

## **Contribution of the European Association for the Study of the Liver (EASL) to the European Cancer Inequalities Registry**

### **Inequalities in liver cancer prevention**

The European Association for the Study of the Liver (EASL) welcomes the European Commission's initiative to build an EU Cancer Inequalities Registry and recommends the inclusion of inequalities in liver cancer and in its key causes: liver cirrhosis due to viral hepatitis, alcohol-related liver disease (ARLD), or non-alcoholic fatty liver disease (NAFLD). Around 90% of patients with liver cancer have liver cirrhosis.

Liver cancer is a global burden. It is the 6th most common cancer, and the 3rd most common cause of cancer deaths<sup>i ii</sup>. Most liver cancers are caused by viral hepatitis followed by ARLD, NAFLD or rarer causes of cirrhosis, and liver cancer is the leading cause of death in people with cirrhosis. Furthermore, the predicted increase in the prevalence of fatty liver disease will further increase the incidence of HCC. It is estimated that the number of new cases and deaths from liver cancer could rise by >55% by 2040<sup>iii</sup>. Hepatocellular carcinoma (HCC) is the most common liver cancer, accounting for ~90% of all liver cancers.

Viral hepatitis B and C are responsible for more than 70% of liver cancer cases and are recognised as cancer-preventable risk factors in Europe's Beating Cancer Plan and by the World Health Organisation (WHO). Thanks to the effective implementation of HBV immunisation programmes and treatment regimens for HCV, the epidemiological attribution of HCC is shifting from viral hepatitis to NAFLD and alcoholic liver disease or both combined.

### **Inequalities and liver diseases**

Socio economic inequalities and liver diseases are very much interrelated. They are one of the main contributors and key players in some liver diseases including viral hepatitis, Non-Alcoholic Fatty Liver Disease (NAFLD) and alcohol-related liver disease. Inequality plays a double role in impacting both the etiological agents that lead to liver cirrhosis and subsequent liver cancer as well as the access to proper medical and social services. Regarding viral hepatitis, the Covid-19 pandemic has increased these inequalities and severely hampered plans to eliminate viral hepatitis across the globe. As it is reported by an EASL multinational survey, limitations in the cascade of care for both HBV and HCV were linked to limited access to screening, consultations, specific testing, and actual treatment.

Unhealthy lifestyle, alcohol consumption as well as viral hepatitis are closely related to socio-economic background. There is also evidence they impact chronic liver disease and cirrhosis complications mortality both in man and women, mostly in urban areas

These inequalities are related to the different factors associated with chronic liver diseases and cirrhosis, namely unhealthy life-style, alcohol consumption, and hepatitis B and C.<sup>iv</sup> It is important to take into account that deprived areas have a higher proportion of vulnerable populations, such as drug users and marginalised groups, who can be at greater risk of

contracting hepatitis B and C, exhibit higher alcohol consumption and have less access to healthy food and physical activity. Moreover, studies that have analysed socioeconomic inequalities in alcohol-attributable mortality have found it is higher in lower socioeconomic groups in most countries and is similar in men and women<sup>v vi vii</sup>. Likewise, the inability to afford or make healthy life-style choices on nutrition and exercise are strongly related to social inequalities.

Large numbers of people have left Ukraine since the onset of Russia's aggression towards Ukraine. Refugees and patients in Ukraine for all stages along the continuum of care from prevention through treatment of liver disease are facing increasing inequalities and this becomes a key challenge for their health.

Evidence	Reference
<b>Hepatitis B, C and D</b>	
<p>There is a need to implement hepatitis prevention strategies with specific populations at national level to avoid regional disparities.</p>	<ul style="list-style-type: none"> <li>• Hepahealth Project Report, Risk Factors and the Burden of Liver Disease in Europe and Selected Central Asian Countries</li> <li>• Karlsen TH, Sheron N, Zelber-Sagi S, et al. The EASL–Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. <i>The Lancet</i> 2021; published online Dec 2.</li> </ul>
<p>Currently, immigrants from countries with high HDV prevalence are responsible for most new cases of HDV infection in Europe. Chronic Hepatitis D results in more rapid progression to cirrhosis and hepatocellular carcinoma.</p>	<ul style="list-style-type: none"> <li>• Karlsen TH, Sheron N, Zelber-Sagi S, et al. The EASL–Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. <i>The Lancet</i> 2021; published online Dec 2.</li> </ul>
<p>It is estimated that worldwide, hepatitis D virus (HDV) affect nearly 5% of people who have a chronic infection with hepatitis B virus (HBV) and that HDV co-infection could explain about 1 in 5 cases of liver diseases and liver cancer in people with HBV infection.</p> <p>Although it is less common that hepatitis B, hepatitis D is a serious disease that often affects underprivileged and vulnerable populations, says Dr Meg Doherty, Director of the WHO Global Hepatitis Programme. Those who are more likely to have HBV and HDV co-infection include people who inject drugs and people with hepatitis C or HIV infection. The risk of co-infection also appears to be higher in recipients of hemodialysis, men who have sex with men, and commercial sex workers. This information helps in identifying the groups with HBV among whom we should be looking for HDV. However, HDV testing should be performed once in HBsAg positive individuals.</p>	<ul style="list-style-type: none"> <li>• International Agency for Research on Cancer, WHO, press release N°282, April 2020</li> <li>• International Agency for Research on Cancer (IARC) – <a href="#">New estimates highlight the need to step up the response to hepatitis D</a></li> <li>• EASL guideline sin hepatitis B 2017</li> </ul>
<p>HDV has long been neglected, because for decades the prevalence of infection remained uncertain and effective treatment was lacking. Mapping the epidemiology of the infection is just the first step. More efforts are needed to reduce the global burden of chronic hepatitis B and develop medicines that are safe and effective against hepatitis D and are affordable enough to be deployed on a large scale to those who are most in need.</p>	<ul style="list-style-type: none"> <li>• Stockdale AJ, Kreuels B, Henrion MYR, Giorgi E, Kyomuhangi I, de Martel C, Hutin Y, Geretti AM (2020). The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. <i>J Hepatol</i>. Published online 23 April 2020.</li> </ul>

<p>Although the trends in burden are decreasing and the Quality of Care Index (QCI) improved from 1990 to 2019 globally, there is a wide gap between countries. Given the inequities in health care quality, there is an urgent need to address discrimination and bridge the gap.</p> <p>With the effective implementation of HBV and treatment regimens for HCV, the epidemiological attribution of HCC is shifting from viral hepatitis to NAFLD.</p>	<ul style="list-style-type: none"> <li>• Ghamari SH, Yoosefi M, Abbasi-Kangevari M, Malekpour, et al. Trends in Global, Regional, and National Burden and Quality of Care Index for Liver Cancer by Cause from Global Burden of Disease 1990-2019. <i>Hepatology</i>. 2022 Jul;6(7):1764-1775. doi: 10.1002/hep4.1910. Epub 2022 Feb 8. PMID: 35134275; PMCID: PMC9234674.</li> <li>• Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. <i>J Hepatol</i>. 2020 Feb;72(2):250-261. doi: 10.1016/j.jhep.2019.08.025. PMID: 31954490; PMCID: PMC6986771.</li> </ul>
<p>In socioeconomically vulnerable patients, however, individual-level barriers (e.g., insurance status) and contextual-level disparities (e.g. health facilities) may not be readily available, thus limiting HCC screening. Additional challenges faced by racial/ethnic minorities can further challenge the spectrum of HCC care and lead to inadequate screening, delayed diagnosis, and unequal access to treatment.</p>	<ul style="list-style-type: none"> <li>• Kronenfeld JP, Goel N. An Analysis of Individual and Contextual-Level Disparities in Screening, Treatment, and Outcomes for Hepatocellular Carcinoma. <i>J Hepatocell Carcinoma</i>. 2021 Sep 28;8:1209-1219. doi: 10.2147/JHC.S284430. PMID: 34611524; PMCID: PMC8487287.</li> </ul>
<p><b>Alcohol-Related Liver Disease (ARLD)</b></p>	
<p>There are geographical socioeconomic inequalities in chronic liver diseases and cirrhosis mortality.</p>	<ul style="list-style-type: none"> <li>• Socioeconomic Inequalities in Chronic Liver Diseases and Cirrhosis Mortality in European Urban Areas before and after the Onset of the 2008 Economic Recession.</li> </ul>
<p>There is evidence of socioeconomic inequalities in chronic liver diseases and cirrhosis mortality in men and women. These inequalities are related to the different factors associated with chronic liver diseases and cirrhosis, namely alcohol consumption, and hepatitis B and C. It is important to take into account that deprived areas have a higher proportion of vulnerable populations, such as drug users and marginalised groups, who can be at greater risk of contracting hepatitis B and C and exhibit higher alcohol consumption. Previous studies have shown also socioeconomic inequalities in cirrhosis mortality in urban areas of European cities. Moreover, studies that have analysed socioeconomic inequalities in alcohol-attributable mortality have found it is higher in lower socioeconomic groups in the majority of countries, and is similar in men and women.</p>	<ul style="list-style-type: none"> <li>• World Health Organization Global Hepatitis Report. World Health Organization; Geneva, Switzerland: 2017.</li> <li>• Collins S.E. Associations Between Socioeconomic Factors and Alcohol Outcomes. <i>Alcohol Res. Curr. Rev</i>. 2016;38:83–94. [<a href="#">PMC free article</a>] [<a href="#">PubMed</a>] [<a href="#">Google Scholar</a>]</li> <li>• Santana P., Costa C., Marí-Dell’Olmo M., Gotsens M., Borrell C. Mortality, material deprivation and urbanization: Exploring the social patterns of a metropolitan area. <i>Int. J. Equity Health</i>. 2015;14:1–13. doi: 10.1186/s12939-015-0182-y. [<a href="#">PMC free article</a>] [<a href="#">PubMed</a>] [<a href="#">CrossRef</a>] [<a href="#">Google Scholar</a>]</li> </ul>

	<ul style="list-style-type: none"> <li>• Marí-Dell’Olmo M., Gotsens M., Palència L., Burström B., Corman D., Costa C., Deboosere P., Diez E., Domínguez-Berjón M.F., Dzurova D., et al. Socioeconomic inequalities in cause-specific mortality in 15 European cities. <i>J. Epidemiol. Commun. Health.</i> 2015;69:432–441. doi: 10.1136/jech-2014-204312. [<a href="#">PubMed</a>] [<a href="#">CrossRef</a>] [<a href="#">Google Scholar</a>]</li> </ul>
<p>“Inequality is one of the main contributors to liver disease and a key player in some liver diseases such as alcohol-related liver disease. Inequality plays a double role in impacting both the etiological agents that lead to the development of the disease as well as the access to proper medical and social resources”</p>	<ul style="list-style-type: none"> <li>• Meritxell Ventura-Cots, Ramon Bataller, Jeffrey V. Lazarus, Joan Benach, Juan M. Pericàs, Applying an equity lens to liver health and research in Europe, <i>Journal of Hepatology</i>, 2022.</li> </ul>
<p>“Sex influences on chronic liver disease are cause specific, with men exhibiting a higher risk of primary sclerosing cholangitis, chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma, whereas women exhibit a higher risk of primary biliary cholangitis and autoimmune hepatitis. Alcoholic liver disease is more common among men because men have higher alcohol consumption than women. However, the threshold amount of alcohol that results in alcoholic liver disease in women is half that of men”</p>	<ul style="list-style-type: none"> <li>• Franck Mauvais-Jarvis, Noel Bairey Merz, Peter J Barnes, Roberta D Brinton, Juan-Jesus Carrero, Dawn L DeMeo, Geert J De Vries, C Neill Epperson, Ramaswamy Govindan, Sabra L Klein, Amedeo Lonardo, Pauline M Maki, Louise D McCullough, Vera Regitz-Zagrosek, Judith G Regensteiner, Joshua B Rubin, Kathryn Sandberg, Ayako Suzuki,</li> <li>• Sex and gender: modifiers of health, disease, and medicine, <i>The Lancet</i>, Volume 396, Issue 10250, 2020.</li> </ul>
<p>“Of 17,473 patients with ALD (alcohol-related liver disease), 78% of whom had cirrhosis, 86% had a low or medium-low education levels and only 29% were employed.”</p> <p>“Mortality among the lower educated rose in many countries for conditions linked to smoking (lung cancer, women only) and excessive alcohol consumption (liver cirrhosis).”</p>	<ul style="list-style-type: none"> <li>• Gro Askgaard, Morten Grønbaek, Mette S. Kjær, Anne Tjønneland, Janne S. Tolstrup, Alcohol drinking pattern and risk of alcoholic liver cirrhosis: A prospective cohort study, <i>Journal of Hepatology</i>, Volume 62, Issue 5, 2015, Pages 1061-1067,</li> <li>• Mackenbach JP, Kulhánová I, Menvielle G for the Eurothine and EURO-GBD-SE consortiums, et al Trends in inequalities in premature mortality: a study of 3.2 million deaths in 13 European countries <i>J Epidemiol Community Health</i> 2015;69:207-217.</li> </ul>
<p>“By employment status, the incidence rate per million person-years was 211 (95% CI, 189–236) for employed and 3449 (95% CI, 2785–4271) for unemployed”</p>	<ul style="list-style-type: none"> <li>• Gro Askgaard, Morten Grønbaek, Mette S. Kjær, Anne Tjønneland, Janne S. Tolstrup, Alcohol drinking pattern and risk of alcoholic liver cirrhosis: A prospective cohort study,</li> </ul>

<p>“It has been consistently shown that mortality from ALD is substantially greater for individuals from more disadvantaged socioeconomic classes. While the frequency and levels of consumption are increased in higher-educated groups in some European countries, high-risk drinking patterns leading to alcohol-related harm remain greater in more deprived populations”</p> <p>“In some European countries alcohol now accounts for at least 10% of the socioeconomic inequality in overall mortality”</p>	<p>Journal of Hepatology, Volume 62, Issue 5, 2015, Pages 1061-1067,</p> <ul style="list-style-type: none"> <li>Theresa Hydes, William Gilmore, Nick Sheron, Ian Gilmore, Treating alcohol-related liver disease from a public health perspective, Journal of Hepatology, Volume 70, Issue 2, 2019, Pages 223-236,</li> </ul>
<p>“People living in urban areas experienced higher alcohol-related mortality relative to those living in rural areas, with differences remaining after adjustment for socioeconomic deprivation” (Erskine, et., al.)</p>	<ul style="list-style-type: none"> <li>Erskine, S., Maheswaran, R., Pearson, T. <i>et al.</i> Socioeconomic deprivation, urban-rural location and alcohol-related mortality in England and Wales. <i>BMC Public Health</i> <b>10</b>, 99 (2010). <a href="https://doi.org/10.1186/1471-2458-10-99">https://doi.org/10.1186/1471-2458-10-99</a></li> </ul>
<p>“Within Europe, there is huge heterogeneity between countries in terms of liver deaths, with decreasing mortality rates in Western and Southern Europe since 1970, and high stable or increasing levels across Northern and Eastern European countries”</p> <p>“Rates of alcohol-related mortality are higher in lower educational and occupational groups in all countries. Both relative and absolute inequalities are largest in Eastern Europe, and Finland and Denmark also have very large absolute inequalities in alcohol-related mortality”</p>	<ul style="list-style-type: none"> <li>Mackenbach JP, Kulhánová I, Menvielle G for the Eurothine and EURO-GBD-SE consortiums, et al Trends in inequalities in premature mortality: a study of 3.2 million deaths in 13 European countries <i>J Epidemiol Community Health</i> 2015;69:207-217.</li> <li>Theresa Hydes, William Gilmore, Nick Sheron, Ian Gilmore, Treating alcohol-related liver disease from a public health perspective, Journal of Hepatology, Volume 70, Issue 2, 2019, Pages 223-236,</li> </ul>
<p><b>Non-Alcoholic Fatty Liver Disease (NAFLD)</b></p>	
<p>Available evidence suggests that NAFLD distribution and outcomes show large inequalities by social group. “Non-alcoholic fatty liver disease (NAFLD) affects men and women differently across age groups. Women of reproductive age are protected from NAFLD, with an around 50% decreased risk compared with men. Women of reproductive age with NAFLD are also protected from hepatic fibrosis, hepatocellular carcinoma, and mortality. However, postmenopausal women lose this protection, and premature menopause and bilateral oophorectomy are associated with a higher risk of non-alcoholic fatty liver disease and related complications among women”</p>	<ul style="list-style-type: none"> <li>Talens M, Tumas N, Lazarus JV, Benach J, Pericàs JM. What Do We Know about Inequalities in NAFLD Distribution and Outcomes? A Scoping Review. <i>J Clin Med.</i> 2021 Oct 28;10(21):5019. doi: 10.3390/jcm10215019. PMID: 34768539; PMCID: PMC8584385.</li> <li>Franck Mauvais-Jarvis, Noel Bairey Merz, Peter J Barnes, Roberta D Brinton, Juan-Jesus Carrero, Dawn L DeMeo, Geert J De Vries, C Neill Epperson, Ramaswamy Govindan, Sabra L Klein, Amedeo Lonardo, Pauline M Maki, Louise D McCullough, Vera Regitz-Zagrosek, Judith G Regensteiner,</li> </ul>

<p>Inability to make healthy life-style choices or access safe neighbourhoods for e.g. exercise based on inequalities (income, education, race, gender) are major contributor to chronic fibrosing liver disease and HCC.</p> <p>“Gender constructs probably play a role in sex differences of NAFLD risk, as women follow healthier diets by eating more fruits and vegetables and less fat and meat than men”</p> <p>“Sex differences in response to pharmacological treatment of NAFLD are mostly unknown, which is mainly due to the absence of gender or sex consideration in clinical trial design”</p> <p>Gender-inherent body fat distribution adds to differences in risk HCC risk.</p> <p>Social inequalities contribute to NAFLD.</p>	<p>Joshua B Rubin, Kathryn Sandberg, Ayako Suzuki,</p> <ul style="list-style-type: none"> <li>Rich NE, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, Mayo H, Singal AG. Racial and Ethnic Disparities in Nonalcoholic Fatty Liver Disease Prevalence, Severity, and Outcomes in the United States: A Systematic Review and Meta-analysis. <i>Clin Gastroenterol Hepatol.</i> 2018 Feb;16(2):198-210.e2. doi: 10.1016/j.cgh.2017.09.041. Epub 2017 Sep 29. PMID: 28970148; PMCID: PMC5794571.</li> </ul>
<p><b>Screening for NAFLD and cirrhosis</b></p>	
<p>“The application of case-finding or screening for cirrhosis in Europe is variable and inconsistent, with low levels of awareness about the possible benefits of it among many health-care professionals managing patient groups at high risk of liver disease”.</p> <p>HCC incidence in NASH is lower compared to chronic viral hepatitis and occurs at an older age. Incidence</p> <p>“It has been clearly shown that late diagnosis of chronic liver disease was associated with aetiology; the odds of a late diagnosis were 12 times higher for an individual with alcohol-related liver disease than for an individual with viral hepatitis” (Lancet)</p> <p>“Screening for unhealthy alcohol use in primary care is infrequent and physicians who practise it are also those recognising that controlled drinking should be a key therapeutic goal” (Lancet)</p> <p>Stigma related to alcohol prevents patients with NAFLD and emergent HCC risk to seek medical attention and participate in screening.</p>	<ul style="list-style-type: none"> <li>Karlsen TH, Sheron N, Zelber-Sagi S, et al. The EASL–Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. <i>The Lancet</i> 2021; published online Dec 2.</li> <li>Weinmann A, Alt Y, Koch S, Nelles C, Düber C, Lang H, Otto G, Zimmermann T, Marquardt JU, Galle PR, Wörns MA, Schattenberg JM. Treatment and survival of non-alcoholic steatohepatitis associated hepatocellular carcinoma. <i>BMC Cancer.</i> 2015 Apr 1;15:210. doi: 10.1186/s12885-015-1197-x. PMID: 25884354; PMCID: PMC4407550.</li> <li>Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. <i>Nat Rev Gastroenterol Hepatol.</i> 2021 Apr;18(4):223-238. doi: 10.1038/s41575-020-00381-6. Epub 2020 Dec 21. PMID: 33349658; PMCID: PMC8016738.</li> </ul>
<p><b>Liver cancer screening</b></p>	

<p>“Although management of cirrhosis in primary care is critical and the majority of GPs see people with cirrhosis in their practice, only a minority assume responsibility for hepatocellular carcinoma surveillance and their knowledge of current complex modalities of treatment of hepatocellular carcinoma are understandably low” (Lancet)</p> <p>“In most European centres, hepatocellular carcinoma surveillance falls under the responsibility of secondary care. Although the adherence to hepatocellular carcinoma surveillance programmes in Europe in a published meta-analysis was 70% higher than that in other regions of the world, the true adherence is heterogenous” (Lancet)</p> <p>Screening for NAFLD-related HCC is hampered by obesity as a risk factor for impaired US-performance</p> <p>Low awareness of NAFLD as a risk factor for cirrhotic and non-cirrhotic HCC hampers enrolment of patients in screening programs.</p>	<ul style="list-style-type: none"> <li>• Karlsen TH, Sheron N, Zelber-Sagi S, et al. The EASL–Lancet Liver Commission: protecting the next generation of Europeans against liver disease complications and premature mortality. <i>The Lancet</i> 2021; published online Dec 2.</li> </ul>
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<sup>i</sup> International Agency for Research on Cancer. Liver. Available at: <https://bit.ly/3qNCdEe>, accessed September 2022.

<sup>ii</sup> EASL. *J Hepatol* 2018; 69:182-236

<sup>iii</sup> [https://www.journal-of-hepatology.eu/article/S0168-8278\(22\)03022-7/fulltext](https://www.journal-of-hepatology.eu/article/S0168-8278(22)03022-7/fulltext)

<sup>iv</sup> World Health Organization . Global Hepatitis Report. World Health Organization; Geneva, Switzerland: 2017. [[Google Scholar](#)]

<sup>v</sup> Collins S.E. Associations Between Socioeconomic Factors and Alcohol Outcomes. *Alcohol Res. Curr. Rev.* 2016;38:83–94. [[PMC free article](#)] [[PubMed](#)] [[Google Scholar](#)]

<sup>vi</sup> Santana P., Costa C., Marí-Dell’Olmo M., Gotsens M., Borrell C. Mortality, material deprivation and urbanization: Exploring the social patterns of a metropolitan area. *Int. J. Equity Health.* 2015;14:1–13. doi: 10.1186/s12939-015-0182-y. [[PMC free article](#)] [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]

<sup>vii</sup> Marí-Dell’Olmo M., Gotsens M., Palència L., Burström B., Corman D., Costa C., Deboosere P., Diez E., Domínguez-Berjón M.F., Dzurova D., et al. Socioeconomic inequalities in cause-specific mortality in 15 European cities. *J. Epidemiol. Commun. Health.* 2015;69:432–441. doi: 10.1136/jech-2014-204312. [[PubMed](#)] [[CrossRef](#)] [[Google Scholar](#)]