From Past to Pandemic: Health Disparities in U.S. Hepatobiliary Cancer Mortality Before and During COVID-19

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Hepatobiliary cancers, and the disparities associated with them, reflect a multitude of complex, and often compounding factors rooted within determinants of health in the United States (U.S.). Comprised of a group of etiologically, epidemiologically, and molecularly distinct cancer subsites, hepatobiliary cancers include liver cancer (largely hepatocellular carcinoma [HCC]), intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), gallbladder cancer (GBC), and ampulla of Vater cancer (AVC). HCC, frequently grouped alongside ICC, is by far the most prevalent of the subsites, contributing to an estimated 41,630 new cases and 29,840 deaths in the U.S. in 2024. Exhibiting a male predominance, most HCC patients present with concomitant advanced liver disease, frequently associated with chronic hepatitis B (HBV), chronic hepatitis C (HCV), alcohol-related liver disease (ALD), or metabolic dysfunction associated-steatotic liver disease (MASLD). Several studies have shown increased prevalence and mortality from chronic liver disease among racially and ethnically underrepresented populations, which are similarly reflected in HCC incidence. Recent data from the Surveillance, Epidemiology, and End Results (SEER) program reported a higher burden of HCC among all racial/ethnic groups when compared to non-Hispanic White persons (6.24 per 100,000 persons); notably, American Indian/Alaskan Native (AI/AN) individuals had the highest incidence (17.05), followed by Asian/Pacific Islander (15.66), Hispanic (15.43), and Black (11.23) individuals.

Compared to HCC, biliary tract cancers (BTCs) are much rarer, contributing an estimated 12,350 new cases and 4,530 deaths in the U.S. in 2024. The etiology for most BTCs remains largely unclear, with high geographical variability; nevertheless, gallstones and cholecystitis have consistently been implicated as the primary risk factors for GBC, coinciding with the fact that GBC is the only hepatobiliary cancer with a female predominance. Incidence rates of GBC, ECC, and AVC have been shown to be stable in the U.S. between 2003 and 2018, nevertheless, ICC incidence rose by an annual percent change (APC) of 7.7 (95% CI, 6.9–8.5) and 7.0 (95% CI, 6.0–8.0) for males and females, respectively, during this timeframe. Compared to non-Hispanic White individuals (9.4 per 100,000 persons), BTC rates have repeatedly been shown to be highest among Hispanic (16.6), and Asian/Pacific Islander individuals (13.8); interestingly, the greatest increase in BTC incidence between 2001-2015 was observed among Black individuals (APC=2.78 [95% CI: 2.23 to 3.34]), attributable to increases in all BTC subsites except AVC.

In a recent issue of the Clinical and Molecular Hepatology, Kim and colleagues utilize vital statistics data from the Wide-ranging Online Data from Epidemiologic Research (WONDER) to investigate hepatobiliary cancer mortality reported as the underlying or multiple cause of death. Leveraging the National Cancer Institute’s Joinpoint regression program, the research team evaluated temporal age-standardized mortality trends before and during the COVID-19 pandemic (2018-2023) overall, as well as stratified by race/ethnicity and sex. When analyzing data related to underlying cause of death, the authors found decreased HCC (APC: -1.4 [95%CI: -2.0 to -0.7]) mortality; whilst males generally had higher HCC-related mortality rates, sex stratified analyses further elucidated that the decreasing HCC trends were largely driven by rates among males (APC: -1.9 [95%CI: -2.7 to -1.2]), while no significant changes were noted among females. Further, decreases in age-standardized HCC mortality were observed among all race/ethnic groups, with the most pronounced (albeit not statistically significant) decrease among non-Hispanic AI/AN individuals (APC: -4.7 [95%CI: -9.8 to 0.7]), followed by non-Hispanic Black (APC: -3.9 [95%CI: -6.6 to -1.0]), non-Hispanic Asian (APC: -2.8 [95%CI: -4.3 to -1.3]), Hispanic (APC: -2.2 [95%CI: -4.1 to -0.3]), and then White (APC: -0.6 [95%CI: -1.1 to -0.1]) individuals.
These decreasing mortality trends coincide with reports of decreased incidence of this cancer subsite, believed to largely be attributable to the advent and uptake of direct-acting antiviral agents (DAAs) against HCV infection, the leading etiological factor underlying liver disease and HCC in the U.S.\textsuperscript{7} This fact is further highlighted in the manuscript, with HCV related HCC mortality estimated to be decreasing by 8.5% annually. Etiologic shifts may also explain some of the trends observed in stratified analyses; for instance, HCV prevalence is markedly higher among men and racially/ethnically minoritized populations, consequently, the use of DAAs to elicit sustained virological response may partially explain the decreased mortality trends observed among these groups. Interestingly, when analyzing HCC as the contributing cause of death, the authors noted steep increases before and during the early phases of the COVID-19 pandemic. In the context of HCV, concomitant risk and lifestyle factors, such as low socioeconomic status (SES), HIV/AIDS diagnosis, drug use, homelessness, and type-2 diabetes may have exacerbated the disproportionate effect of COVID-19 on these high-risk individuals who likely already had limited access to necessary screening, prevention, and treatment resources. While stratified analyses were not conducted on HCV-associated HCC mortality as a contributing cause of death, nor were data presented on the other aforementioned factors, it is plausible that the complex interaction of determinants present within the lived experience of these individuals may contribute to the observed trends.

While improved management of HCV infection may partially explain the decreasing HCC incidence and mortality, these trends might be attenuated by increased rates of MASLD. In this manuscript, the authors demonstrate HCC-related mortality due to MASLD to be increasing by 9.7% annually, and with disproportionate effects seen among females. Although only contributing modestly to the underlying causes of HCC cases, prevalence of MASLD is and will continue to be a growing risk factor for HCC. In a recent study utilizing data from the National Health and Nutrition Examination Survey (NHANES; 1999-2018), MASLD prevalence was shown to have significantly increased from 30.8% to 37.7% in adults; factors associated with high MASLD prevalence included male sex, Mexican American ethnicity, being >50 years old, being unmarried, low SES (poverty income ration <130), and having comorbid conditions (chronic disease, overweight/obese, and having poor to fair health)\textsuperscript{8}. With global prevalence estimates reported as high as 30% and growing, MASLD is now the most widespread global chronic liver disease\textsuperscript{9}. Future studies are consequently warranted to further understand the impact of this condition in its own right, as well as in relation to HCC.

In contrast to the trends observed in HCC, ICC as the underlying cause of death increased (APC: 3.1 [95%CI: 1.2 to 4.9]) during the study period, and this increase was noted to be even more pronounced when analyzed as contributing cause of death during the COVID-19 pandemic. Although males had higher mortality rates, trends in ICC appeared similar among males (APC: 2.4 [95%CI: 0.7 to 4.1]) and females (APC: 2.9 [95%CI: 0.2 to 5.7]), with notable increases among Black (APC: 3.8 [95%CI: 1.0 to 6.6]) and White individuals (APC: 3.1 [95%CI: 1.8 to 4.4]). While these results coincide with recent trends in ICC incidence, period specific impacts correlated to the COVID-19 pandemic likely disproportionately impacted BTC mortality rates due to the poor prognosis associated with these cancers, as was seen with AVC mortality (APC: 4.1 [95%CI: 0.5 to 7.9]). Cancer care delivery was undoubtedly affected during the pandemic, with early reports suggesting increased postoperative mortality due to COVID-19\textsuperscript{10}. In addition to presenting with immunosuppression, which is exacerbated by treatment, individuals with cancer frequently have coexisting medical conditions\textsuperscript{11}; additionally, the lack of resources available during the COVID-
19 pandemic intensified adverse conditions among this already vulnerable population, as exemplified by the above-mentioned ‘contributing cause of death’ results. Early detection is paramount in improving cancer patient outcomes, especially in BTC, which confers a five-year relative survival of 15.2%⁵; lack of available healthcare, in conjunction with fear of COVID-19 exposure, and disruptions in employment and health insurance hindered early intervention and treatment, resulting in significant loss of life among these patients¹². While Kim et al. did not present data on stage or treatment, others have demonstrated substantial decreases in newly diagnosed hepatobiliary cancers, alongside consequent increases in advanced stage at diagnosis, especially at the initial phase of the pandemic ¹².

Kim et al. reported GBC mortality to be decreasing, specifically among males (APC: -2.2 [95%CI: -4.2 to -0.2]). GBC, especially at early stages, is frequently asymptomatic or otherwise exhibits nonspecific symptoms. GBC cases are often identified through incidental finding on imaging or through pathology review after cholecystectomy¹³. Nonetheless, cases diagnosed as early as T1b may present with regional or systemic spread¹⁴, stressing the importance of early intervention. During the onset of COVID-19, elective procedures such as cholecystectomy were significantly reduced or postponed; this limitation has likely led to underreporting of GBC incidence, which could have similarly impacted diagnosis on death records. While the report of decreased GBC mortality is plausible, GBC disproportionately effects racially/ethnically underserved groups ⁵, who were hardest hit by the pandemic; therefore, an analysis of GBC as a contributing cause of death would have been informative.

In conclusion, Kim and colleagues present an important update on the state of hepatobiliary mortality before and during the COVID-19 pandemic. Results should be interpreted with caution, largely due to the innate limitations of death record data; nonetheless, future analyses should build upon this, and other bodies of literature related to the pandemic to inform and improve clinical response in the face of emergency, particularly from a health equity lens.
References:


