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The Changing Landscape of Liver Cancer in India: A Comprehensive Analysis of the Global Burden of Disease Study 2023

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ABSTRACT

Background: In India, liver cancer poses a major public health concern, with changing causes and geographical heterogeneity involved. To analyze the most recent trends, we assess the most recent Global Burden of Disease (GBD) 2023 estimates.
Methods: The most recent GBD 2023 (estimates) for India and the 31 States/Union Territories (UTs) from 2019-2023 and a secondary analysis of GBD 2023 (estimates) were conducted. Age Standardised Rate (ASR) of incident, mortality, prevalence and disability-adjusted life years (DALYs) were measured. ASR of the aetiological factors (hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol, non-alcoholic steatohepatitis (NASH), were analysed. Male and female and State-wise variations were assessed along with evidence from 76 publications in a systematic review.
Results: From 2019 to 2023, age-standardized mortality jumped 13.0%, incidence 11.4%, prevalence 10.0%, and DALYs 13.8%. The male burden was 2.1-2.4 times higher than for females. Liver cancer in 2023 was attributed to Hepatitis B (18.3%) of total deaths, followed by alcohol use (13.6%), Hepatitis C (10.2%), and NASH (5.9%). Disparities in mortality were observed by state, with deaths per 100,000 people in Gujarat (2.55) vs. Arunachal Pradesh (33.89). The review noted that HBV's contribution to mortality was decreasing (41.0%, 95% CI 35.8-46.1%), and NAFLD-related burden was increasing (16.9%, 95% CI 12.1-21.7%).
Conclusion: The burden of liver cancer in India has increased. There is a male predominance and there are substantial differences by region. The shift toward metabolic risk factors and the ongoing burden from viral hepatitis indicate the need for regionally-appropriate focused prevention efforts.

Keywords: Hepatocellular carcinoma, India, Global Burden of Disease, liver cancer, epidemiology, mortality, incidence, hepatitis B, hepatitis C, NAFLD

INTRODUCTION

Liver cancer is one of the most common cancers and third leading cause of cancer related mortality worldwide. [1] There is considerable variability in the magnitude of the global burden of liver cancer across the world. Age-standardized incidence of liver cancer varies by more than 20 folds across the world. [2] More than 70% of the incident

cases of liver cancer are reported from the Asia Pacific region, in particular, the East and South East regions. [3]

Recently, the profile of the causes of liver cancer has changed. In the past, especially in the case of high burden countries, liver cancer has been caused by chronic viral hepatitis infection, primarily with the hepatitis B virus (HBV) and hepatitis C virus (HCV). However, now metabolic risk factors have been shown, in addition to those of alcohol related liver disease, to be included in the cause of liver cancer. [4-6] These changes appear to correlate with increasing prevalence of obesity, diabetes and other lifestyle associated risk factors.

India represents a unique epidemiological setting due to its dual burden of both communicable and non-communicable diseases and their associated risk factors. Infections and chronic illnesses have overlapping epidemiological factors. There is also evidence of rising trends of liver cancer in Indian men as a result of changing risk factor exposures Studies have reported wide variation in incidence rates across regions, ranging from low to moderate levels compared to other Asian countries, but with a substantial absolute burden due to the large population size.[7]

India has complex set of risk factors and root illnesses. Of all causes of hepatocellular carcinoma in India, Hepatitis B (HBV) is the most common. The other factors listed in order of their frequency are: Hepatitis C (HCV), Alcohol, Non-alcoholic fatty liver disease (NAFLD), and more recently, due to a shift in metabolic diseases, are viral diseases. [7-9] This highlights the epidemiological transition of disease patterns in the country. The patterns provide clues to the prevention and treatment strategies needed in India. Healthcare access, endemicity of Hepatitis B virus (HBV), metabolic diseases, and alcohol consumption are some of the reasons for the heterogeneous issues depicted in the epidemiological studies of India. In addition, the studies have consistently shown that men are more affected than women. [10] This is mostly due to the exposed behavioral risk factors. There is also a possibility for some biological reasons, which include hormonal differences.

Despite these insights, analyses using the most recent Global Burden of Disease (GBD) 2023 estimates remain limited, particularly with respect to recent trends, state-level variations, and the potential impact of the COVID-19 pandemic. In order to address these gaps, this study therefore aimed to assess the burden of liver cancer in India from 2019 to 2023 using GBD 2023 data, by examining national trends in age-standardized incidence, mortality, prevalence, and DALYs; evaluating sex-specific patterns and male-to-female differences; identifying the contribution of key etiologies including HBV, HCV, alcohol use, and NASH; assessing geographic variation across states and union territories; integrating findings from a systematic review to contextualize etiological transitions; and informing evidence-based strategies for prevention and control.

MATERIALS & METHODS

The Global Burden of Disease Study 2023 (GBD 2023) from the Institute for Health Metrics and Evaluation (IHME) has been used for this analysis. The GBD 2023 is the world's largest systematic health loss quantification reporting effort pertaining to health loss from diseases, injuries, and health risk factors. For this research, we analyzed the data pertaining to India (national) and all 31 Indian states and union territories for the years 2019 to 2023.

The GBD 2023 database is the most recent and comprehensive set of estimates for all major components of the burden of disease, including incidence, prevalence, mortality, and disability-adjusted life years (DALYs). For instance, incidence refers to the number of new cases, and prevalence refers to the number of total existing cases. DALYs refers to years of life lost (YLL) and years lived with a disability (YLD). All estimates

are provided as age-standardized rates (ASR) per 100,000 individuals, with ASR being adjusted to the GBD standard population, and accompanied by a 95% uncertainty interval (UI) to account for the variability of the data and the different complexities of the modeling process.[11]

Liver Cancer Burden

Liver cancer burden is segmented by etiology according to the Global Burden of Disease (GBD) classification system, which includes causes such as hepatitis B, hepatitis C, alcohol consumption, NASH, and other causes, hepatoblastoma, and liver cancer of unspecified origin. To supplement the GBD estimates, data were used from a systematic literature review of 76 studies, including the key meta-analysis of 60 studies from India (n=12,327), and other pertinent analyses at the global and regional levels. [1-5], [8], [9], [12-14]

GBD Methodology

Estimates of the GBD 2023 mortality were synthesized from several data sources, including vital registration, verbal autopsy data, cancer registries, and mortality surveillance data, and were supplemented by ensemble modeling (CODEm) to estimate causes of death. For cancer incidence, registries and hospital data were used, and where data were unavailable, mortality to incidence ratios were used. Incidence and survival estimates were used to derive the prevalence.[11]

The disability-adjusted life years (DALY) were calculated as the sum of years of life lost (YLL) and years lived with disability (YLD) based on standard life expectancy and disability weights. To determine the etiology of liver cancer, methods of comparative risk assessment were used, and population attributable fractions were calculated based on the prevalence of the risk factor, relative risk, and theoretical minimum risk thresholds, while controlling for overlapping risk factors.[11]

Statistical Analysis

For all burden measures, absolute and relative changes in age-standardized rates (ASR) were calculated for the year 2023 and compared to 2019.

Percentage change was calculated as: percentage change in ASR = [ASR (2023)-ASR (2019)/ ASR (2019)] * 100. Analysis was conducted on each year's ASR to look for patterns and breaks in the data, especially during the COVID-19 pandemic.

All analyses were conducted using R software. Trends were assessed descriptively due to modeled estimates. For the analysis by sex, male-to-female ratios were calculated for each indicator and trends were compared over time by sex. For geographic analysis, 2023 state-level mortality rates were ranked and regional clusters in the 4 major zones of India were analyzed to determine the ratio of the highest and lowest mortality rates.

For clinical context, findings were cross-verified with a systematic review and meta-analysis pertaining to hepatocellular carcinoma in India, focusing on the alignment of GBD-derived population attributable fractions with hospital-based etiological fractions. [9] This study combines secondary analysis of GBD 2023 estimates with a narrative synthesis of published literature (n=76 studies)

RESULTS

National Trends in the Burden of Liver Cancer (2019-2023)

Mortality Trends

From 2019 to 2023, age-standardized liver cancer mortality in India increased by 13.0%. It increased from 4.88 (95% UI 3.39-6.68) to 5.52 (95% UI 3.73-7.76) per 100,000 (Table 1). Over this time period, mortality exhibited a fluctuating pattern, with a notable high in 2021 at 5.53 (95% UI 3.78-7.58) per 100,000, before declining in 2022 to 5.25 (95% UI 3.54-7.30) per 100,000, and subsequently increasing again in 2023. [15]

It was found that males had far greater mortality rates than females. For age-

standardized mortality in 2023, males had 7.58 (95% UI 4.53-11.75) per 100,000, whereas females had 3.56 (95% UI 2.09-5.68) per 100,000, giving a male-to-female ratio of 2.13:1. Male mortality increased 13.5% between 2019 and 2023, and female mortality increased 12.7% in the same period.

Table 1. Age-Standardized Liver Cancer Mortality Rates in India, 2019-2023

Year	Both Sexes	Male	Female	M: F Ratio
2019	4.88 (3.39-6.68)	6.68 (4.24-9.78)	3.16 (1.84-4.87)	2.12:1
2020	5.05 (3.50-6.85)	6.99 (4.32-10.21)	3.20 (1.92-4.91)	2.18:1
2021	5.53 (3.78-7.58)	7.89 (4.81-11.41)	3.27 (1.99-5.03)	2.41:1
2022	5.25 (3.54-7.30)	7.24 (4.31-10.71)	3.37 (1.94-5.20)	2.15:1
2023	5.52 (3.73-7.76)	7.58 (4.53-11.75)	3.56 (2.09-5.68)	2.13:1

Note: All rates are per 100,000 population. Values in parentheses represent 95% uncertainty intervals.

Incidence Trends

Between 2019 and 2023, age-standardized liver cancer incidence in India rose by 11.4%. In 2019, the incidence was 5.03 (95% UI 3.61-6.72) per 100,000, and in 2023, the incidence was 5.61 (95% UI 3.80-7.89) per 100,000 (Table 2). The incidence trajectory was characterized by consistent increases, apart from a slight plateau from 2020 to 2021.

Throughout the study period, male incidence rates were 2.2-2.3 times higher than females. In 2023, male age-standardized incidence was 7.78 (95% UI 4.61-12.05) per 100,000 and female age-standardized incidence was 3.53 (95% UI 2.06-5.64) per 100,000. Between 2019 and 2023, males had an 11.0% increase of incidence, and females had a 12.8% increase of incidence. From 2019-2023, females had a higher increase of incidence than males.[15]

Table 2. Age-Standardized Liver Cancer Incidence Rates in India, 2019-2023

Year	Both Sexes	Male	Female	M: F Ratio
2019	5.03 (3.61-6.72)	7.01 (4.49-9.87)	3.13 (1.88-4.77)	2.24:1
2020	5.11 (3.53-6.93)	7.12 (4.40-10.39)	3.17 (1.89-4.80)	2.25:1
2021	5.20 (3.61-7.04)	7.24 (4.44-10.47)	3.24 (2.02-4.92)	2.24:1
2022	5.33 (3.59-7.39)	7.41 (4.38-10.95)	3.34 (1.93-5.09)	2.22:1
2023	5.61 (3.80-7.89)	7.78 (4.61-12.05)	3.53 (2.06-5.64)	2.20:1

Note: All rates are per 100,000 population. Values in parentheses represent 95% uncertainty intervals.

Prevalence Trends

From 2019 to 2023, India's age-standardized prevalence of liver cancer jumped 10%. Liver cancer prevalence in 2019 was 5.76 (95% UI 4.06-7.86) and it rose to 2023's 6.34 (95% UI 4.34-9.13) per 100,000, (Table 3).[15] Prevalence showed consistent upward trends over the years and reflected increasing incidence in prevalence.[15]

Prevalence was 2.4 times higher in males as compared to females. In 2023, males had 9.02 (95% UI 5.48-13.70) per 100,000 and females had 3.73 (95% UI 2.18-5.96) per 100,000.[15] The male to female prevalence ratio maintained consistent stability of approximately 2.4:1 for all years.[15]

Table 3. Age-Standardized Liver Cancer Prevalence Rates in India, 2019-2023

Year	Both Sexes	Male	Female	M: F Ratio
2019	5.76 (4.06-7.86)	8.15 (5.21-11.74)	3.43 (2.09-5.18)	2.38:1
2020	5.89 (4.00-8.17)	8.37 (5.13-12.40)	3.48 (2.14-5.38)	2.40:1
2021	5.94 (4.07-8.20)	8.45 (5.15-12.37)	3.50 (2.19-5.49)	2.41:1
2022	6.03 (4.07-8.38)	8.58 (5.24-12.81)	3.55 (2.14-5.63)	2.42:1
2023	6.34 (4.34-9.13)	9.02 (5.48-13.70)	3.73 (2.18-5.96)	2.42:1

Note: All rates are per 100,000 population. Values in parentheses represent 95% uncertainty intervals.

Disability-Adjusted Life Years (DALYs)

From 2019 to 2023, age-standardized DALYs due to liver cancer in India rose 13.8%. DALYs in 2019 were 132.94 (95% UI 92.70-181.50) and rose to 151.27 (95% UI 101.87-212.08) per 100,000 in 2023 (Table 4). DALY trends showed significant yearly variation, most notably a peak in 2021 of 155.39 (95% UI 105.79-214.07) per 100,000, with a following drop in 2022 and another rise in 2023. [15]

Across the entire time series, the DALY rates for males outnumbered those for females by a factor of 2.3 to 2.6. The 2023 male age-standardized DALYs were 212.28 (95% UI 125.21-328.71) per 100,000 as opposed to 91.51 (95% UI 52.90-145.84) per 100,000 for females, thus the male to female ratio is 2.32:1. The male to female DALY ratio reached its peak in 2021, with a ratio of 2.63:1. This may signify the varying effects of the COVID-19 pandemic in relation to the diagnosis and treatment of liver cancer.[15]

Table 4. Age-Standardized DALYs for Liver Cancer in India, 2019-2023

Year	Both Sexes	Male	Female	M: F Ratio
2019	132.94 (92.70-181.50)	185.72 (117.36-270.97)	80.93 (47.07-124.42)	2.29:1
2020	137.81 (95.27-187.83)	194.14 (120.20-283.63)	82.45 (49.33-125.82)	2.35:1
2021	155.39 (105.79-214.07)	225.95 (137.82-326.87)	86.00 (52.38-131.21)	2.63:1
2022	143.75 (96.99-200.53)	202.07 (118.54-299.29)	86.70 (50.00-132.33)	2.33:1
2023	151.27 (101.87-212.08)	212.28 (125.21-328.71)	91.51 (52.90-145.84)	2.32:1

Note: All rates are per 100,000 population. Values in parentheses represent 95% uncertainty intervals.

Etiological Contributions to Liver Cancer Burden

Etiological Distribution in 2023

From the age-standardized mortality rates per specific cause with respect to the year 2023, the mortality attributable to the hepatitis B virus (HBV) was the highest with a total of 18.3% of the total liver cancer deaths (1.01 per 100,000, 95% UI 0.66-1.44) (Table 5). Alcohol consumption was the second largest cause of death, accounting for 13.6% (0.75 per 100,000, 95% UI 0.50-1.09), followed by Hepatitis C Virus (HCV) at 10.2% (0.56 per 100,000, 95% UI 0.38-0.81), and Non-Alcoholic Steatohepatitis (NASH) at 5.9% (0.33 per 100,000, 95% UI 0.22-0.47). [15]

Notably, 50.0% of liver cancer deaths were classified as "Liver cancer" without specific etiological attribution in the GBD framework (2.76 per 100,000, 95% UI 1.91-3.79) [15]. This category represents cases where specific risk factor attribution could not be definitively established, potentially including cases with multiple overlapping risk factors or insufficient data for attribution. [15]

Table 5. Age-Standardized Liver Cancer Mortality by Etiology in India, 2023

Cause	Rate per 100,000 (95% UI)	Percentage of Total
Liver cancer (unspecified)	2.76 (1.91-3.79)	50.0%
Liver cancer due to hepatitis B	1.01 (0.66-1.44)	18.3%
Liver cancer due to alcohol use	0.75 (0.50-1.09)	13.6%
Liver cancer due to hepatitis C	0.56 (0.38-0.81)	10.2%
Liver cancer due to NASH	0.33 (0.22-0.47)	5.9%
Liver cancer due to other causes	0.10 (0.07-0.15)	1.8%
Hepatoblastoma	0.01 (0.01-0.01)	0.2%
Total	**5.52 (3.73-7.76)**	**100.0%**

Note: Rates are age-standardized per 100,000 population for both sexes combined.

Temporal Trends in Etiological Contributions (2019-2023)

From 2019-2023, there were relative stability and minor yearly fluctuation in the proportional distribution of causes of liver

cancer deaths (Table 6). The liver cancer deaths that were caused by HBV increased from 0.88 (2019) to 1. 01 (2023) per 100,000 (14.8 % increase) and sustained proportional contributions of 17.9 - 18.6% [15]. The liver cancer deaths caused by alcohol increased from 0.67 (2019) to 0.75 (2023) per 100,000 (11.9 % increase) with proportional contributions of 13.5 - 13.8%.[15]

Death by HCV increased from 0.51 per 100,000 (2019) to 0.56 per 100,000 (2023, 9.8% increase) and their proportional contribution decreased from 10.5 % to 10.2 % [15]. NASH-attributable mortality from liver cancer increased from 0.29 per 100,000 (2019) to 0.33 per 100,000 (2023, 13.8 % increase) and proportionally contributed approximately 5.9 % to liver cancer deaths. [15]

Table 6. Temporal Trends in Etiological Contributions to Liver Cancer Mortality, 2019-2023

Cause	2019	2020	2021	2022	2023	% Change
HBV	0.88 (17.9%)	0.90 (17.9%)	1.03 (18.6%)	0.96 (18.3%)	1.01 (18.3%)	+14.8%
Alcohol	0.67 (13.7%)	0.70 (13.8%)	0.76 (13.8%)	0.71 (13.5%)	0.75 (13.6%)	+11.9%
HCV	0.51 (10.5%)	0.53 (10.4%)	0.54 (9.9%)	0.54 (10.2%)	0.56 (10.2%)	+9.8%
NASH	0.29 (5.9%)	0.30 (5.9%)	0.32 (5.7%)	0.31 (5.9%)	0.33 (5.9%)	+13.8%
Other	0.09 (1.8%)	0.09 (1.8%)	0.10 (1.8%)	0.10 (1.8%)	0.10 (1.8%)	+11.1%

Note: Rates are age-standardized per 100,000 population for both sexes combined. Percentages represent proportional contribution to total liver cancer mortality.

Integration with Systematic Review Evidence

In-depth analysis of 60 Indian hospital-based studies (n=12,327 HCC patients) systematic review and meta-analysis HCC patients explored the relation of HCC and HBV positivity [9]. The pooled percentage of Indian HCC cases with HBV positivity was 41.0% (95% CI 35.8-46.1%) which is significantly greater than the GBD attributable fraction of 18.3%. This reflects differences in the study approaches. While GBD considers methodological population attributable fractions which account the background prevalence and relative risks, hospital-based studies consider marker (presence of HBsAg) positivity. [9], [15]

The meta-analysis also examined the pooled HCV positivity which was 20.3% (95% CI 17.0-23.6%) and alcohol use 19.0% (95% CI 15.6-22.4%) and NAFLD 16.9% (95% CI 12.1-21.7%) of the cases. Notably, the meta-regression analysis showed significant temporal trends from 1990-2023 which demonstrated declining HBV proportions and increased NAFLD proportions in hospital-based series. [9] The complexity of the etiological attribution is highlighted in the approximately 7.9% (95% CI 5.8-10.0%) of cases with multiple etiologies.[9]

Geographic Variations Across Indian States

State-Level Mortality Patterns in 2023

Geographic analysis of age-standardized liver cancer mortality across 31 states and union territories for 2023 has shown significant geographic heterogeneity (Table 7). [15] Arunachal Pradesh has the highest mortality rate of 33.89 (95% UI 22.26-49.02) per 100,000 and is more than six times the national average. [15] Other high burden states are Sikkim (11.20 per 100,000), Mizoram (11.17 per 100,000) and 11.13 and 8.47 per 100,000); respectively, Telangana and Andhra Pradesh. [15]

Contrarily, Gujarat has the lowest mortality rate of 2.55 (95% UI 1.67-3.81) per 100,000 followed by 2.91, 3.02, 3.71 and 3.81 per 100,000 mortality rates in Tamil Nadu, Maharashtra, Tripura, and Punjab, respectively. The difference in mortality between states is 13.3 times, translating to massive geographic disparity of state-wise mortality. [15]

Table 7. State-Level Age-Standardized Liver Cancer Mortality Rates in India, 2023

	State/UT	Mortality Rate (95% UI)
Highest Burden States		
1	Arunachal Pradesh	33.89 (22.26-49.02)
2	Sikkim	11.20 (7.46-16.41)
3	Mizoram	11.17 (7.21-16.40)
4	Telangana	11.13 (7.18-16.31)
5	Andhra Pradesh	8.47 (5.28-12.71)
6	Jharkhand	7.92 (5.15-12.04)
7	Nagaland	7.92 (5.30-11.69)
8	Chhattisgarh	7.53 (4.89-10.80)
9	Meghalaya	7.12 (4.66-10.71)
10	Bihar	7.06 (4.57-10.41)
National Average	**India**	**5.52 (3.73-7.76)**
Lowest Burden States		
22	Himachal Pradesh	4.64 (3.02-6.84)
23	Delhi	4.74 (3.25-6.83)
24	Madhya Pradesh	4.95 (3.20-7.35)
25	Jammu & Kashmir and Ladakh	5.15 (3.29-7.79)
26	Other Union Territories	5.18 (3.31-7.76)
27	Punjab	3.81 (2.52-5.48)
28	Tripura	3.71 (2.45-5.34)
29	Maharashtra	3.02 (2.19-3.97)
30	Tamil Nadu	2.91 (2.16-3.88)
31	Gujarat	2.55 (1.67-3.81)

Note: All rates are age-standardized per 100,000 population for both sexes combined.

Evidence of geographic clustering of high burden states is shown in the northeastern states (Arunachal Pradesh, Sikkim, Mizoram, Nagaland, and Meghalaya) which have extremely high mortality. Endemicity is usually high with HBV in northeastern regions as supported by seroprevalence studies. [16] There is also an above average burden in southern states of Telangana and Andhra Pradesh, which is possibly attributed to high alcohol use and other metabolic risk factors. [9], [15]

States like Gujarat, Maharashtra, and Tamil Nadu show lesser mortality than other regions and this could be attributed to better health care and lesser viral hepatitis. [15,16] Prevention and control schemes must be assigned to specific states to aid in greater control of mortality.[17]

Sex-Specific Patterns and Male Predominance

Consistent Male-to-Female Ratios

Across the three major indicators—mortality, incidence, and DALYs—males consistently showed higher burden than females. [15] Their ratio in mortality lies between 2.12:1 and 2.41:1, 2.20:1 and 2.25:1 in incidence, 2.38:1 and 2.42:1 in prevalence, 2.29:1 and 2.63:1 in DALYs. The study period reflects remarkable consistency, save for one instance in 2021 where DALYs of males peaked at 2.63:1. [15] Risk factor prevalence among men such as tobacco and alcohol use, and chronic HBV infections explain the significant male excess. Estrogen could be protective in liver cancer and other biological differences could account for the remaining gap. [7], [9], [10]

Sex-Specific Temporal Trends

Both males and females experienced increasing burden from 2019 to 2023, though with slightly different trajectories. Male mortality increased 13.5% (from 6.68 to 7.58 per 100,000), while female mortality increased 12.7% (from 3.16 to 3.56 per 100,000). For incidence, males experienced an 11.0% increase compared to 12.8% in females, suggesting potentially faster growth in female incidence rates. [15]

The slightly faster increase in female incidence may reflect changing risk factor

profiles, including rising obesity and metabolic syndrome prevalence among Indian women, as well as potential increases in alcohol consumption in some demographic groups. [17-19]

DISCUSSION

Between 2019 and 2023, the rise of liver cancer burden in all 4 of the measured metrics (mortality, incidence, prevalence, and DALYs) has been consistent in India. This shows that the prevention and control methods India needs to strengthen and adapt innovatively to control the burden of the infectious and emerging metabolic causes of liver cancer.

It is important to note the sustained male predominance across all burden indicators. Studies have attributed this disparity to greater male exposure to known risk factors such as alcohol use, tobacco use, and HBV infection, as well as some biological factors, such as certain hormonal and immune response differences.[10], [20-23], The long-lasting nature of this trend underscores the importance of integrating gender into prevention approaches.

HBV continuing to be the highest contributor to the burden of liver cancer in India has been confirmed through the etiological distribution. Alcohol use, HCV, and NASH are also significant contributors, and therefore, a change to a multifactorial risk profile is occurring. India's path is unique when compared to many high-income countries, as a result of effective HBV vaccination and HCV antiviral therapies, the burden of liver cancer in these countries has levelled off or even declined.[1], [2], [24-27] India's rising trends highlight the need for improvement in vaccination, screening, and treatment, especially in viral hepatitis. While the major driving factor is still viral hepatitis, the increasing contribution of metabolic factors is indicative of the continuing epidemiological transition related to urbanization, sedentary lifestyle, and dietary habits. [28-30]

The impacts of rising metabolic risk factors such as NAFLD/NASH carry considerable significance. Given the increasing prevalence of obesity and diabetes in the country, the metabolic triggers of liver cancer will likely increase in the years to come.[29], [30], [32-33] Thus, it is imperative to incorporate liver cancer prevention into the existing frameworks of non-communicable disease (NCD) control. [31-33]

The high and persistent mortality-to-incidence ratio indicates poor survival outcomes, which is likely due to late-stage diagnoses and a lack of access to specialized treatment. Research has identified inadequate knowledge and awareness, the absence of organized high risk population surveillance, and health systems barriers as contributory factors for late detection and poor treatment outcomes.[7], [21] Therefore, it is necessary to improve early detection to promote further advanced screening activities among high-risk populations.

Marked geographic heterogeneity was evident, with state-level mortality rates exhibiting wide-ranging extremes. Northeastern states showed the highest burden, possibly due to greater HBV endemicity, alcohol-related cultural behavior, and healthcare accessibility.[16], [34-35] On the other hand, western and southern states have reported healthcare system, early diagnosis, and risk factor-controlled barriers. These findings call for place-based strategies and not standard strategies at the country's level.

Gender-based differences in immune response and hormonal regulation may contribute to the higher burden of liver cancer observed in men, with estrogen potentially offering a protective effect. Additionally, gender disparities in healthcare access and utilization patterns further influence disease detection and outcomes between males and females. [36-38]

The COVID-19 pandemic is likely to have affected the healthcare system in a way that the observed trends can be attributed to the disruptions in healthcare delivery, such as the postponement of diagnoses and

treatments. Previous studies have suggested that such disruptions may have led to the estimations of the cancer burden during the studied time epochs. [39], [40] These results demonstrate the need for a health system that is built to endure a public system failure and also provides the basic health services during that time.

In terms of policy, a system-wide, multidisciplinary, and collaborative strategy is vital. This encompasses the optimization of the HBV vaccination drive, along with the expansion of the HCV screening and treatment program, the introduction of a robust framework for the regulation of alcohol consumption, and the provision of support for metabolic risk factors through structured lifestyle modifications. Importantly, the cancer registries, the health system, and the cancer treatment available to the public at a reduced cost through the improvement of all components listed here will contribute to better results. [41–46]

Overall, the findings underscore the need for a dual strategy addressing both infectious and metabolic determinants of liver cancer. Tailored, region-specific interventions combined with strengthened health systems will be essential to reduce the growing burden in India.

CONCLUSION

There is a rising concern of liver cancer in India, particularly with the continued increasing male predominance, large contrasts in affected regions, and evolving causes of liver cancer. Viral hepatitis, specifically HBV, continues to be a significant problem; however, the increasing metabolic risk factors is significant and indicative of an epidemiological transition. This phenomenon is a consequence of the dual burden and requires, comprehensive, specific, and strategically assembled interventions. This includes the provision of vaccines, the elimination of viral hepatitis, the regulation of alcohol consumption, and the management of metabolic risks. To reverse the trend of liver cancer in India, in addition to the aforementioned actions, a system for the prompt identification of cases and the strengthening of healthcare systems where necessary are required. The recommendations are critical for the formulation of a policy framework and the identification of operational strategies to manage the growing problem of liver cancer in India.

Declaration by Authors

Ethical Approval: This study involved the use of publicly accessible aggregate data from the GBD 2023 database and the literature. No data on individual patients were obtained. Therefore, ethical approval is not needed for this type of secondary data analysis.

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