



Letters to the editor

On the risk of further excluding outcast patient populations in South America



It is with great interest that we read the article by Farah and colleagues on the epidemiological transition at work regarding risk factors for hepatocellular carcinoma (HCC) in South America [1]. In this study, the authors compiled data from 339 patients seen between 2019 and 2021 in six countries of the region, with Peruvian patients accounting for the most significant proportion, i.e., 125 HCC cases (37%) collected at one general services hospital. The results suggest a rise in HCCs associated with non-alcoholic fatty liver disease (37%) at the regional level, whereas infection with the hepatitis B virus (HBV) tends to decrease as an associated risk factor for HCC in South America (12%). However, our experience at the National Cancer Institute of Peru (INEN), the country's main specialist cancer hospital, gives a contrasting picture of HCC epidemiology in Peru and may provide deeper insights into the real socio-epidemiological situation at the regional level. Due to the multi-tiered health systems in Peru and South America, it is unlikely that data from a single center per country can provide an accurate picture of HCC epidemiology and its risk factors. For example, INEN treats more socially marginalized people (ca. 120 HCC patients/year) while representing a larger fraction of the country's population [2], many of whom are of Native ancestry, in comparison to the gentrifying population living in metropolises and having the benefit of health insurance [3]. Our team has published a series of articles that shed light on the elevated ratio of HBV-related HCC (81.5%) in the patient population treated at INEN [4,5]. Intriguingly, HBV infection in these patients is associated with a very low viral DNA burden, disclosing a significant rate of occult infections (33.8%) with HBV sub-genotype F1b, only detectable by ultra-sensitive molecular tests [4]. Furthermore, we identified through integrative genomic analysis a distinct molecular subtype of HBV-associated HCC with ancestry-related molecular traits [6,7]. Such higher prevalence rates of occult infection with autochthonous HBV clades (F, G, H) have been documented to a great extent in Latin American patients [8–12], stressing the need for precautions when identifying risk factors for HCC in the region [13]. Another issue concerning the study by Farah and colleagues is the data collection period between 2019 and 2021 amid the COVID-19 pandemic. Indeed, cancer patients originating from remote and underserved regions, which correspond in Peru with areas where HBV is highly endemic [14], could not reach metropolitan health centers during the COVID-19 lockdowns [15], creating thereby the possibility of recruitment bias in the collection of data. We understand that the article by Farah and colleagues has particular relevance for health policymakers in South America, who could then be deterred from persisting in their efforts to combat hepatitis B. Therefore, it appears of the utmost importance for decision-making to provide a truly comprehensive overview of the HCC epidemiology in the region by considering all published literature, in order to prevent further exclusion from cancer control programs of populations already among the most deprived in South America.

Declaration of interest

None

References

- [1] Farah M, Anugwom C, Ferrer JD, Baca EL, Mattos AZ, Possebon JPP, et al. Changing epidemiology of hepatocellular carcinoma in South America: A report from the South American liver research network. *Ann Hepatol* 2023;28:100876. <https://doi.org/10.1016/j.aohp.2022.100876>.
- [2] Bertani S, Pineau P, Loli S, Moura J, Zimic M, Deharo E, et al. An atypical age-specific pattern of hepatocellular carcinoma in Peru: A threat for Andean populations. *PLoS ONE* 2013;8:e67756. <https://doi.org/10.1371/journal.pone.0067756>.
- [3] Samuel J, Flores W, Frisancho A. Social exclusion and universal health coverage: Health care rights and citizen-led accountability in Guatemala and Peru. *Int J Equity Health* 2020;19:216. <https://doi.org/10.1186/s12939-020-01308-y>.
- [4] Marchio A, Cerapio JP, Ruiz E, Cano L, Casavila S, Terris B, et al. Early-onset liver cancer in South America associates with low hepatitis B virus DNA burden. *Sci Rep* 2018;8:12031. <https://doi.org/10.1038/s41598-018-30229-8>.
- [5] Cano L, Cerapio JP, Ruiz E, Marchio A, Turlin B, Casavila S, et al. Liver clear cell foci and viral infection are associated with non-cirrhotic, non-fibrolamellar hepatocellular carcinoma in young patients from South America. *Sci Rep* 2018;8:9945. <https://doi.org/10.1038/s41598-018-28286-0>.
- [6] Cerapio JP, Marchio A, Cano L, López I, Fournié JJ, Régault B, et al. Global DNA hypermethylation pattern and unique gene expression signature in liver cancer from patients with Indigenous American ancestry. *Oncotarget* 2021;12:475–92. <https://doi.org/10.18632/oncotarget.27890>.
- [7] Marchio A, Bertani S, Rojas-Rojas T, Doimi F, Terris B, Deharo E, et al. A peculiar mutation spectrum emerging from young Peruvian patients with hepatocellular carcinoma. *PLoS ONE* 2014;9:e114912. <https://doi.org/10.1371/journal.pone.0114912>.
- [8] Panduro A, Maldonado-Gonzalez M, Fierro NA, Roman S. Distribution of HBV genotypes F and H in Mexico and Central America. *Antivir Ther* 2013;18:475–84. <https://doi.org/10.3851/IMP2605>.
- [9] Roman S, Panduro A. HBV endemicity in Mexico is associated with HBV genotypes H and G. *World J Gastroenterol* 2013;19:5446–53. <https://doi.org/10.3748/wjg.v19.i33.5446>.
- [10] Roman S, Tanaka Y, Khan A, Kurbanov F, Kato H, Mizokami M, et al. Occult hepatitis B in the genotype H-infected Nahuas and Huichol native Mexican population. *J Med Virol* 2010;82:1527–36. <https://doi.org/10.1002/jmv.21846>.
- [11] Escobedo-Melendez G, Panduro A, Fierro NA, Roman S. High prevalence of occult hepatitis B virus genotype H infection among children with clinical hepatitis in west Mexico. *Mem Inst Oswaldo Cruz* 2014;109:728–37.
- [12] Jose-Abrego A, Panduro A, Fierro NA, Roman S. High prevalence of HBV infection, detection of subgenotypes F1b, A2, and D4, and differential risk factors among Mexican risk populations with low socioeconomic status. *J Med Virol* 2017;89:2149–57. <https://doi.org/10.1002/jmv.24913>.
- [13] Roman S, Jose-Abrego A, Fierro NA, Escobedo-Melendez G, Ojeda-Granados C, Martinez-Lopez E, et al. Hepatitis B virus infection in Latin America: A genomic medicine approach. *World J Gastroenterol* 2014;20:7181–96. <https://doi.org/10.3748/wjg.v20.i23.7181>.
- [14] Cabezas C, Trujillo O, Gonzales-Vivanco Á, Benites Villafane CM, Balbuena J, Borda-Olivas AO, et al. Seroepidemiology of hepatitis A, B, C, D and E virus infections in the general population of Peru: A cross-sectional study. *PLoS One* 2020;15:e0234273. <https://doi.org/10.1371/journal.pone.0234273>.
- [15] Valdiviezo N, Alcarraz C, Castro D, Salas R, Begazo-Mollo V, Galvez-Villanueva M, et al. Oncological care during first Peruvian national emergency COVID-19 pandemic: A multicentric descriptive study. *Cancer Manag Res* 2022;14:1075–85. <https://doi.org/10.2147/CMAR.S350038>.

Eloy Ruiz
Ramiro Fernández
Francisco Berrosqui
Sandro Casavila-Zambrano

Juan Contreras-Mancilla
Juan Pablo Cerapio
Pascal Pineau
Stéphane Bertani*

*Departamento de Cirugía en Abdomen, Instituto Nacional de
Enfermedades Neoplásicas (INEN), Lima, Peru*
*International Joint Laboratory of Molecular Anthropological Oncology
(LOAM), INEN, IRD, Lima, Peru*
*Departamento de Patología, Instituto Nacional de Enfermedades
Neoplásicas (INEN), Lima, Peru*

*Biobanco de Tejidos Tumorales, Instituto Nacional de Enfermedades
Neoplásicas (INEN), Lima, Peru*
UMR 1037 CRCT, Université de Toulouse, INSERM, UPS, Toulouse, France
*Unité Organisation Nucléaire et Oncogénèse, INSERM, Institut Pasteur,
Paris, France*
*UMR 152 PHARMADEV, Université de Toulouse, IRD, UPS, Toulouse,
France*

*Corresponding author.
E-mail address: stephane.bertani@ird.fr (S. Bertani).