

ORIGINAL ARTICLE

Alcohol-Related Liver Disease, Followed by Metabolic Dysfunction-Associated Steatotic Liver Disease, Emerges as the Fastest-Growing Aetiologies for Primary Liver Cancer in the United States

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ABSTRACT

Objective: Primary liver cancer (PLC) is projected to be the third leading cause of cancer mortality in the United States in 2040. We examine the burden of PLC in the United States, stratified by sex, state and aetiological risk factors.

Methods: Data on PLC prevalence, incidence, death and disability-adjusted life years (DALYs) were extracted from the Global Burden of Disease Study 2021. Changes in these parameters were calculated using the Joinpoint regression model.

Abbreviations: ALD, alcohol-related liver disease; APC, annual percent change; ASDALYs, age-standardised disability-adjusted life years; ASDR, age-standardised death rate; ASIR, age-standardised incidence rate; ASPR, age-standardised prevalence rate; ASR, age-standardised rate; CI, confidence interval; DALYs, disability-adjusted life years; GBD, Global Burden of Disease; GHDx, Global Health Data Exchange; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction and alcohol-associated liver disease; PLC, primary liver cancer; PNPLA3, patatin-like phospholipase domain containing 3; SEER, Surveillance, Epidemiology and End Results; UI, uncertainty interval; WHO, World Health Organization.

Pojasorn Danpanichkul and Kwanjit Duangsonk shared co-first authorship.

Ju Dong Yang and Karn Wijarnpreecha contributed equally to this study and co-senior authors.

Results: There were 47,970 cases, 31,450 incident cases, 24,770 deaths and 576,920 DALYs from PLC in the United States. The highest prevalence (16,980), incidence (12,040), death (9840) and DALYs (213,410) from PLC were due to chronic hepatitis C virus infection. From 2000 to 2021, PLC incidences increased by 141%, and PLC deaths increased by 136%. Age-standardised incidence rates (ASIRs) and death rates (ASDRs) per 100,000 population for PLC increased, primarily driven by alcohol-related liver disease (ALD) (ASIR: annual percent change [APC]: +2.40%; ASDR: APC: +2.22%) and metabolic dysfunction-associated steatotic liver disease (MASLD) (ASIR: APC: +2.32%; ASDR: APC: +2.04%).

Conclusion: The burden of PLC in the United States has risen in the past two decades, driven mainly by ALD and followed by MASLD. These findings offer policymakers an accurate assessment of the PLC burden and emphasise the need for targeted risk factor mitigation, especially regarding alcohol related policy.

1 | Introduction

Primary liver cancer (PLC) is a leading cause of cancer-related mortality worldwide [1, 2]. Hepatocellular carcinoma (HCC) is the most common primary liver malignancy, accounting for over 75%–85% of PLCs. Other forms of liver cancer, such as cholangiocarcinoma and angiosarcoma, also contribute to the overall burden of liver cancer cases [3, 4]. Alarming, in the United States, PLC is estimated to surpass colorectal and breast cancer to rank as the third most common cause of cancer-related deaths in 2040 [5]. The predominant aetiological factors for PLC include hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-related liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD) [4].

Although chronic HBV and HCV infections contribute to the highest burden of HCC, other factors have gained prominence. Advances in vaccination coverage and the availability of highly effective nucleotide analogs have contributed to a gradual decline in HBV-related HCC [6–8], and the introduction of direct-acting antiviral agents led to marked reductions in HCV burden. Concurrently, the rising prevalence of metabolic diseases and MASLD has led to a rise in metabolic dysfunction-associated steatohepatitis (MASH) [9]. Furthermore, increased global alcohol consumption per capita leads to an increase in ALD [10]. Consequently, the epidemiological landscape of HCC is undergoing rapid transformation due to these multifaceted factors [11, 12]. Although cholangiocarcinoma does not have an attributable cause in many cases, risk factors include the presence of cirrhosis, metabolic dysfunction and alcohol misuse. Indeed, several studies have shown increases in cholangiocarcinoma burden over the last several years [13, 14].

Given the evolving epidemiology of PLC, continuous monitoring of its burden is crucial. However, updated epidemiological data in the United States have not yet been reported [15]. Understanding the evolving trends of PLC can enhance public awareness of its risks and inform health policies. Herein, we present temporal trends in PLC incidence, mortality and disability-adjusted life years (DALYs) within the United States spanning the period from 2000 to 2021. Additionally, although numerous studies have utilised the Surveillance, Epidemiology and End Results (SEER) programme to report on PLC epidemiology, SEER lacks data on the aetiological causes of PLC. In contrast, the GBD study provides detailed aetiological information for each type of PLC [16, 17].

2 | Methods

2.1 | Data Source

This study utilised data from the Global Burden of Disease (GBD) 2021, a comprehensive effort to estimate the burden of 371 diseases and 88 risk factors across 204 countries/territories. Annual frequencies and age-standardised rates (ASRs) of PLC-related prevalence, incidence, mortality and DALYs from 2000 to 2021, stratified by sex and state, were obtained from the Global Health Data Exchange (GHDx) query tool (<http://ghdx.healthdata.org/gbd-results-tool>), maintained through ongoing multinational collaboration and coordinated by the Institute for Health Metrics and Evaluation [15].

2.2 | Estimation Methods

The general estimation methods for the GBD 2021 and the methods for estimating the burden of PLC have been previously detailed. Data were sourced from population-based cancer registries, vital registration systems and verbal autopsy studies. The ICD-10 codes used by GBD 2021 for PLC were C22.0–C22.8, with a portion of C22.9 reflecting PLC. The GBD 2021 demographic analysis enhanced GBD 2019 by incorporating additional data sources and refined methods to update estimates of mortality, life expectancy and population size at global, regional, national and subnational levels from 1950 to 2021 [15]. For the first time in the GBD cycle, the GBD 2021 database provided the data not only for ALD, HBV, HCV, MASLD and other aetiologies but also provided data for hepatoblastoma as well [15]. To estimate the proportions of liver cancer cases attributed to the six aetiology groups in the GBD, the GBD collaborators conducted a systematic literature search using PubMed. They included only population-based studies that provided data on the contribution of liver cancer aetiologies. Cases labelled as ‘cryptogenic’, ‘idiopathic’ or ‘unknown’ were categorised under ‘other causes’, along with other liver disease aetiologies such as haemochromatosis. The proportions of liver cancer attributed to each of the specific risk factors were calculated for each study, and these proportions were pooled and used in distinct DisMod-MR 2.1 models (a Bayesian meta-regression model) to determine the share of liver cancers caused by the different liver disease aetiologies. When multiple risk factors were reported for individual patients, the risk factors were assigned proportionally. These estimated proportions were then used to break down the total liver cancer estimates by their respective aetiologies. Since the proportion models were run independently, the final models were scaled to sum to 100% within each age, sex, year and location

by dividing each proportion by the total sum [18]. Statistical methods were applied to reduce data heterogeneity, comprising misclassification correction, garbage code redistribution and noise reduction algorithms. Mortality was estimated using the Cause of Death Ensemble model (CODEm), a Bayesian geospatial regression analysis, by age, sex, location and year. Incidence was derived by dividing mortality estimates by mortality-to-incidence ratio estimates. DALYs were calculated as the sum of years of life lost and years lived with disability [15].

2.3 | Data and Statistical Analysis

Estimates for the frequency of cases and deaths were reported with 95% uncertainty intervals (UIs), represented as the 2.5th and 97.5th ranked values across all 1000 draws from a posterior distribution. ASRs were derived using the direct method to the GBD 2019 population estimate. The change in any category between 2000 and 2021 was calculated as follows: (value in 2021—value in 2000)/value in 2000. For changes in ASRs over time, we calculated the annual percent change (APC) and 95% confidence interval (CI) in ASRs using the Joinpoint regression programme, Version 4.6.0.0 (Statistical Research and Applications Branch, National Cancer Institute, Bethesda, MD, USA). An increasing trend was considered when the annualised rate of change and the lower boundary of its 95% CI were both positive, whereas a decreasing trend was identified when the annualised rate of change and the upper boundary were negative. In addition to APC from 2000 to 2021, since the direct-acting antiviral agents for HCV were launched in 2013, we, therefore, analysed the burden of PLC by aetiology from 2015 to 2021 [19].

3 | Results

3.1 | Burden of PLC in the United States in 2021

In 2021, there were 47,970 cases (95% UI: 45,240–49,850), 31,450 incident cases (95% UI 29,170 to 32,720), 24,770 deaths (95% UI 22,900 to 25,830) and 576,920 DALYs (95% UI: 546,180 to 597,640) attributable to PLC in the United States (Table 1, Figure 1A–C and Table S1). The estimated age-standardised prevalence rate (ASPR), age-standardised incidence rate (ASIR), age-standardised death rate (ASDR) and age-standardised DALYs (ASDALYs) of PLC were 9.31 (95% UI 8.85 to 9.65), 5.58 (95% UI 5.20 to 5.79), 4.24 (95% UI 3.94 to 4.42) and 106.24 (95% UI 101.12 to 110.00), respectively (Table 1, Figure 1D–F and Table S1). Between 2000 and 2021, there was a 141% increase in the number of incident PLC cases, a 136% increase in PLC deaths and a 123% increase in DALYs. During this period, ASPR, ASIR, ASDR and ASDALYs due to PLC each increased overall, with an estimated APC of 2.17% (95% CI 2.04% to 2.29%), 2.01% (95% CI 1.88% to 2.15%), 1.82% (95% CI 1.28% to 2.36%) and 1.65% (95% CI 1.16% to 2.15%), respectively (Table 1 and Table S1).

3.2 | Burden of PLC in the United States in 2021, by Sex

Table 1 summarises the estimated frequencies of PLC incident prevalence, incident cases, death and DALYs, along with their

rates (ASPR, ASIR, ASDR and ASDALYs), stratified by sex. Males had a higher frequency of prevalence (2.71 times higher in males), incident cases (2.23 times higher in males), deaths (1.96 times higher in males) and DALYs (2.21 times higher in males) in 2021 compared to females. Between 2000 and 2021, ASPR increased in females (APC 2.00%, 95% CI 1.85% to 2.14%) and males (APC 2.23%, 95% CI 2.14% to 2.33%), and ASIR increased in both females (APC 1.88%, 95% CI 1.76% to 1.99%) and males (APC 2.04%, 95% CI 1.89% to 2.19%). ASDR increased in both females (APC 1.69%, 95% CI 1.41% to 1.96%) and males (APC 1.82%, 95% CI 1.21% to 2.43%). ASDALYs increased in both females (APC 1.65%, 95% CI 1.37% to 1.92%) and males (APC 1.60%, 95% CI 1.12% to 2.09%; Table 1 and Table S1).

3.3 | Burden of PLC in the United States in 2021, by Aetiology

The frequency of incident PLC cases, deaths, DALYs, ASIR, ASDR and ASDALYs are summarised in Table 1. In 2021, HCV accounted for the highest prevalence (38%), followed by ALD (31%), HBV (12%), MASLD (11%), other causes (8%) and hepatoblastoma (0.5%). HCV accounted for 38% of liver cancer incident cases, followed by ALD (31%), HBV (11%), MASLD (11%), other causes (8%) and hepatoblastoma (0.5%). Similarly, HCV accounted for the largest number of PLC deaths in 2021 (40%), followed by ALD (30%), MASLD (11%), HBV (11%), other causes (8%) and hepatoblastoma (0.2%). The largest proportion of PLC-associated DALYs in 2021 was due to HCV (37%), followed by ALD (31%), HBV (12%), MASLD (10%), other causes (9%) and hepatoblastoma (0.6%).

From 2000 to 2021, the ASIR, ASDR and ASDALYs increased in all aetiologies, with ALD-related PLC showing the greatest increase in ASIR (APC 2.40%, 95% CI 2.18% to 2.62%) and ASDR (APC 2.22%, 95% CI 1.70% to 2.74%), whereas ASDALYs increased the most in MASLD (APC 2.08%, 95% CI 1.87% to 2.29%; Table 1 and Figure 2A–D). ASPR, on the other hand, showed the highest increase in MASLD (APC 2.73%, 95% CI 2.54 to 2.93%; Table S1). The burden of PLC from 2015 to 2021 is detailed in Table 2. Briefly, the ASIR from HBV-related PLC remained stable, whereas those from ALD (1.81% vs. 2.40%), HCV (0.56% vs. 1.98%), MASLD (0.88% vs. 2.32%) and other causes (1.70% vs. 1.77%) increased at a lower degree compared to the period from 2000 to 2021. ASDR and ASDALYs for PLC from HBV, HCV and MASLD remained stable, whereas ASDR and ASDALYs from PLC due to ALD and other aetiologies continued to rise from 2015 to 2021 (Table 2).

3.4 | Burden of PLC in the United States in 2021, by State

Figure 3A and Table S2 summarise the estimated frequencies of PLC incident cases and their ASIR in each state and the District of Columbia. In 2000, only two states had ASIRs exceeding 5.0: Hawaii (ASIR 5.91) and the District of Columbia (ASIR 5.36). Between 2000 and 2021, all states (including the District of Columbia), except New Jersey, had a significant increase in ASIR. The fastest increases in ASIR were

TABLE 1 | Incidence, death, disability-adjusted life years and age-standardised rates from 2000 to 2021 in patients with primary liver cancer, stratified by sex and aetiology.

	Incidence				Death				DALYs			
	2021 number (95% UI)	2021 ASIR per 100,000 (95% UI)	2000 to 2021 APC (95% CI)	<i>p</i>	2021 number (95% UI)	2021 ASDR per 100,000 (95% UI)	2000 to 2021 APC (95% CI)	<i>p</i>	2021 number (95% UI)	2021 ASDALYs per 100,000 (95% UI)	2000 to 2021 APC (95% CI)	<i>p</i>
Both	31,450 (29,170 to 32,720)	5.58 (5.20 to 5.79)	2.01 (1.88 to 2.15)	<0.001	24,770 (22,900 to 25,830)	4.24 (3.94 to 4.42)	1.82 (1.28 to 2.36)	<0.001	576,920 (546,180 to 597,640)	106.24 (101.12 to 110)	1.65 (1.16 to 2.15)	<0.001
By sex												
Female	9740 (8770 to 10,260)	3.19 (2.92 to 3.34)	1.88 (1.76 to 1.99)	<0.001	8370 (7450 to 8870)	2.59 (2.34 to 2.73)	1.69 (1.41 to 1.96)	<0.001	179,860 (165,780 to 188,120)	62.60 (58.45 to 65.08)	1.65 (1.37 to 1.92)	<0.001
Male	21,710 (20,340 to 22,670)	8.27 (7.78 to 8.62)	2.04 (1.89 to 2.19)	<0.001	16,410 (15,420 to 17,140)	6.13 (5.76 to 6.4)	1.82 (1.21 to 2.43)	<0.001	397,050 (378,190 to 413,320)	154.41 (147.53 to 160.46)	1.6 (1.12 to 2.09)	<0.001
By aetiology												
ALD	9660 (8500 to 10,980)	1.69 (1.48 to 1.91)	2.4 (2.18 to 2.62)	<0.001	7410 (6500 to 8420)	1.26 (1.11 to 1.43)	2.22 (1.7 to 2.74)	<0.001	178,040 (155,920 to 202,460)	31.94 (27.99 to 36.4)	1.98 (1.36 to 2.60)	<0.001
HBV	3570 (2970 to 4180)	0.68 (0.58 to 0.79)	1.3 (1.19 to 1.42)	<0.001	2640 (2190 to 3110)	0.49 (0.41 to 0.57)	1.09 (0.88 to 1.31)	<0.001	70,550 (59,080 to 83,220)	14.25 (12.22 to 16.66)	0.85 (0.65 to 1.06)	<0.001
HCV	12,040 (10,580 to 13,410)	2.05 (1.81 to 2.28)	1.98 (1.72 to 2.24)	<0.001	9840 (8600 to 10,990)	1.64 (1.44 to 1.83)	1.79 (1.38 to 2.22)	<0.001	213,410 (189,530 to 238,710)	37.33 (33.14 to 41.64)	1.64 (1.26 to 2.02)	<0.001
MASLD	3380 (2850 to 3960)	0.58 (0.49 to 0.68)	2.32 (2.14 to 2.5)	<0.001	2800 (2340 to 3270)	0.47 (0.4 to 0.55)	2.04 (1.8 to 2.29)	<0.001	59,670 (50,450 to 70,050)	10.59 (9.08 to 12.28)	2.08 (1.87 to 2.29)	<0.001
Others	2640 (2240 to 3090)	0.49 (0.42 to 0.57)	1.77 (1.65 to 1.89)	<0.001	2040 (1730 to 2380)	0.36 (0.31 to 0.42)	1.57 (0.91 to 2.23)	<0.001	51,580 (44,390 to 60,330)	10.17 (8.9 to 11.72)	1.35 (0.75 to 1.95)	<0.001
Hepatoblastoma	160 (140 to 180)	0.09 (0.08 to 0.10)	1.00 (0.41 to 1.60)	0.001	40 (40 to 50)	0.02 (0.02 to 0.02)	0.83 (0.65 to 1.02)	<0.001	3670 (3280 to 4080)	1.96 (1.75 to 2.18)	0.85 (0.66 to 1.03)	<0.001

Note: Joinpoint regression was used to analyse the progression from 2000 to 2019, $p < 0.05$ signifies the statistical significance (the p value was shown in the p panel).

Abbreviations: APC, annual percent change; ASDALYs, age-standardised disability-adjusted life years; ASDR, age-standardised death rate; ASIR, age-standardised incidence rate; CI, confidence interval; UI, uncertainty interval.

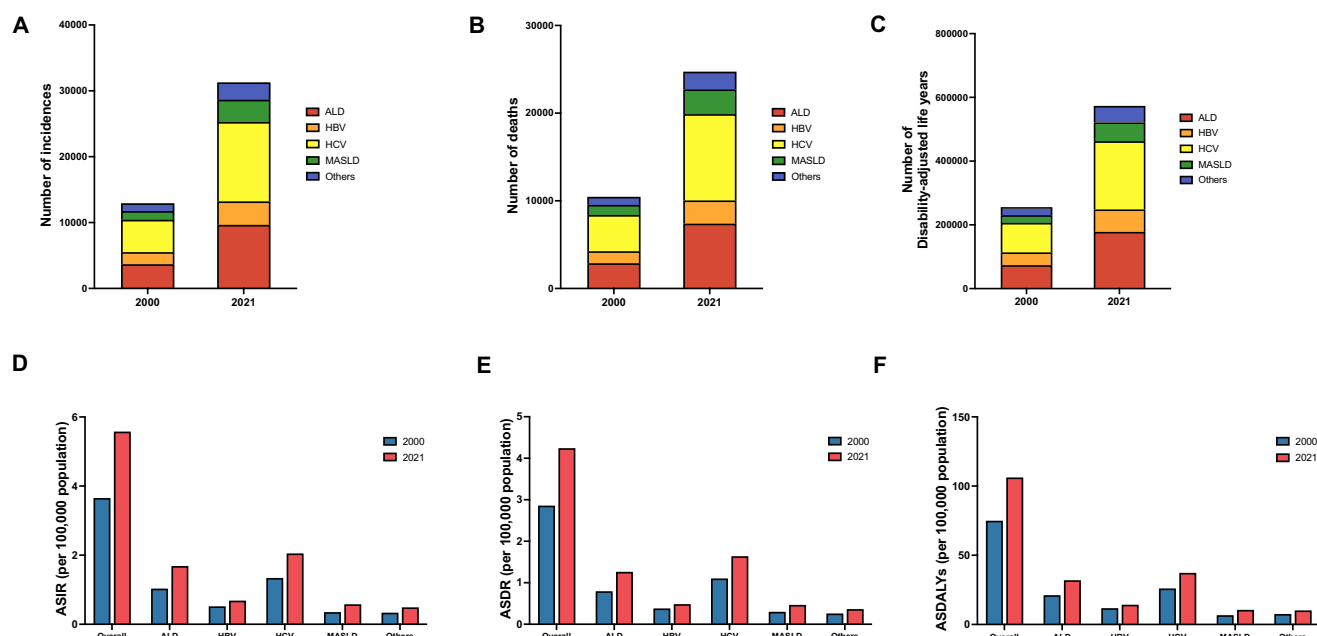


FIGURE 1 | (A) Number of primary liver cancer incidences by aetiology in 2000 and 2021. (B) Number of primary liver cancer deaths by aetiology in 2000 and 2021. (C) Number of primary liver cancer disability-adjusted life years by aetiology in 2000 and 2021. (D) Age-standardised incidence rate due to primary liver cancer incidences by aetiology in 2000 and 2021. (E) Age-standardised death rate due to primary liver cancer incidences by aetiology in 2000 and 2021. (F) Age-standardised disability-adjusted life years due to primary liver cancer incidences by aetiology in 2000 and 2021. ALD, alcohol-associated liver disease; HBV, Hepatitis B virus; HCV, Hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease.

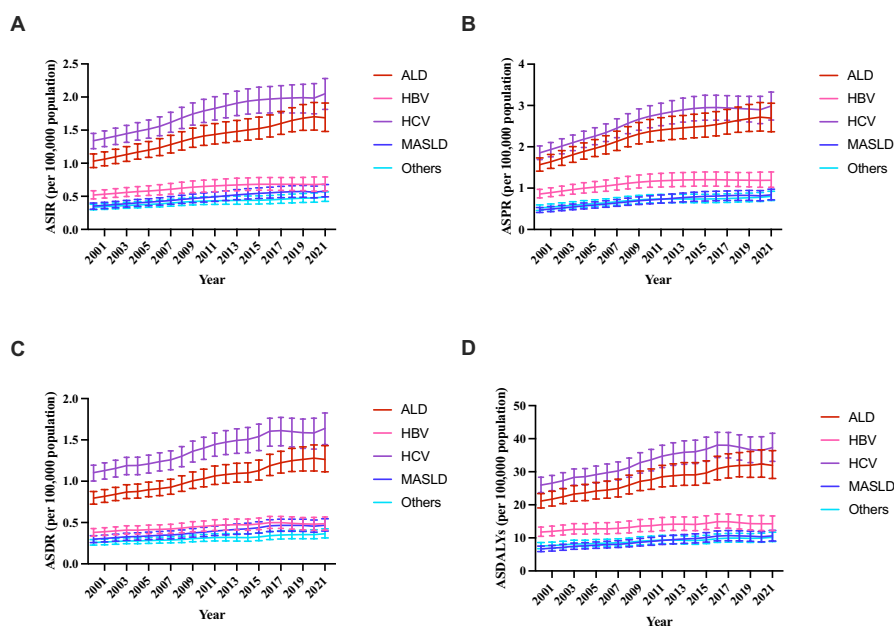


FIGURE 2 | (A) Age-standardised incidence rates due to primary liver cancer per 100,000 population from 2000 to 2021, by aetiology. (B) Age-standardised prevalence rates due to primary liver cancer per 100,000 population from 2000 to 2021, by aetiology. (C) Age-standardised death rates due to primary liver cancer per 100,000 population from 2000 to 2021, by aetiology. (D) Age-standardised disability-adjusted life years due to primary liver cancer per 100,000 population from 2000 to 2021, by aetiology. ALD, alcohol-associated liver disease; ASDALYs, age-standardised disability-adjusted life years; ASDR, age-standardised death rate; ASIR, age-standardised incidence rate; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction-associated steatotic liver disease.

observed in Kansas (APC 3.11%, 95% CI 2.96% to 3.27%), New Mexico (APC 3.06%, 95% CI 2.85% to 3.28%) and Tennessee (APC 3.04%, 95% CI 2.87% to 3.20%; Figure 3B). By 2021,

all but 13 states had ASIRs exceeding 5.0, with the highest ASIRs observed in Hawaii (ASIR 8.98), New Mexico (ASIR 7.69) and Alaska (ASIR 7.34). The change of PLC by aetiology

TABLE 2 | Annual percent change from age-standardised incidence, death and disability-adjusted life years rates from 2000 to 2021 and 2015 to 2021, stratified by aetiology.

	ASIR			ASDR			ASDALYs		
	2000–2021			2000–2021			2000–2021		
	APC (95% CI)	p	APC (95% CI)	APC (95% CI)	p	2015–2021 APC (95% CI)	p	2015–2021 APC (95% CI)	p
ALD	2.4 (2.18 to 2.62)	<0.001	1.81 (1.46 to 2.16)	2.22 (1.7 to 2.74)	<0.001	2.06 (1.09 to 3.05)	<0.001	1.98 (1.36 to 2.6)	<0.001
HBV	1.3 (1.19 to 1.42)	<0.001	−0.04 (−0.16 to 0.09)	1.09 (0.88 to 1.31)	0.48	−0.31 (−1.13 to 0.51)	0.378	0.85 (0.65 to 1.06)	<0.001
HCV	1.98 (1.72 to 2.24)	<0.001	0.56 (0.14 to 0.98)	1.79 (1.38 to 2.22)	0.019	0.53 (−0.31 to 1.38)	0.164	1.64 (1.26 to 2.02)	<0.001
MASLD	2.32 (2.14 to 2.5)	<0.001	0.88 (0.33 to 1.44)	2.04 (1.8 to 2.29)	0.009	0.65 (−0.37 to 1.68)	0.162	2.08 (1.87 to 2.29)	<0.001
Others	1.77 (1.65 to 1.89)	<0.001	1.7 (1.47 to 1.93)	1.57 (0.91 to 2.23)	<0.001	1.58 (0.8 to 2.37)	0.003	1.35 (0.75 to 1.95)	<0.001

Note: Joinpoint regression was used to analyse the progression from 2000 to 2019, $p < 0.05$ signifies the statistical significance (the p -value was shown in the p panel).

Abbreviations: ALD, alcohol-related liver disease; APC, annual percent change; ASDALYs, age-standardised disability-adjusted life years; ASDR, age-standardised death rate; ASIR, age-standardised incidence rate; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; MASLD, metabolic dysfunction associated steatotic liver disease.

is designated in Table S3. The burden of chronic HCV infection by states (including the District of Columbia) is listed in Figure 3C and Table S4.

3.5 | Burden of PLC in the United States in 2021, by Age Group

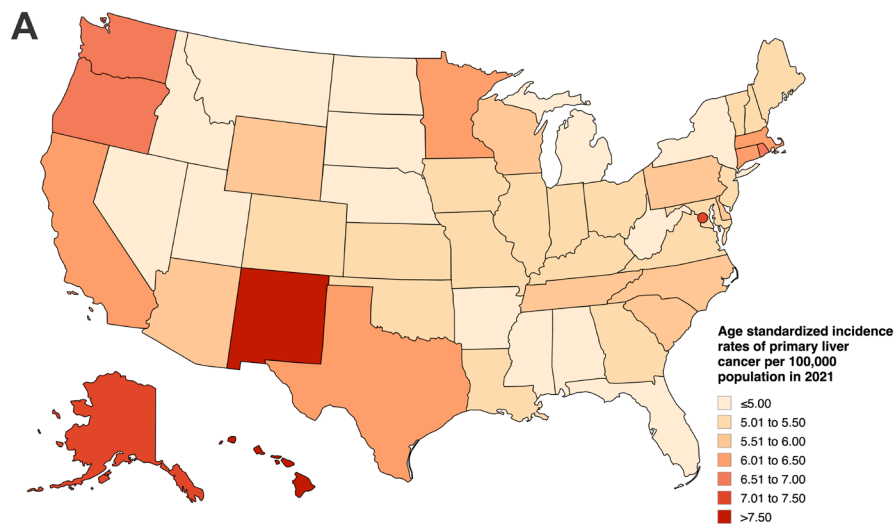
The detailed burden of PLC in each age group by aetiology is listed in Figure 4A–E and Table S5. The ASIR was highest in the age group 65–69 years for ALD (10.73, 95% 8.93 to 12.84) and HBV (3.00, 95% UI 2.18 to 3.88), while that of HCV (15.01, 95% UI 12.74 to 16.98), MASLD (4.57, 95% UI 3.62 to 5.57) and other aetiologies (2.50, 95% UI 2.00 to 3.05) were highest in those over 70 years, and hepatoblastoma was highest in those under 5 years (0.77, 95% UI 0.68 to 0.87; Figure 4A–E and Table S5).

4 | Discussion

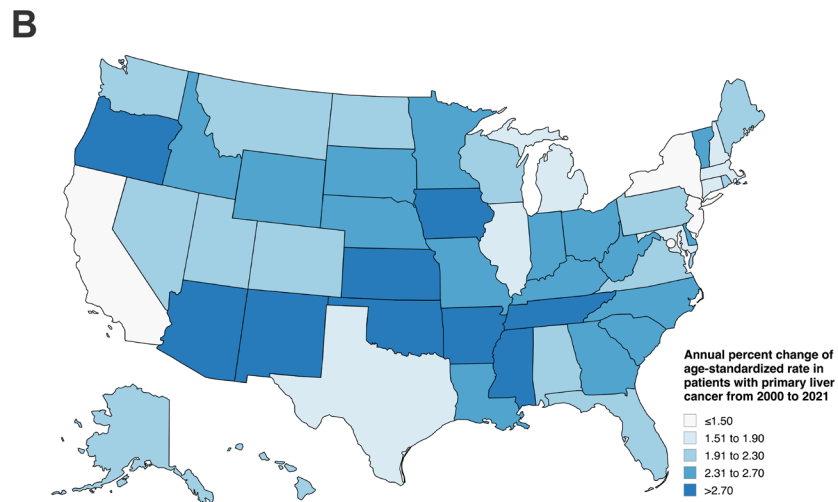
This study builds upon prior studies on PLC using the GBD 2019 database and provides an updated and comprehensive analysis of the temporal trends of PLC using the most recent data from GBD 2021 [15, 18]. In 2021, there were an estimated 47,970 prevalence, 31,450 incident cases, 24,770 deaths and 576,920 DALYs attributable to PLC. Between 2000 and 2021, there was a 142% increase in prevalence, a 141% increase in incident cases, a 136% increase in deaths and a 123% increase in DALYs. By aetiology, ALD is the fastest-growing aetiology of PLC. These data demonstrate an ongoing challenge against this high-mortality malignancy.

Aligned with the SEER database from 1975 to 2017 [20], our study found that the ASIR for PLC increased in the United States. Contrary to global data from the previous GBD cycle (GBD 2019) [18], which identified MASLD as the most rapidly increasing cause of PLC, ALD is now the fastest-growing cause of PLC in the United States. When analysed by state, there is geographic heterogeneity, with ALD as the fastest-growing ASIR for PLC in 32 states and MASLD as the highest-growing ASIR in 19 states. Besides alcohol, other substance use, such as the opioid epidemic, has further exacerbated liver health issues, with alcohol use disorder frequently co-occurring in individuals with opioid misuse, complicating both the diagnosis and treatment of liver disease [21, 22]. Furthermore, the COVID-19 pandemic has had a significant impact on liver health by increasing alcohol consumption and disrupting care for individuals with ALD [23]. Given the ongoing rise in metabolic diseases and alcohol consumption [24, 25], the burden of PLC from steatotic liver disease is expected to escalate further in the United States over the next decade. This is particularly alarming, considering the high mortality rate associated with this malignancy.

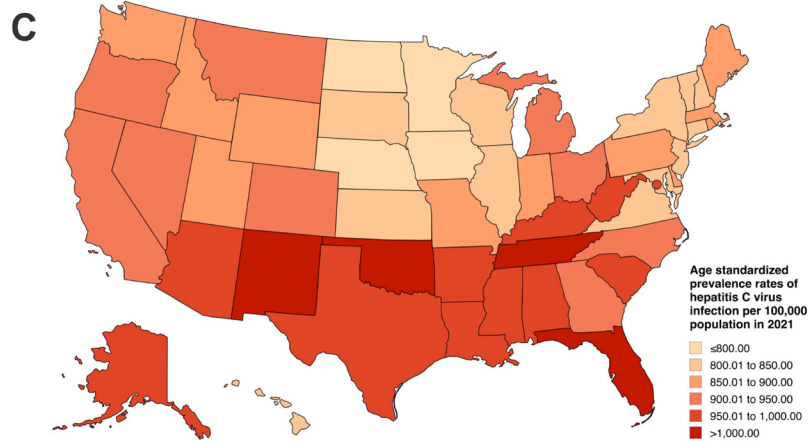
Our study aligns with previous research showing that PLC is more prevalent in males while females generally exhibit better overall survival rates [26]. This sex-based disparity is thought to result from a higher clustering of risk factors among men and the potential influence of androgens on HCC risk [27]. However, the gender gap in risk factors is beginning to narrow. For instance, multiple studies have reported a disproportionate increase in alcohol consumption and ALD development among



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FIGURE 3 | Legend on next page.

FIGURE 3 | (A) Age-standardised incidence rates due to primary liver cancer per 100,000 population in 2021, by state, including the District of Columbia. (B) Annual percent change in age-standardised incidence rates due to primary liver cancer per 100,000 population from 2000 to 2021, by state, including the District of Columbia. (C) Age-standardised prevalence rates due to chronic hepatitis C virus infection per 100,000 population in 2021, by state, including the District of Columbia.

females compared to males [28, 29]. Furthermore, MASH-associated PLC, the second fastest-growing aetiology of PLC, has a higher female-to-male ratio (0.8) compared to other aetiologies, such as HBV-associated PLC (0.2) [30]. These trends suggest that the gender gap in PLC incidence is likely to decrease in the future.

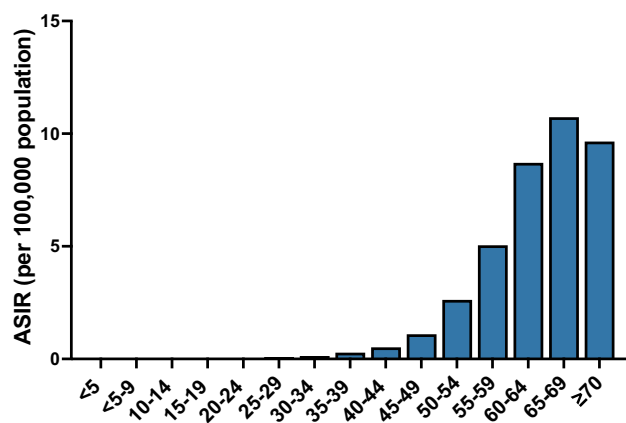
Interestingly, our study revealed a lack of correlation between stringent alcohol regulations and the observed trends in ALD-associated PLC [31]. For instance, Arizona and Utah are states recognised for their stringent alcohol policies (31) and paradoxically exhibit one of the most accelerated increases in ASIR of PLC attributable to ALD, yet the policy needs to be measured over time. This discrepancy may also be attributed to other contributing factors, such as genetic polymorphisms or other social determinants of health [32, 33]. For instance, the patatin-like phospholipase domain containing 3 (PNPLA3) is strongly linked to steatosis and fibrosis/cancer in multiple liver diseases, including, but not limited to, ALD [34–37]. Considering variations in socioeconomic, demographic, comorbidities and genetic factors, these differences may influence outcomes beyond the impact of public health policies targeting alcohol [38–41]. Despite variations at the state level, there remains a substantial potential for enhancing the restrictiveness of alcohol policies across all states, particularly those aimed at curbing alcohol consumption, possibly through adding additional taxes to alcohol sales, restrictions on advertisement for alcohol products or limiting hours of sale [42]. In addition, reformulation of policy for healthier food, mass media campaigns for healthy diets, comprehensive nutrition labeling and campaigns to promote physical activity needed to be implemented to tackle the burden of MASLD and metabolic disease [43–45]. Public health campaigns should emphasise the risks associated with excessive alcohol consumption and metabolic dysfunction; early screening and intervention programmes aimed at both could reduce the burden of PLC by providing at-risk populations with the necessary resources and support [46, 47].

HCV-associated PLC contributes significantly to the burden of PLC in the United States. While the burden of viral hepatitis-associated PLC increased, the extent of this rise was less pronounced than that observed for MASLD and ALD. This trend could potentially be attributed to the implementation of vaccination programs, effective antiviral therapies and elimination strategies [48, 49]. Additionally, heightened awareness and improved detection of these diseases might have contributed to the observed increase [48, 49]. However, HCV treatment coverage remains insufficient to meet elimination goals, with only one-third of diagnosed individuals receiving treatment and even lower rates among uninsured patients [50]. Considering these factors, along with the delays in HCV testing and treatment initiation caused by the COVID-19 pandemic, HCV may continue to be the predominant cause of PLC in the United States [51]. When analysed from 2015 to 2021, our study still found an increase in

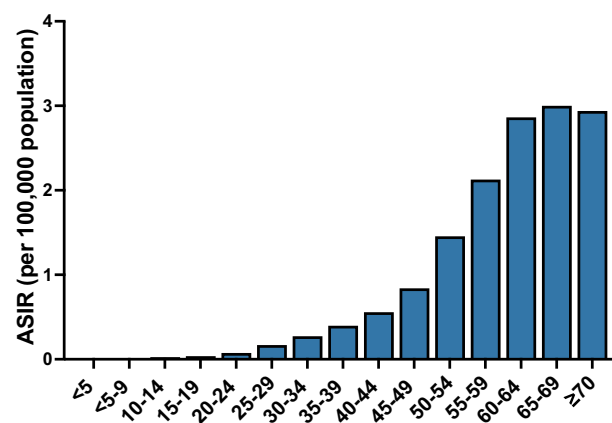
the burden of HCV-associated PLC, though to a lesser extent compared to the period from 2000 to 2021. Contrary to a study that reported plateauing trends in mortality due to HCC from 2009 to 2018 [52], a recent study reported a decrease in HCC-related mortality from 2018 to 2023 in the United States [53]. This study showed that HCC-related mortality from HCV infection decreased with an average APC of -8.5% from 2018 to 2023 [53]. Major reforms in national hepatitis programmes are essential to achieve the health and economic benefits HCV elimination [54]. Indeed, HBV and HCV accounted for 12% and 37% of PLC incidences in 2021, underscoring the substantial ongoing burden that viral hepatitis-related PLC continues to impose on the United States healthcare system. Gaps in diagnosis and linkage to care persist, as evidenced by the underutilisation of clinical assessment and treatment recommendations in patients with chronic viral infection [55–57].

Our study is subject to the inherent limitations of the GBD 2021 methodology, particularly its reliance on the quality of primary data from national registries. In regions with missing data, estimates are based on modelling and historical trends, which may introduce variability and discrepancy [15]. Additionally, the burden of disease reported in this study may be influenced by the evolving recognition of MASH-associated PLC over the study's extended timeframe (2000–2021). However, a prior study indicated limited progress in PLC surveillance in the past years [58, 59]. The American Association for the Study of Liver Diseases recommends screening high-risk groups, including individuals with Child–Pugh A–B cirrhosis of any cause, transplant-eligible patients with Child–Pugh C cirrhosis and particular groups of patients with chronic hepatitis B infection without cirrhosis [60]. Despite this, PLC screening, especially for ALD- and MASH-related cases, appears to be underutilised [46, 61]. Estimates of PLC burden and certain aetiologies, such as alcohol, may be affected by reporting biases, necessitating cautious interpretation [36, 62]. Since the nomenclature change of steatotic liver disease and the introduction of metabolic dysfunction and alcohol-associated liver disease (MetALD), some ALD and MASLD could fall into the MetALD category [63–67]. GBD 2021 also lacks data on histological subgroups of PLC, such as hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Furthermore, GBD did not report on ethnicity, such as Hispanics having a higher prevalence of MASLD [68], or other social determinants of health, which previous studies have shown to influence PLC outcomes [69, 70]. In addition, the sociodemographic index, the composite tool that includes income, fertility rate and educational attainment, could affect the burden of liver disease [7]. However, we did not examine the relationships between SDI and PLC, as our study focused exclusively on the United States without comparisons to other countries. Future research incorporating social determinants of health data is necessary. Additionally, although several studies have highlighted discrepancies between cancer data in GBD and other

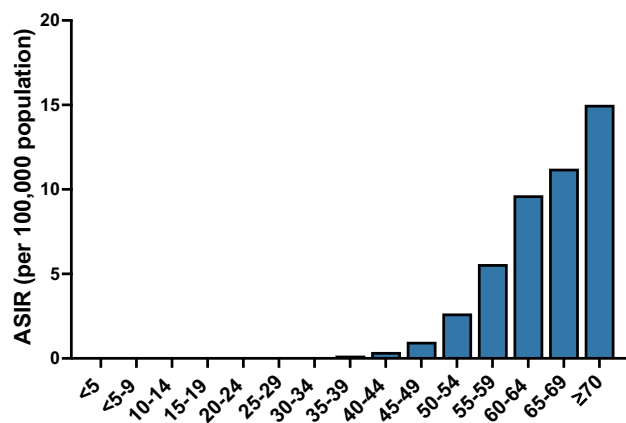
A ALD



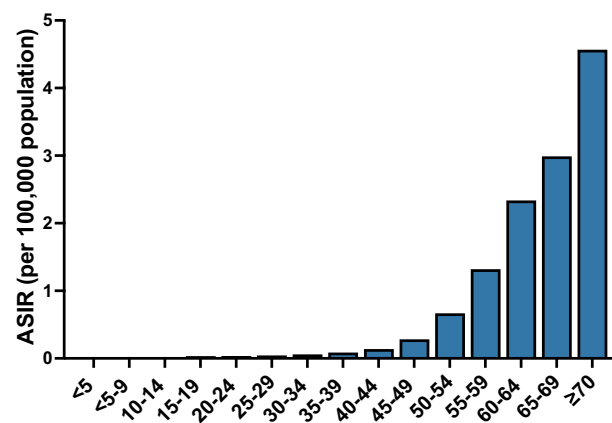
B HBV



C HCV



D MASLD



E Others

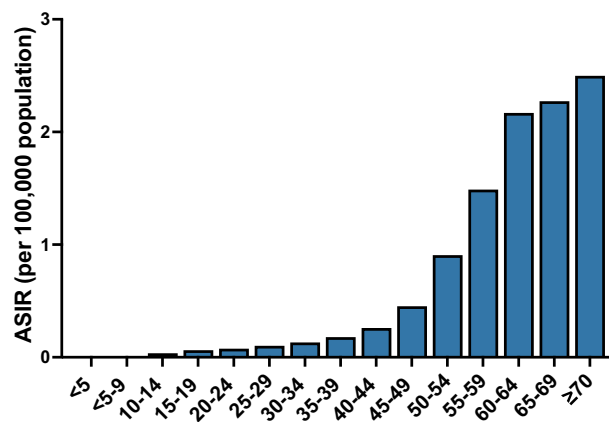


FIGURE 4 | Legend on next page.

FIGURE 4 | (A) Age-standardised incidence rates due to primary liver cancer due to alcohol-related liver disease per 100,000 population in 2021, by age group. (B) Age-standardised incidence rates due to primary liver cancer due to chronic hepatitis B virus infection per 100,000 population in 2021, by age group. (C) Age-standardised incidence rates due to primary liver cancer due to chronic hepatitis C virus infection per 100,000 population in 2021, by age group. (D) Age-standardised incidence rates due to primary liver cancer due to metabolic dysfunction associated steatotic liver disease per 100,000 population in 2021, by age group. (E) Age-standardised incidence rates due to primary liver cancer due to other causes per 100,000 population in 2021; by age group. ALD, Alcohol-related liver disease; HBV, Hepatitis B virus; HCV, Hepatitis C virus; MASLD, metabolic dysfunction associated steatotic liver disease.

databases, such as GLOBOCAN, no studies have yet compared SEER with GBD [71, 72]. Regarding differences between databases, GBD provides aetiological information for each PLC case and associated mortality, whereas GLOBOCAN and SEER do not include this detail [16, 17]. On the other hand, the United Network for Organ Sharing (UNOS) database also provides aetiological data on PLC but only includes patients listed for liver transplantation [73]. Given that multiple studies have identified MASH as the leading cause of liver transplantation, comparing GBD with other databases could yield valuable insights into PLC trends over the past decades [73, 74].

In conclusion, the overall burden of PLC has increased in the United States over the past two decades. HCV-associated PLC contributed to the highest burden in 2021, whereas ALD is the fastest-growing aetiology of PLC in 32 states, and MASLD is the rapidly growing aetiology in the remaining 19 states. These data underscore the need for public health specialists and healthcare providers to advocate for increased political will and resources to develop national and state-based policies aimed at curbing alcohol consumption and the growing prevalence of metabolic diseases [75].

Author Contributions

Pojasorn Danpanichkul: conceptualization, methodology, data curation, investigation, software, formal analysis, validation, writing – original draft, project administration. **Kwanjit Duangsonk:** conceptualization, writing – original draft, project administration. **Markos Kalligeros:** writing – original draft, visualization. **Michael B. Fallon:** writing – review and editing. **Chawinthorn Vuthithammee:** methodology, validation. **Chun Wei Pan:** methodology, validation, writing – original draft. **Preenapun Saokhieo:** writing – original draft, validation, visualization. **William Derrick:** writing – original draft, visualization. **Yanfeng Pang:** writing – original draft, validation, investigation, formal analysis. **Vincent L. Chen:** writing – review and editing. **Donghee Kim:** writing – review and editing. **Amit G. Singal:** writing – review and editing, supervision. **Ju Dong Yang:** writing – review and editing, supervision, project administration. **Karn Wijarnpreecha:** writing – review and editing, writing – original draft, project administration, supervision, conceptualization.

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Graphical abstract was created using biorender.com.

Conflicts of Interest

Ju Dong Yang consults for AstraZeneca, Eisai, Exact Sciences and FujiFilm Medical Sciences. Amit G. Singal has served as a consultant or on advisory boards for Genentech, AstraZeneca, Eisai, Exelixis, Bayer, Elevar, Boston Scientific, Sirtex, Histosonics, FujiFilm Medical Sciences, Exact Sciences, Roche, Abbott, Glycotest, Freenome and GRAIL.

Data Availability Statement

Data from the Global Burden of Disease (GBD) study 2021 can be accessed utilising the GlobalHealth Data Exchange (GHDx) query tool (<http://ghdx.healthdata.org/gbd-results-tool>), which the Institute for Health Metrics and Evaluation maintains.

Institutional Review Board Approval

The data utilised in this article were obtained from the publicly available GBD database and, thus, did not necessitate any Institutional Review Board approval, ethics clearance or consent from study subjects.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.