Enriched MACK-3 following CHAI and MACK-3 for the noninvasive diagnosis of nonalcoholic steatohepatitis

Keywords:
CHAI
Fibrosis
MACK-3
Nonalcoholic fatty liver disease
Nonalcoholic steatohepatitis
Noninvasive index

Dear Editor,

The noninvasive diagnosis of nonalcoholic steatohepatitis (NASH) and advanced hepatic fibrosis remain hot issues in the field of nonalcoholic fatty liver disease (NAFLD) [1], recently renamed to metabolic (dysfunction)-associated fatty liver disease (MAFLD) [2]. Appropriate noninvasive indices target to limit the need of liver biopsy, facilitate the follow-up of patients and enable the set up of clinical trials for this highly prevalent, with epidemic characteristics, disease without any approved treatment [3].

In 2013, we initially introduced cytokeratin [**C**K]-18, homeostasis model assessement insulin resistance [**H**OMA-IR], aspartate transaminase [**A**ST] **I**ndex (CHAI) [4], which was shown to be higher in patients with NASH than simple nonalcoholic fatty liver (NAFL). The area under the receiver operating characteristic (ROC) curve (AUROC) of CHAI to differentiate NASH from NAFL was 0.72, presenting satisfactory specificity (80%), albeit low sensitivity (46%) [4].

In 2018, Boursier et al. introduced HO**M**A-IR, **A**ST and **CK**-18 (MACK-3), as an index of fibrotic NASH (defined as NAFLD activity score ≥4 and fibrosis stage [F] ≥2) [5], by using exactly the same combination of parameters as CHAI. MACK-3 showed an AUROC of 0.85 with high specificity (94%) and sensitivity (90%) for the diagnosis of fibrotic NASH [5]. Subsequently, the authors provided an online calculator (http://forge.info.univ-angers.fr/~gh/wstat/mack3-calculator.php). In 2019, Chuah et al. validated MACK-3, with AUROC of 0.80 and comparable accuracy to NAFLD fibrosis score (NFS) and fibrosis-4 index (FIB-4) for fibrotic NASH [6].

In 2020, Gao et al. further validated MACK-3 and extended it by adding platelets count and the presence of metabolic syndrome (MetS) [7]. This enriched MACK-3, named "novel nomogram", provided AUROC of 0.85 with sensitivity 79% and 95%, and specificity 95% and 89% in the training and validation cohort, respectively, for the diagnosis of fibrotic NASH. Notably, when the enriched MACK-3 was combined with the liver stiffness measurement of vibration-controlled transient elastography in a sequential approach, 68% and 47% of liver biopsies could have been avoided in the training and validation cohort, respectively [7].

CHAI/MACK-3 consists of parameters that reflect insulin resistance (HOMA-IR), hepatocellular dysfunction (AST) and hepatocellular apoptosis (CK-18), all contributing to the pathogenesis of MAFLD [8]. The inclusion of AST instead of ALT in CHAI/MACK-3 may seem paradoxical, since higher alanine aminotransferase (ALT) than AST appears to differentiate MAFLD from other liver diseases presenting with hepatic steatosis (e.g. alcoholic or drug-induced fatty liver disease); however, higher AST seems to be a better predictor of advanced disease within MAFLD patients, when the diagnosis of MAFLD is established [9]. Gao et al. added platelets and MetS to MACK-3 [7], which had been previously incorporated in other noninvasive indices of NASH and fibrosis, including NFS [10] and FIB-4 [11] (platelets) or Nice Model [12] (MetS), the latter being in close association with MAFLD [13].

In conclusion, the use of CK-18, HOMA-IR and AST for the noninvasive diagnosis and management of fibrotic NASH has been validated by three independent groups [5–7]. Whether the addition of other parameters essentially adds to the diagnostic accuracy of the CHAI/MACK-3 remains to be validated by further studies.

Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransaminase
AUROC	area under the receiver operating characteristic curve
CHAI	CK-18 HOMA-IR AST index
CK	cytokeratin
FIB-4	fibrosis-4 index
HOMA-IR	homeostasis model assessement insulin resistance
MACK-3	HOMA-IR AST CK-18 index
MAFLD	metabolic (dysfunction)-associated fatty liver disease
MetS	metabolic syndrome
NASH	nonalcoholic steatohepatitis
NAFL	nonalcoholic fatty liver
NAFLD	nonalcoholic fatty liver disease
NFS	NAFLD fibrosis score
ROC	receiver operating characteristic

Conflict of interest

None.

Acknowledgments

Funding: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Polyzos SA, Mantzoros CS. Necessity for timely noninvasive diagnosis of nonalcoholic fatty liver disease. Metabolism 2014;63:161–7, http://dx.doi.org/10.1016/j.metabol.2013.10.010.
[2] Eslam M, Sanyal AJ, George J. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158:1999–2014, http://dx.doi.org/10.1053/j.gastro.2019.11.312.
[3] Polyzos SA, Kang ES, Boutari C, Rhee EJ, Mantzoros CS. Current and emerging pharmacological options for the treatment of nonalcoholic steatohepatitis. Metabolism 2020, http://dx.doi.org/10.1016/j.metabol.2020.154203 [Epub ahead of print].
[4] Polyzos S, Kountouras J, Papatheodorou A, Katsiki E, Patsiaoura K, Zafeiriadou E, et al. Adipocytokines and cytokeratin-18 in patients with nonalcoholic fatty liver disease – introduction of CHA index. Ann Hepatol 2013;12:749–57.
[5] Boursier J, Anty R, Vonghia L, Moal V, Vanwolleghem T, Canivet CM, et al. Screening for therapeutic trials and treatment indication in clinical practice: MACK-3, a new blood test for the diagnosis of fibrotic NASH. Aliment Pharmacol Ther 2018;47:1387–96, http://dx.doi.org/10.1111/apt.14621.
[6] Chuah KH, Wan Yusoff WNI, Sthaneshwar P, Nik Mustapha NR, Mahadeva S, Chan WK. MACK-3 (combination of hoMa, Ast and CK18): a promising novel biomarker for fibrotic non-alcoholic steatohepatitis. Liver Int 2019;39:1315–24, http://dx.doi.org/10.1111/liv.14084.
[7] Gao F, Huang JF, Zheng KI, Pan XY, Ma HL, Liu WY, et al. Development and validation of a novel non-invasive test for diagnosing fibrotic non-alcoholic steatohepatitis in patients with biopsy-proven non-alcoholic fatty liver disease. J Gastroenterol Hepatol 2020, http://dx.doi.org/10.1111/jgh.15055 [Epub ahead of print].
[8] Polyzos SA, Kountouras J, Zavos C. Nonalcoholic fatty liver disease: the pathogenetic roles of insulin resistance and adipocytokines. Curr Mol Med 2009;72:299–314.
[9] Polyzos SA, Kountouras J. CHAI and MACK-3 as noninvasive indices for nonalcoholic steatohepatitis. Liver Int 2019;39(1587), http://dx.doi.org/10.1111/liv.14123.
[10] Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846–54.

[11] McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. Gut 2010;59:1265–9, http://dx.doi.org/10.1136/gut.2010.216077.
[12] Anty R, Iannelli A, Patouraux S, Bonnafous S, Lavallard VJ, Senni-Buratti M, et al. A new composite model including metabolic syndrome, alanine aminotransferase and cytokeratin-18 for the diagnosis of non-alcoholic steatohepatitis in morbidly obese patients. Aliment Pharmacol Ther 2010;32:1315–22, http://dx.doi.org/10.1111/j.1365-2036.2010.04480.x.
[13] Polyzos SA, Bugianesi E, Kountouras J, Mantzoros CS. Nonalcoholic fatty liver disease: updates on associations with the metabolic syndrome and lipid profile and effects of treatment with PPAR-gamma agonists. Metabolism 2017;66:64–8, http://dx.doi.org/10.1016/j.metabol.2016.08.001.

Stergios A. Polyzos*
First Laboratory of Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Jannis Kountouras
Second Medical Clinic, School of Medicine, Aristotle University of Thessaloniki, Ippokration Hospital, Thessaloniki, Greece

* Corresponding author.
E-mail address: spolyzos@auth.gr (S.A. Polyzos)

https://doi.org/10.1016/j.aohep.2020.07.001
1665-2681/ © 2020 Fundación Clínica Médica Sur, A.C. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).