and Instrumentarium Science Foundations.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the content of this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Fredrik Åberg: conceptualization, writing - original draft, visualization, project administration; Panu Luukkonen: conceptualization, writing - review & editing, visualization; Martti Färkkilä: conceptualization, writing - review & editing, supervision.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.05.034.

References

[1] Song J, Jiang ZG. A good step toward low-cost prognostication of liver-related outcome awaits more validation. J Hepatol 2022;77(3):887–889.
[2] Flores YN, Yee HF, Leng M, Escarce JJ, Bastani R, Salmerón J, et al. Risk factors for chronic liver disease in Blacks, Mexican Americans, and Whites in the United States: results from NHANES IV, 1999-2004. Am J Gastroenterol 2008;103:2231–2238. http://dx.doi.org/10.1111/j.1572-0241.2008.02022.x.
[3] Browning MG, Khoraki J, DeAntonio JH, Mazzini G, Mangino MJ, Siddiqui MS, et al. Protective effect of black relative to white race against non-alcoholic fatty liver disease in patients with severe obesity, independent of type 2 diabetes. Int J Obes (Lond) 2018;42:926–929. http://dx.doi.org/10.1038/ijo.2017.309.
[4] Stefan N. Causes, consequences, and treatment of metabolically unhealthy fat distribution. Lancet Diabetes Endocrinol 2020;8:616–627. http://dx.doi.org/10.1016/S2213-8587(20)30110-8.
[5] Danielsson O, Nissinen MJ, Jula A, Salomaa V, Männistö S, Lundqvist A, et al. Waist and hip circumference are independently associated with the risk of liver disease in population-based studies. Liver Int 2021;41:2903–2913. http://dx.doi.org/10.1111/liv.15053.
[6] Andreasson A, Carlsson AC, Önnerhag K, Hagström H. Waist/hip ratio better predicts development of severe liver disease within 20 years than body mass index: a population-based cohort study. Clin Gastroenterol Hepatol 2017;15:1294–1301.e2. http://dx.doi.org/10.1016/j.cgh.2017.02.040.
[7] Neufeld EV, Seltzer RA, Sazzad T, Dolezal BA. A multidomain approach to assessing the convergent and concurrent validity of a mobile application when compared to conventional methods of determining body composition. Sensors (Basel) 2020;20:E6165. http://dx.doi.org/10.3390/s20216165.
[8] Dillon JF, Miller MH. Gamma glutamyl transferase "To be or not to be" a liver function test? Ann Clin Biochem 2016;53:629–631. http://dx.doi.org/10.1177/0004563216659887.
[9] Hagström H, Talbäck M, Andreasson A, Walldius G, Hammar N. Ability of noninvasive scoring systems to identify individuals in the population at risk for severe liver disease. Gastroenterology 2020;158:200–214. http://dx.doi.org/10.1053/j.gastro.2019.09.008.

Fredrik Åberg[1,*]
Panu K. Luukkonen[2,3]
Martti Färkkilä[4]
[1]*Transplantation and Liver Surgery, Helsinki University Hospital, University of Helsinki, Helsinki, Finland*
[2]*Minerva Foundation Institute for Medical Research, Helsinki, Finland*
[3]*Department of Medicine, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[4]*University of Helsinki and Helsinki University Hospital, Abdominal Center, Helsinki, Finland*
[*]Corresponding author. Address: HUCH Meilahti Hospital, PB 372, 00029 HUS, Finland.
E-mail address: Fredrik.Aberg@helsinki.fi (F. Åberg)

The association of microvascular invasion with satellite nodule, tumor multiplicity, tumor encapsulation and resection margin of hepatocellular carcinoma

To the Editor:

We read with great interest the article by Beaufrère *et al.*[1] Microvascular invasion (MVI) is known to be a major risk associated with worse prognosis after resection of hepatocellular carcinoma (HCC), but it can only be detected by microscopic examination of the surgical specimen. By using their routine formalin-fixed paraffin-embedded (FFPE) biopsies and RNA-sequencing analysis, Beaufrère *et al.* developed and validated a 6-gene signature panel which can accurately predict MVI preoperatively. Meanwhile, this biogenetical panel was also demonstrated to be independently associated with overall survival after HCC resection. Although inspiring, we would like to raise a discussion on the association between MVI and other clinicopathological features in this study.

First, MVI and satellite nodules. Generally, satellite nodules are derived from MVI.[2,3] Similar to MVI, satellite nodules are only detectable by microscopy in the peritumoral liver of the surgical specimen.[2] While difficult to distinguish MVI and satellite nodule histologically, a diagnosis of satellite nodules is appropriate.[3] Not surprisingly, Beaufrère *et al.* also revealed an independently high correlation between MVI and satellite nodules in their study, with adjusted odds ratios (ORs) of 158.41 by univariate and multivariate analysis. However, what puzzles us is why the authors used satellite nodules as a variable in the multivariate analysis to predict MVI, given that their purpose was actually to preoperatively predict MVI, while the presence of satellite nodules also needs to be identified postoperatively like MVI. This approach appears to be incorrect and will likely change the adjusted OR value of the 6-gene signature when predicting MVI.

Received 30 March 2022; accepted 31 March 2022; available online 11 April 2022
https://doi.org/10.1016/j.jhep.2022.03.036