

## Spotlight

## Alarming increase of NASH as cause of liver cancer

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A very interesting recent article by Huang and colleagues evaluated the global epidemiology of liver cancer from 2010 to 2019 and showed that non-alcoholic steatohepatitis (NASH) is the fastest growing cause of hepatocellular carcinoma (HCC).<sup>1</sup>

Non-alcoholic fatty liver disease (NAFLD) is already the most prevalent liver disease worldwide, affecting at least a quarter of the global population.<sup>2</sup> All the spectrum prevalence, including advanced liver disease, will continue to increase significantly for at least another decade.<sup>3</sup> Besides that, the burden of advanced liver disease because of NAFLD will more than double during next 10 years<sup>2</sup>

Additionally, our vision needs to englobe the pediatric population, as we are witnessing the beginning of this silent pandemic from a young age, becoming the most common childhood chronic liver disease in many Western countries.<sup>4</sup> The development and progression of the disease so early in life will certainly increase the risk of future liver-related complications, as illustrated by the increasing number of liver transplant young registrants (<40 years old) with youth-onset NASH. Therefore, having a holistic insight of the natural history of NAFLD, from conception to adulthood, is essential to a better prevention and management.<sup>5</sup>

Another concern is the increasing incidence of liver cancer deaths worldwide, demonstrated in this article.<sup>1</sup> This may be partly explained by several obstacles encountered in the early diagnosis of NASH-related HCC. First, there is a higher incidence of cirrhosis absence (24–46%) in these patients and therefore they do not have routine indication for HCC surveillance based on current practice guidelines.<sup>3</sup> This has already been illustrated by the lower percentages of NASH-related HCC cases diagnosed during surveillance.<sup>3,6</sup> Second, HCC screening is affected in uninsured patients who do not have access to care. Also, the use of ultrasonography still misses one-third of

patients at an early stage.<sup>7</sup> Besides that, it is operator-dependent and more challenging in centrally overweight patients with heterogeneous livers. Third, and in consequence of the first two points, most NASH-related HCC cases are detected at advanced stage, precluding the option of curative treatment.<sup>3</sup> Furthermore, several studies have shown that these patients are less likely to receive liver transplantation due to their metabolic syndrome comorbidities. However, in case it does, the development of fatty liver or steatohepatitis on transplanted liver can potentially impact their post-transplant course.<sup>8</sup>

Huang and colleagues demonstrated that NASH and alcohol had the fastest growing age-standardized death rates (ASDRs) in liver cancer, particularly in America.<sup>1</sup> These two prevalent causes, in particular NASH, have the characteristic to share the metabolic syndrome features as risk factors for HCC in a synergistic interaction rather than being merely additive.<sup>2</sup> Several independent risk factors are associated with HCC, namely heavy alcohol use, tobacco smoking, type 2 diabetes mellitus, severity of obesity, waist circumference, and socioeconomic status: the greater the number of metabolic components, the higher the risk of adverse long-term outcomes, including mortality.<sup>8</sup>

The impressive increase in NAFLD cases represents a pressing public health problem that needs to be seriously considered and managed in a global perspective. In fact, this significant increase in NAFLD is heavily related with the increased prevalence of obesity and type II diabetes. To overcome this huge burden of disease, there is need of pol-

icies and strategies oriented not only toward the patients, but also toward societies and governments at national and global levels. In the first situation, we need to prioritize all the stages of NASH spectrum, from its risk factors' control to appropriate HCC surveillance protocols.<sup>2</sup> In addition, we need to shift our paradigm toward a non-invasive approach, by identifying markers that will stratify patients at risk for more cost-effective target surveillance.<sup>7</sup> Hopefully, artificial intelligence will help us improve the HCC clinical care, through a better risk prediction, diagnosis, and prognostication.<sup>9</sup>

Also, we need to acknowledge that a purely liver-oriented focus does not cover the multisystemic implications of NAFLD and therefore this approach requires the development of interdisciplinary and multiprofessional teams focusing on patient-centered training and care, supported by telemedicine and electronic systems, with primary care having a fundamental role through reinforced partnership and training programs.<sup>2,7</sup>

In what concerns NAFLD and its risk factors, the most prevalent non-communicable diseases, they depend less on individual choices and more on socioeconomic and environmental conditions, exacerbated by policies that prioritize profits over health.<sup>2</sup> Despite its high prevalence worldwide and its impact on health, economy, and society, NAFLD has been neglected in the national health agendas.<sup>10</sup> Therefore, we need to overlap the national and global strategic approaches to fight this alarming pandemic by implementing effective policies on food reformulation and taxation on alcohol consumption, starting with the children and adolescents. Also, there is



an urgent need in changing health care funding and reimbursement process, a political problem in several countries with health inequalities.<sup>2</sup>

Our world has faced an unprecedented global pandemic in the last two years, with more than six million deaths worldwide because of COVID-19, forcing our societies, governments, and industries to work fast but also to join efforts toward effective solutions. Therefore, we need to keep up with these principles and focus on this not-so-new, but silent and alarming, pandemic that will continue to rise in the absence of our commitment.

#### DECLARATION OF INTERESTS

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#### REFERENCES

- Huang, D.Q., Singal, A.G., Kono, Y., Tan, D.J., El-Serag, H.B., and Loomba, R. (2022). Changing global epidemiology of liver cancer from 2010 to 2019: NASH is the fastest growing cause of liver cancer. *Cell Metabol.* 34, 969–977.e2. Published online 2022. <https://doi.org/10.1016/j.cmet.2022.05.003>.
- Karlsen, T.H., Sheron, N., Zelber-Sagi, S., Carrieri, P., Dusheiko, G., Bugianesi, E., Pryke, R., Hutchinson, S.J., Sangro, B., Martin, N.K., et al. (2022). The EASL–Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. *Lancet* 399, 61–116. [https://doi.org/10.1016/S0140-6736\(21\)01701-3](https://doi.org/10.1016/S0140-6736(21)01701-3).
- Anstee, Q.M., Reeves, H.L., Kotsiliti, E., Goovaere, O., and Heikenwalder, M. (2019). From NASH to HCC: current concepts and future challenges. *Nat. Rev. Gastroenterol. Hepatol.* 16, 411–428. <https://doi.org/10.1038/s41575-019-0145-7>.
- Bendor, C.D., Bardugo, A., Pinhas-Hamiel, O., Afek, A., and Twig, G. (2020). Cardiovascular morbidity, diabetes and cancer risk among children and adolescents with severe obesity. *Cardiovasc. Diabetol.* 19, 79. <https://doi.org/10.1186/s12933-020-01052-1>.
- Castillo-Leon, E., Cioffi, C.E., and Vos, M.B. (2020). Perspectives on youth-onset nonalcoholic fatty liver disease. *Endocrinology, Diabetes and Metabolism* 3, e00184. <https://doi.org/10.1002/edm2.184>.
- Tan, D.J.H., Ng, C.H., Lin, S.Y., Pan, X.H., Tay, P., Lim, W.H., Teng, M., Syn, N., Lim, G., Yong, J.N., et al. (2022). Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. *Lancet Oncol.* 23, 521–530. [https://doi.org/10.1016/S1470-2045\(22\)00078-X](https://doi.org/10.1016/S1470-2045(22)00078-X).
- Singal, A.G., Lampertico, P., and Nahon, P. (2020). Epidemiology and surveillance for hepatocellular carcinoma: new trends. *J. Hepatol.* 72, 250–261. <https://doi.org/10.1016/j.jhep.2019.08.025>.
- Younossi, Z.M., and Henry, L. (2021). Epidemiology of non-alcoholic fatty liver disease and hepatocellular carcinoma. *JHEP Reports* 3, 100305. <https://doi.org/10.1016/j.jhepr.2021.100305>.
- Calderaro, J., Seraphin, T.P., Luedde, T., and Simon, T.G. (2022). Artificial intelligence for the prevention and clinical management of hepatocellular carcinoma. *J. Hepatol.* 76, 1348–1361. <https://doi.org/10.1016/j.jhep.2022.01.014>.
- Lazarus, J.v., Mark, H.E., Villota-Rivas, M., Palayew, A., Carrieri, P., Colombo, M., Ekstedt, M., Esmat, G., George, J., Marchesini, G., et al. (2022). The global NAFLD policy review and preparedness index: are countries ready to address this silent public health challenge? *J. Hepatol.* 76, 771–780. <https://doi.org/10.1016/j.jhep.2021.10.025>.