presenting HRV <5%. This is not the case of the Expanded VI Criteria: when we apply the cut-offs to the nomogram, the model indicates an HRV risk superior to 10% and therefore is not able to identify a subset of patients with risk <5%. Interestingly, the same result can be obtained when we apply these cut-offs to the original nomogram drawn by Abraldes et al. [6] for the Anticipate Study.

In conclusion, the Expanded Baveno VI criteria represent a seemingly attractive strategy to rule out HRV, as they allow to vastly increase the rate of spared EGDs. However, this happens at the expense of the missed HRV rate, which is above the accepted threshold of 5%. Therefore, we believe that some concerns should be raised about their safety and ability to identify compensated cirrhotic patients that can avoid screening EGD. This issue should be carefully addressed by further large prospective studies evaluating screening strategies for HRV.

Conflict of interest

None declared.

References

[1] Augustin S, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology 2017;00:1–9, http://dx.doi.org/10.1002/hep.29363.

[2] de Franchis R, Baveno Faculty VI. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–52, http://dx.doi.org/10.1016/j.jhep.2015.05.022.

[3] Petta S, Sebastiani G, Bugianesi E, Viganò M, Wong VW-S, Berzigotti A, et al. Non-invasive prediction of esophageal varices by stiffness and platelet in non-alcoholic fatty liver disease cirrhosis. J Hepatol 2018;69:878–85, http://dx.doi.org/10.1016/j.jhep.2018.05.019.

[4] Bae J, Sinn DH, Kang W, Gwak G-Y, Choi MS, Paik Y-H, et al. Validation of the Baveno VI and the expanded Baveno VI criteria to identify patients who could avoid screening endoscopy. Liver Int 2018;38:1442–8, http://dx.doi.org/10.1111/liv.13732.

[5] Colecchia A, Ravaioli F, Marasco G, Colli A, Dajti E, Di Biase AR, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. J Hepatol 2018;69:308–17, http://dx.doi.org/10.1016/j.jhep.2018.04.023.

[6] Abraldes JG, Bureau C, Stefanescu H, Augustin S, Ney M, Blasco H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: The “Anticipate” study. Hepatology 2016;64:2173–84, http://dx.doi.org/10.1002/hep.28824.

Elton Dajti
Federico Ravaioli
Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Via Massarenti 9, 40138, Bologna, Italy

Antonio Colecchia *
Gastroenterology Unit, Borgo Trento University Hospital, Piazzale Aristide Stefani 1, 37126, Verona, Italy

Giovanni Marasco
Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Via Massarenti 9, 40138, Bologna, Italy

Paul Calès
Hepatology department, University Hospital Angers, 4 Rue Larrey, 49100, Angers, France

Davide Festi
Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Via Massarenti 9, 40138, Bologna, Italy

* Corresponding author at: Gastroenterology Unit, Borgo Trento University Hospital, Piazzale Aristide Stefani 1, 37126, Verona, Italy.
E-mail address: antonio.colecchia@aovr.veneto.it (A. Colecchia)

21 September 2018

https://doi.org/10.1016/j.dld.2018.12.013

Time to revise the definition of NAFLD: A purist vision

Keywords:
Non-alcoholic fatty liver disease
NAFLD
Alcohol
Definition

Dear Editor,

In 2018, Wood et al. published in *The Lancet* an analysis of individual-participant data from 600,000 current drinkers of 83 prospective studies, reporting that the threshold of alcohol consumption for lowest risk of all-cause mortality was ~100 g/week (i.e., ~14 g/day) and that a lower alcohol consumption was associated with a lower risk of cardiovascular complications [1].

In the same years, Åberg et al. published a study of nearly 6750 individuals followed for 11 years, showing that metabolic syndrome and alcohol consumption (even within the limits defining non-alcoholic fatty liver disease [NAFLD]) were associated with an increased risk of severe liver disease [2].

In another study, involving 8162 participants (56% with NAFLD) from NHANES followed for 12 years, Hajifathalian et al. documented that, among NAFLD patients, modest alcohol consumption (i.e., 0.5–1.5 drinks/day) was associated with a decrease in all-cause mortality, whereas high alcohol consumption (i.e., ≥1.5 drinks/day) was associated with an increased mortality [3].

In a recent cohort study of 4264 individuals with hepatic steatosis followed for 20 years, Younossi et al. observed that the presence of metabolic syndrome and excessive alcohol consumption were independently associated with an increased risk of death in individuals with hepatic steatosis and that the association of excessive alcohol use with mortality was significant in individuals with metabolic syndrome, but not in those without [4].

Again in 2018, using approximately 700 data sources of individual and population-level alcohol consumption, along with nearly 600 prospective and retrospective studies on the risk of alcohol use, the GBD (Global Burden of Disease) 2016 Alcohol Collaborators found that alcohol use was a leading risk factor for global disease burden, causing substantial health loss [5]. In particular, they reported that the risk of all-cause mortality, and of cancers specifically, increased with increasing levels of alcohol consumption and that the level of alcohol consumption able to minimize health loss was zero [5].

To date, the diagnosis of NAFLD is based on the following criteria: (a) hepatic steatosis on imaging or histology, (b) no excessive alcohol consumption (a threshold of 20 g/day [~140 g/week] for women and 30 g/day [~210 g/week] for men is conventionally adopted), and (c) no competing causes for hepatic steatosis [6].

Over the last decade, it has become clear that, compared to those without, patients with NAFLD have an increased risk of all-cause mortality and that NAFLD is not only associated with hepatic complications, but also with an increased risk of serious extra-hepatic complications, including cardiovascular diseases and cancers [7,8].

Although recommendations regarding health effects of alcohol remain controversial (even in NAFLD patients), based on recent data [1–5], not only the nomenclature (as suggested by Bellentani and Tiribelli [9]), but also the definition of NAFLD should be timely revised. In particular, the conventional threshold of alcohol consumption should be changed. As it was documented that (a) the threshold for lowest risk of all-cause mortality is ~14 g/day [1,5]; (b) for cardiovascular complications (with the exception of ischemic heart disease), there is no evident thresholds below which lower alcohol consumption stopped being associated with a lower disease risk, thus suggesting a dose-response curve rather than a single J-shaped association [1,5]; and (c) any alcohol consumption in the context of metabolic syndrome is associated with an increased risk of important liver complication [2,4], we should include only non-drinker individuals in the "NAFLD definition". In other words, given that there is now convincing evidence demonstrating that even "safe" levels of alcohol consumption are associated with adverse outcomes [5], it is time to take into consideration that, for a diagnosis of NAFLD, the limits of alcohol should be zero or close to zero.

In this context, I already see many colleagues stand up and argue that, whilst at present the deleterious effects of alcohol are evident [1–5], the problems of more stringent alcohol cut-offs in the definition of NAFLD are amplified by the fact that no questionnaire is able to exclude alcohol consumption to zero or near zero levels and that, importantly, social drinking (whatsoever that means) is epidemic.

It is certainly true, but it is equally evident that, from a purely scientific point of view, not all observational studies assessing the (adverse) effect of NAFLD on hepatic and extra-hepatic complications have adjusted for alcohol consumption as continuous variable. Therefore, in the interpretation of data, we should increasingly consider that, among all the confounders, alcohol plays a relevant and intrinsic role, given that it is included in the definition of NAFLD. Notably and importantly, we are also physicians and, in light of all the data regarding alcohol use [1–5], we have to encourage (all) patients to abstain from alcohol consumption (impractical though it may seem).

Coordinated actions are required to obtain this important acknowledgement, which is not solely that of a purist. I hope that the proposal to revise the definition of NAFLD will be supported by international Experts on NAFLD.

Conflict of interest

None declared.

References

[1] Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet 2018;391:1513–23.
[2] Åberg F, Helenius-Hietala J, Puukka P, Färkkilä M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. Hepatology 2018;67:2141–9.
[3] Hajifathalian K, Torabi Sagvand B, McCullough AJ. Effect of alcohol consumption on survival in nonalcoholic fatty liver disease: a national prospective cohort study. Hepatology 2018, http://dx.doi.org/10.1002/hep.30226.
[4] Younossi ZM, Stepanova M, Ong J, Yilmaz Y, Duseja A, Eguchi Y, et al. Effects of alcohol consumption and metabolic syndrome on mortality in patients with non-alcoholic and alcohol-related fatty liver disease. Clin Gastroenterol Hepatol 2018, http://dx.doi.org/10.1016/j.cgh.2018.11.033, pii: S1542-3565(18)31276-X.
[5] GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018;392:1015–35.
[6] Italian Association for the Study of the Liver (AISF). AISF position paper on non-alcoholic fatty liver disease (NAFLD): updates and future directions. Dig Liver Dis 2017;49:471–83.
[7] Anstee QM, Mantovani A, Tilg H, Targher G. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2018;15:425–39.
[8] Mantovani A, Dauriz M, Byrne CD, Lonardo A, Zoppini G, Bonora E, et al. Association between nonalcoholic fatty liver disease and colorectal tumours in asymptomatic adults undergoing screening colonoscopy: a systematic review and meta-analysis. Metabolism 2018;87:1–12.
[9] Bellentani S, Tiribelli C. Is it time to change NAFLD and NASH nomenclature? Lancet Gastroenterol Hepatol 2017;2:547–8.

Alessandro Mantovani*
Section of Endocrinology, Diabetes and Metabolism, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy

*Correspondence to: Section of Endocrinology, Diabetes and Metabolism, University and Azienda Ospedaliera Universitaria Integrata, Piazzale A. Stefani, 1, 37126 Verona, Italy.
E-mail address: alessandro.mantovani@univr.it

8 December 2018
https://doi.org/10.1016/j.dld.2018.12.018