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Variation in attributable fraction of hepatitis B virus and hepatitis C virus among primary liver cancer cases across mainland China: a systematic literature review and meta-analysis

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Abstract

Aim: Our objective was to describe variations in attributable fractions (AFs) of hepatitis B virus (HBV) and hepatitis C virus (HCV) to primary liver cancer (PLC) across mainland China.

Methods: We conducted a systematic review and meta-analysis of studies published up to July 2024 in PubMed, Embase, WanFang, and China National Knowledge Infrastructure. Eligible studies reported the prevalence of HBV and HCV infection, alone and in combination, in PLC. AFs of HBV, HCV, and non-viral etiology in PLC were estimated by province and, when possible, by sex, age, histological diagnosis, and study periods. Regional and overall AFs were estimated by weighting by provincial and regional population size. Publication bias and heterogeneity were assessed by funnel plots of AFs of HBV, HCV, and non-viral etiology in PLC cases, using Egger

test by study size.

Results: We included 240 studies with 71,905 PLC cases from 31 provinces, autonomous regions and municipalities across mainland China. AFs of HBV, HCV, and non-viral etiology for PLC across mainland China were 76.5%, 6.6%, and 16.9%, respectively. The AFs of HBV and HCV varied by region, with HBV AFs ranging from 68.7% in Northwest China to 82.9% in South Central China. Respective HCV AFs ranged from 12.7% in Northeast China down to 3.7% in South Central China. Non-viral AFs ranged from 13.4% to 21.0% by region. AFs of non-viral etiology were 57.9% in intrahepatic cholangiocarcinoma (ICC), and AF of HBV was double prevalence ratio (PR), 2.11 (95%CI: 1.89-2.34) in hepatocellular carcinoma (HCC, 76.3%) than ICC (37.3%) cases. Prevalence of HBV was higher in male (83.9%) than female (74.6%) PLC cases, and the mean age at diagnosis was 10 years higher for PLC with HCV (64.9 years) than HBV (54.4 years).

Conclusion: HBV, HCV, and non-viral AFs varied substantially by region across China, as well as by sex and age, which can inform strategies for liver cancer prevention and control.

Keywords: Hepatitis B virus, hepatitis C virus, primary liver cancer, meta-analysis

INTRODUCTION

Primary liver cancer (PLC) is the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2022[1]. PLC ranks as the fourth most common cancer and the second leading cause of cancer death in China in 2022, according to the latest report from National Cancer Center[2]. Hepatocellular carcinoma (HCC) accounts for the majority of PLC cases, followed by intrahepatic cholangiocarcinoma (ICC) and other histological types[3,4]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the predominant etiologies of PLC in comparison with other risk factors, including heavy alcohol intake, smoking, metabolic disorders (e.g., obesity and diabetes), and aflatoxin exposure[5]. The contribution of HBV and HCV to liver cancer burden varies between countries. HBV is predominant in most high-prevalence countries from Asian and African regions, whereas HCV surpasses HBV in most European and North American countries[6,7].

Although HBV infection has been increasingly well controlled in China in the past decades, there remain geographical differences in HBV prevalence across China[8], and the HBV-associated liver cancer burden is still huge[7]. The estimated prevalence of HCV infection is around 0.9% in the general population in mainland China[9]. HCV is far less prevalent than HBV, but China has the largest population with HCV infection, which has been increasing in recent decades[10,11]. Again, there is evidence that the HCV-associated liver cancer burden varies across China, for example being potentially higher in Korean ethnic regions in Jilin province[12]. Meanwhile, the burden of PLC caused by etiologies other than HBV and HCV, such as alcohol-related liver disease (ALD) and Metabolic dysfunction-associated fatty liver disease (MAFLD), has been increasing in China over time[13,14].

Given the heavy burden of liver cancer in China, for which the attributable etiologies (HBV, HCV, and non-viral causes) may vary across sub-populations, we conducted a systematic review and meta-analysis on the burden of PLC attributed to HBV and HCV by geography, sex, age, histological types (HCC and ICC), and study periods across China, in order to estimate attributable fractions (AFs) and to inform tailored strategy of liver cancer prevention and control.

METHODS

Search strategy

We performed a literature search in PubMed, Embase, and Chinese databases, including WanFang and China National Knowledge Infrastructure (CNKI), up to July 2024. We used various combinations of the following terms: "hepatocellular carcinoma"; "liver neoplasia"; "primary liver cancer"; plus "hepatitis B virus"; "hepatitis B antibodies"; "hepatitis B antigens"; "hepatitis B virus DNA"; "hepacivirus"; "hepatitis C antibodies", and "hepatitis C RNA". Additional relevant studies were identified in the reference lists of selected articles and the theses published in Chinese were also detected. Studies published in English and Chinese were considered. Detailed search strategies are shown in Supplementary Table 1.

Study selection

Two authors (CL and ZL) selected studies in parallel. Case series of patients with a diagnosis of PLC were included in the study. Case series were not considered for inclusion if they were from special populations, such as health care workers, human immunodeficiency virus (HIV)-infected people, patients with a specific comorbidity, or liver transplant patients. Multi-regional studies were eligible for inclusion when overall estimates were reported. Multi-regional studies that only gave overall summaries were also included in pooled regional-level estimates when all provinces were from the same region.

Eligible studies had to report the data on infection with HBV alone, with HCV alone, and with double infection of HBV and HCV. Studies were excluded if: only one of the two viruses was reported; data on double infection could not be inferred from the published data. In cases of multiple publications of the same PLC series, only the most informative article was retained. Study selection is described in Supplementary Figure 1.

Data extraction

For each study, we extracted: first author; journal of publication; publication year; study period; study area; study population; virus test methods; sample size; positive number of HBV and HCV alone, and in both. We also tried to retrieve HBV/HCV data stratified by gender, age group, and histological diagnosis (HCC and ICC) as far as possible. When available, the mean age of PLC positive for HBV or HCV was also extracted. The study period was defined as the median year of the recruitment period. For quite a few small studies for which this information was not available, the study period was set to be 2 years before the publication year.

Data analysis

To calculate AFs, cases in each study were classified into three etiologies: HBV, HCV, and non-viral causes, by reassigning PLC cases with double infections according to a ratio equivalent to the overall prevalence of HBV and HCV in the same study, as used previously[15]. AF estimates and 95%CI (confidence interval) of HBV, HCV, and non-viral etiology in PLC and HCC cases were aggregated at the provincial level and across six administrative regions of mainland China. The regional and overall estimates on AFs of HBV, HCV, and non-viral etiology were weighted by the population size of each province and region [Supplementary Table 2]. There were four age groups, including ages under 55, 55-64, 65-75, and over 75. We cut the study period into two groups: years before 2000 (including 2000) and years after 2000. Pooled AFs of HBV, HCV, and non-viral etiology were estimated by gender, age groups, and histological diagnosis, where possible, and were compared between categories by prevalence ratios (PR) and 95%CI. We evaluated AFs of HBV, HCV, and non-viral etiology in PLC and HCC cases by studied periods, and conducted a sensitive analysis, restricting it to studies with serological testing for HBsAg and anti-HCV. Sensitive analysis was performed to investigate the AFs of HBV, HCV, and non-viral etiology, limited only to confirmed HCC cases.

Publication bias and heterogeneity were assessed by funnel plots [Supplementary Figure 2] of AFs of HBV, HCV, and non-viral etiology in PLC cases, using Egger test by study size. The study was conducted according to the PRISMA guideline. Meta-analyses were implemented using the meta (4.18-0) and metafor (2.4-0) packages in R program (version 4.1.1).

RESULTS

We included 240 studies with 71,905 PLC cases in final analyses from 31 provinces, autonomous regions, and municipalities across mainland China [Table 1]. The detailed information on selected studies is listed in Supplementary Table 3 and references in the appendix. The numbers of PLC cases varied by province and across the six administration regions, including South Central China (n = 20,904), Northeast China (n = 10,978), East China (n = 9,650), North China (n = 8,037), Southwest China (n = 5,889), and Northwest China (n = 3,315) [Table 1, Supplementary Figure 3 and Supplementary Table 4]. Information on HBV and HCV was available for 44,183 PLC cases diagnosed as HCC [Supplementary Tables 5 and 6]. There was heterogeneity in AFs of HBV, HCV and non-viral etiology in PLC cases by study sample size [Supplementary Figure 2]. The AFs of HBV, HCV, and non-viral etiology were 37.6%, 4.5%, and 57.9% in 561 ICC cases and the AF of HBV was double in HCC in comparison with ICC (PR = 2.11, 95%CI: 1.89-2.34) [Supplementary Figure 4].

AFs of HBV and HCV in PLC, by geography

AFs of HBV, HCV, and non-viral etiology in PLC cases by province, region, and overall are shown in Table 1. Pooled AFs of HBV, HCV, and non-viral etiology were 76.5%, 6.6%, and 16.9% in PLC cases overall for mainland China after weighting by population size [Table 1]. These proportions were similar in a sensitivity analysis including HCC only: 76.6%, 6.8% and 16.6%, respectively [Supplementary Table 6].

The majority of PLC cases were attributable to HBV in all regions, but there was variation in the relative AFs of HBV and HCV across mainland China. The pooled AFs of HBV in PLC increased from 68.7% (95%CI: 67.9%-69.5%) in Northwest China to 82.9% (95%CI: 82.6%-83.1%) in South Central China. The AF of HCV in PLC varied between 3.7% (95%CI: 3.6%-3.8%) in South Central China and 12.7% (95%CI: 12.4%-13.1%) in Northeast China, and that of non-viral etiology from 13.4% (95%CI: 13.2%-13.7%) in North China to 21.0% (95%CI: 20.3%-21.7%) in Southwest China [Table 1]. Similar results were obtained in sensitivity analysis including only HCC cases [Supplementary Table 6]. The proportion of co-infection of HBV and HCV (before re-allocation) fluctuated between 3.7% in Southwest China and 5.9% in East China in PLC [Supplementary Table 4] and 2.3% in Southwest China and 6.8% in Northwest China in HCC only [Supplementary Table 5].

As shown in Table 1 and Figure 1, the AF of HBV was over 80% in PLC cases in Hainan, Jiangxi, Guangdong, Hunan, Shandong, Hubei, Beijing, Fujian, Guangxi, and Ningxia, and was lowest in Xinjiang (50.6%, 95%CI: 48.0%-53.1%) and Inner Mongolia (54.8%, 95%CI: 51.5%-58.0%). The AF of HCV was highest in PLC from Jilin (25.1%, 95%CI: 24.6%-25.5%) and Tianjin (20.2%, 95%CI: 18.3%-22.1%) provinces. The AFs of None viral etiologies were highest in PLC from Inner Mongolia (37.0%, 95%CI: 33.8%-40.1%), Xinjiang (38.2%, 95%CI: 35.7%-40.7%), and Guizhou (38.5%, 95%CI: 37.0%-40.0%).

AF of HBV and HCV in PLC, by sex

HBV, HCV, and non-viral AFs in PLC cases by sex are presented in Figure 2, being 83.9%, 4.1% and 11.9% in 10,244 male PLC cases *vs.* 74.6%, 8.6% and 16.8% in 1,862 female PLC cases in mainland China, respectively [Figure 2]. HBV AF was significantly higher in males in comparison with females (PR = 1.12, 95%CI: 1.09-1.16), whereas HCV and non-viral etiology AFs were significantly lower (0.48; 95%CI: 0.40-

Table 1. The AFs of HBV, HCV and non-viral etiology among 71,905 PLC cases in mainland China by region and province

Region/ Province	Studies (*n*)	PLC cases (*n*)	AFs (%, 95%CI)		
			HBV	HCV	Non-viral
South Central China					
Guangdong	26	5,490	85.0% (84.6-85.5)	3.9% (3.6-4.1)	11.1% (10.7-11.5)
Henan	18	2,603	78.8% (78.0-79.6)	5.4% (5.0-5.9)	15.8% (15.1-16.5)
Guangxi	16	10,539	81.4% (81.0-81.8)	1.8% (1.6-1.9)	16.8% (16.5-17.2)
Hunan	5	1,302	85.0% (84.0-86.0)	2.7% (2.2-3.1)	12.3% (11.4-13.2)
Hubei	4	416	83.0% (81.1-84.8)	3.6% (2.6-4.5)	13.5% (11.8-15.1)
Hainan	1	554	89.2% (87.8-90.5)	1.8% (1.2-2.4)	9.0% (7.8-10.2)
Subtotal[a]	70	20,904	82.9% (82.6-83.1)	3.7% (3.6-3.8)	13.4% (13.2-13.7)
East China					
Jiangsu	24	3,811	69.2% (68.5-70.0)	4.4% (4.0-4.7)	26.4% (25.7-27.1)
Shanghai	13	2,137	73.2% (72.3-74.2)	8.4% (7.8-9.0)	18.4% (17.6-19.2)
Shandong	12	1,492	83.6% (82.7-84.6)	6.2% (5.6-6.9)	10.1% (9.3-10.9)
Zhejiang	8	853	77.7% (76.2-79.1)	8.4% (7.4-9.3)	14.0% (12.8-15.1)
Anhui	4	389	75.6% (73.4-77.8)	6.7% (5.4-7.9)	17.7% (15.8-19.7)
Fujian	4	583	82.2% (80.6-83.8)	4.5% (3.6-5.3)	13.4% (12.0-14.8)
Jiangxi	2	385	87.8% (86.1-89.4)	4.9% (3.8-6.1)	7.3% (5.9-8.6)
Subtotal[a]	67	9,650	78.4% (78.0-78.8)	6.1% (5.8-6.3)	15.6% (15.2-15.9)
North China					
Beijing	16	4,552	82.8% (82.2-83.3)	9.0% (8.6-9.4)	8.2% (7.8-8.6)
Shanxi	9	1,444	69.4% (68.2-70.6)	10.1% (9.3-10.9)	20.4% (19.4-21.5)
Hebei	9	1,365	77.5% (76.3-78.6)	8.5% (7.7-9.2)	14.1% (13.1-15.0)
Inner Mongolia	3	230	54.8% (51.5-58.0)	8.3% (6.5-10.1)	37.0% (33.8-40.1)
Tianjin	2	446	66.8% (64.6-69.0)	20.2% (18.3-22.1)	13.0% (11.4-14.6)
Subtotal[a]	39	8,037	72.4% (71.9-72.9)	9.8% (9.5-10.1)	17.8% (17.4-18.2)
Northeast China					
Jilin	15	9,686	62.5% (62.0-62.9)	25.1% (24.6-25.5)	12.5% (12.1-12.8)
Liaoning	9	977	72.8% (71.3-74.2)	10.4% (9.4-11.3)	16.9% (15.7-18.1)
Heilongjiang	5	315	72.8% (70.2-75.3)	6.6% (5.2-8.0)	20.6% (18.4-22.9)
Subtotal[a]	29	10,978	70.2% (69.8-70.7)	12.7% (12.4-13.1)	17.0% (16.7-17.4)
Northwest China					
Shaanxi	8	1,424	78.1% (77.0-79.2)	9.9% (9.1-10.6)	12.1% (11.2-12.9)
Gansu	3	470	69.6% (67.5-71.7)	12.3% (10.8-13.8)	18.1% (16.3-19.9)
Xinjiang	3	385	50.6% (48.0-53.1)	11.3% (9.7-12.9)	38.2% (35.7-40.7)
Ningxia	2	860	80.2% (78.9-81.6)	1.2% (0.8-1.6)	18.6% (17.3-19.9)
Qinghai	1	176	68.2% (64.7-71.7)	11.4% (9.0-13.8)	20.5% (17.4-23.5)
Subtotal[a]	17	3,315	68.7% (67.9-69.5)	10.3% (9.8-10.8)	21.0% (20.3-21.7)
Southwest China					
Sichuan	8	3,801	79.6% (78.9-80.2)	2.5% (2.2-2.7)	17.9% (17.3-18.6)
Chongqing	2	422	77.0% (75.0-79.1)	4.3% (3.3-5.3)	18.7% (16.8-20.6)
Guizhou	2	1,062	57.3% (55.7-58.8)	4.2% (3.6-4.9)	38.5% (37.0-40.0)
Yunnan	2	422	71.8% (69.6-73.9)	15.4% (13.7-17.2)	12.8% (11.2-14.4)
Tibet	1	182	73.1% (69.8-76.4)	1.1% (0.3-1.9)	25.8% (22.6-29.1)
Subtotal[a]	15	5,889	73.1% (72.5-73.6)	6.0% (5.7-6.4)	20.9% (20.4-21.4)
Multiple region					
Subtotal	6	13,132	81.9% (81.5-82.2)	2.1% (1.9-2.2)	16.1% (15.8-16.4)
Overall[b]	239[*]	71,905	76.5% (76.4-76.7)	6.6% (6.5-6.7)	16.9% (16.7-17.0)

[*]One study (2017, Wang *et al.*[17]) was not counted in Table 1 due to duplicated data with the study (2022, Lin *et al.*[4]), but contributed to the

subsequent analysis by age and sex; [a]The regional AFs of HBV, HCV, and non-viral etiology were weighted using pooled estimates for each province and the population sizes of the regions (see method); [b]The overall AFs of HBV, HCV, and non-viral etiology were weighted using pooled estimates for each region and the population sizes of the regions (see method). AFs: Attributable fractions; PLC: primary liver cancer; HBV: hepatitis B virus; HCV: hepatitis C virus; CI: confidence interval.

0.57, and 0.71; 95%CI: 0.64-0.80, respectively).

AF of HBV and HCV in PLC, by age

AFs of HBV, HCV, and non-viral etiology in 2,623 PLC cases with available data stratified by age group are shown in Figure 3. HBV AFs decreased by age, whereas those of HCV and non-viral etiology increased. AFs for HBV, HCV, and non-viral were 91.4%, 0.8%, and 7.9% in 1,092 cases aged under 55 years old; 90.5%, 3.1%, and 6.3% in 885 cases aged 55-64; 84.4%, 6.0%, and 9.6% in 457 cases aged 65-75; and 66.9%, 13.5%, and 19.6% in 189 cases aged over 75 years old, respectively.

We also obtained mean age in PLC cases positive for HBV only, HCV only, co-infection of HBV and HCV, and with non-viral etiology from 8 studies in mainland China, for which the pooled mean age was 54.4 (n = 5,382), 64.9 (n = 1,985), 58.6 (n = 426), and 59.7 (n = 859) years, respectively [Table 2].

AF of HBV and HCV in PLC, by study periods

HBV, HCV, and non-viral AFs in PLC cases by study period are presented in Figure 4, being 74.0%, 7.6%, and 18.4% in 13,056 PLC cases recruited before the 2000 year *vs.* 77.5%, 7.4%, and 15.2% in 58,849 PLC cases after the 2000 year in mainland China, respectively [Figure 4]. HBV AF was significantly lower in PLC cases before the 2000 year in comparison with those after the 2000 year (PR = 0.96, 95%CI: 0.94-0.97). HCV AFs were comparable between the two study periods (PR = 1.04, 95%CI: 0.97-1.11). Non-viral etiology AFs were significantly higher (1.21; 95%CI: 1.16-1.26). Similar trends were observed in the sensitive analysis, such as HBV, and non-viral AFs in HCC cases and PLC cases detected using the same detection approach (HBV: HBsAg, HCV: anti-HCV) by study periods, as presented in Supplementary Figures 5 and 6, respectively. The HBV AFs increased over time, whereas non-viral etiology AFs decreased.

DISCUSSION

In our comprehensive systematic review and meta-analysis on the AF of HBV and HCV in PLC cases across mainland China, we found that 76.5%, 6.6%, and 16.9% of PLC and HCC cases were attributable to HBV, HCV, and non-viral causes in mainland China, respectively. These findings are consistent with the results published in 2015 and 2018 by International Agency for Research on Cancer (IARC) (76.6%, 6.6%, and 16.6%, respectively)[6,16], which only considered HCC cases. HBV and HCV are known to be major risk factors for PLC, most notably HCC, but evidence is increasingly showing they also cause a fraction of ICC[4,17]. HBV and HCV infection could increase the risk of ICC, according to findings from multiple studies[18-21]. The estimated AFs of viral *vs.* non-viral causes in 561 ICC cases from mainland China were around 40% and 60%, respectively.

In this work, for the first time, we systematically estimated the fraction of PLC attributable to HBV, HCV, and non-viral etiologies at a regional and provincial level across mainland China. Although HBV was the predominant cause of PLC in all geographical and sub-group analyses, the relative contribution of HBV HCV and non-viral etiology was shown to vary substantially. HBV prevalence in PLC cases increased from 68.7% in Northwest China to 82.9% in South Central China. HCV prevalence in PLC cases increases from 3.7% in South Central China to 12.7% in Northeast China. The AF of HBV and HCV in PLC cases is the direct consequence of the relative prevalence of these two viruses in the general population in previous

Table 2. Age at diagnosis in PLC cases attributed to HBV and HCV

Region	Studies (*n*)	PLC cases (*n*)	Mean age
HBV only	8	5,382	54.4
HCV only	8	1,985	64.9
Both HBV and HCV	8	426	58.6
Non-viral	8	859	59.7

PLC: Primary liver cancer; HBV: hepatitis B virus; HCV: hepatitis C virus.

decades. Consistently and according to pooled estimates from a large meta-analysis, HBV prevalence was 4% in Northeast China and 11% in South Central China in the general population between 1973 and 1992[8]. In contrast, HCV prevalence was higher in the general population from Northeast China, namely in Jilin and Liaoning provinces, between 1991 and 2015[9].

Non-viral causes of PLC include heavy alcohol consumption and MAFLD, which is associated with obesity and diabetes, aflatoxin exposure, and smoking[22]. The prevalence of non-viral causes in PLC cases in Inner Mongolia, Xinjiang and Guizhou reached over 30%, according to findings in our study. PLC cases associated with non-viral causes have been shown to be more likely prevalent in individuals with higher rates of diabetes and body mass index (BMI) compared to those caused by HBV and HCV in regions of Xinjiang[23].

When looking at variations at a provincial level, HBV tended to be more prevalent in PLC cases from the majority of provinces in South Central China (e.g., Hainan, Hunan, Hubei, Guangdong, Guangxi), and from other provinces known to have high HBV prevalence in the general population (e.g., Jiangxi, Beijing, Ningxia and Shandong)[8]. The HBV AF was comparatively low in the northeastern Jilin province in this study, due to a lower HBV prevalence locally and the presence of cases from the Yanbian Korean Autonomous Prefecture, much more likely to be chronically infected with HCV[12]. In 2019, the cancer registry of Yanji City, the provincial capital of Yanbian Korean Autonomous Prefecture, reported that liver cancer was the leading cause of cancer incidence and mortality in this area (2019)[24]. Accordingly, the AF for HCV was 48% in 3,537 cases recruited from the Affiliated Hospital of Yanbian University between 2000 and 2016[12]. The AF of HBV was reported to be lower at around 51% in 385 PLC cases from the northwestern province of Xinjiang, which might be due to the low prevalence of HBV in Uyghur PLC cases[25].

HBV-associated liver cancer is decreasing due to primary prevention efforts through HBV vaccination in newborns. HCC typically takes several decades to develop following HBV infection, which often occurs during the neonatal period. In our study, the estimated mean age of PLC cases was about 53 years. The AF of HBV in PLC, as analyzed in our study spanning 30 years, mirrors the scenario of HBV infection in the general population during the 1970s to some extent. Chronic HBV infection in the general population in China decreased from 9.6% in 1973-1984 to 3.0% in 2021 overall and from 5.0% in 1973-1992 to 0.6% in 2006-2021 in children aged < 5 years, according to the findings from our research team[8]. With the spread-out of vaccination of HBV in newborns and implementation of anti-viral treatments, the primary causes of PLC are gradually shifting from HBV and/or HCV to non-viral etiology. It is important to figure out how the AFs of non-viral causes, namely ALD and metabolic disorders, evolve over time.

We observed that PLC cases caused by HCV alone were, on average, over ten years older than those with HBV alone, with mean ages of 65 and 54 years, respectively. These findings align with other studies,

Lin *et al. Hepatoma Res.* 2025;11:2 | https://dx.doi.org/10.20517/2394-5079.2024.84

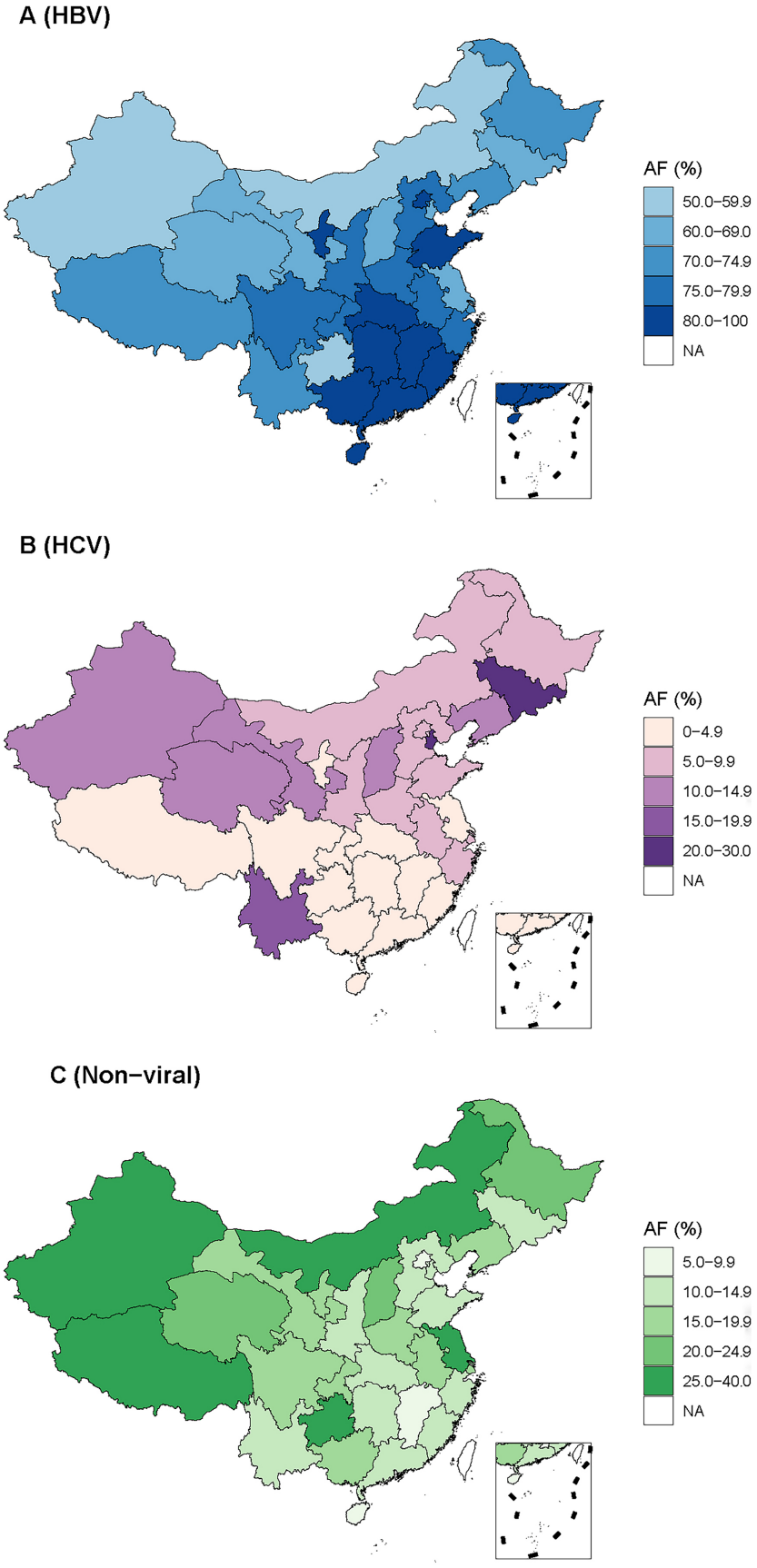

Figure 1. The map of AFs of PLC associated with HBV, HCV, and non-viral etiology at a provincial level across mainland China. (A) map of AFs of HBV in PLC cases; (B) map of AFs of HCV in PLC cases; (C) map of AFs non-viral etiology in PLC cases. AFs: Attributable fractions; PLC: primary liver cancer; HBV: hepatitis B virus; HCV: hepatitis C virus; NA: not applicable.

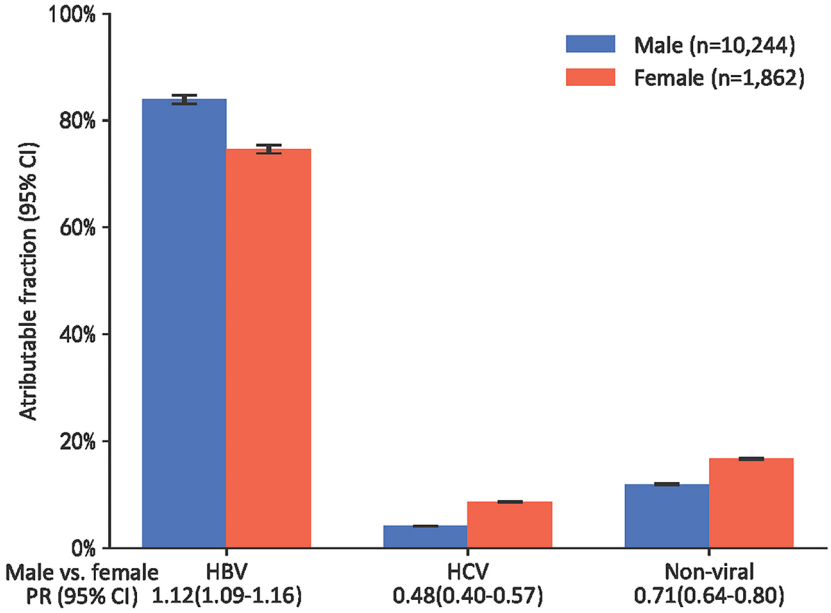

Figure 2. The AFs of HBV, HCV and non-viral etiology with PRs (male *vs.* female) in PLC cases by sex in mainland China. AFs: Attributable fractions; PRs: prevalence ratios; PLC: primary liver cancer; HBV: hepatitis B virus; HCV: hepatitis C virus; CI: confidential interval.

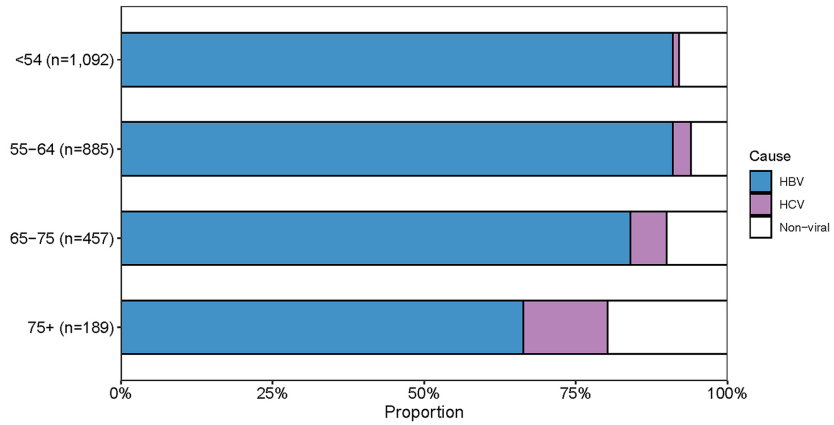

Figure 3. The AFs of PLC attributed to HBV, HCV, and non-viral etiology by age groups in six administration regions in mainland China. AFs: Attributable fractions; PLC: primary liver cancer; HBV: hepatitis B virus; HCV: hepatitis C virus.

particularly those conducted in Eastern and South Eastern Asia and in Sub-Saharan Africa, where HBV is predominantly transmitted from mother to child, whereas HCV infection typically occurs during adulthood[26,27]. The majority of HCC cases under 55 years old were attributable to HBV. However, this proportion of HBV-related HCC decreased with age, while the contributions of HCV and non-viral causes increased. This trend is consistent with our above-reported findings (HBV-related HCC tends to occur at an earlier age than HCV- or non-viral-related HCC), and is expected to persist for the next decade, despite

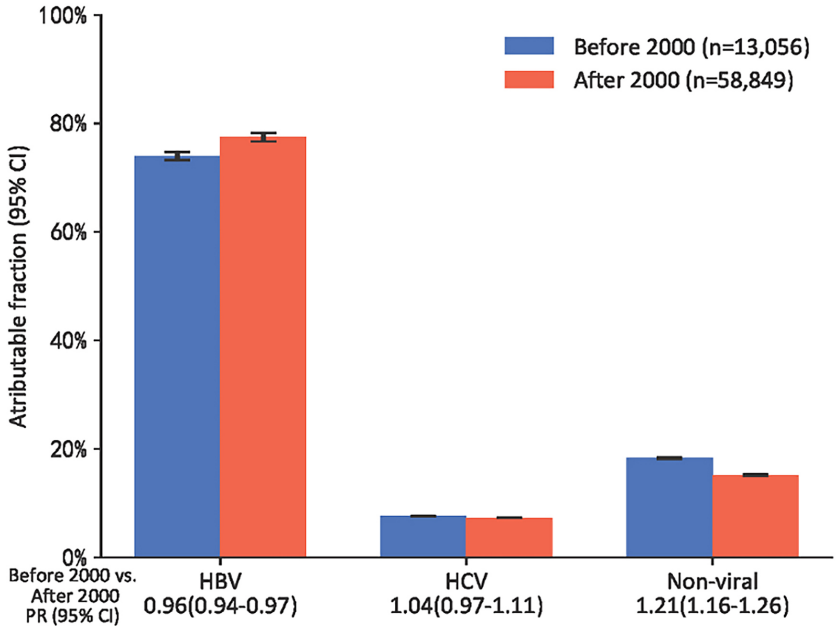

Figure 4. AFs of HBV, HCV and non-viral etiology in PLC cases recruited before and after 2000 years. AFs: Attributable fractions; HBV: hepatitis B virus; HCV: hepatitis C virus; PLC: primary liver cancer; CI: confidential interval.

great progress in vaccine coverage in China, including birth doses, due to the high prevalence of adults born before vaccine implementation, unless HBV treatment is implemented rapidly according to the new Chinese guidelines. Furthermore, studies have shown that the prevalence of HCV in the general population has increased with age since 2006[9,11], also contributing to the age-related trends observed in this review.

The fraction of PLC attributable to HBV was higher in males than females, whereas the HCV AF was higher among females than males. The same phenomena have been observed for the relative prevalence of HBV and HCV infection in the general population[8,28].

There are several limitations to our study. Diagnosis criteria and serological essays varied across studies and may have introduced some unexplained heterogeneity. The contribution of HBV in HCC might have been underestimated in patients with occult infection, which is also associated with PLC. Unfortunately, due to the study design and lack of informative data, we could not perform detailed sub-analyses by etiology in the non-viral group, e.g., heavy alcohol consumption, MAFLD (obesity, mellitus), or aflatoxin exposure. In future studies, it would be important to understand the liver cancer burden attributable to etiologies other than HBV and HCV. Wide vaccination coverage, including birth doses, long-term treatment of HBV and HCV cure through effective direct antiviral agents (DAAs), if implemented widely and rapidly in China, could result in a decreasing PLC cancer burden in the coming decades. The presence of MAFLD has been increasing in China in recent years and, although not thoroughly described yet, may contribute to liver cancer incidence in the future. Lastly, we weighted overall AF estimates by province population size, assuming a similar incidence of PLC across provinces. This may not be the case, and future studies may apply our province- and/or regional-specific AFs to province- and/or regional-specific estimates of PLC burden, if and when they become available, to improve on our pragmatic weighting approach.

Our study is the first to describe the burden of PLC caused by HBV and HCV, alone or conjointly, in mainland China at regional and provincial levels, which is crucial to provide evidence to help refine the

existing strategy for reducing the mortality burden of the two viruses in China.

In conclusion, although HBV infection remains the predominant cause of PLC all over China, the contribution of specific etiologies varies substantially by region, sex, and age, which can inform regionally tailored strategies for liver cancer prevention and early detection. Our work also supports the new WHO and Chinese guidelines extending HBV treatment to younger patients and patients with less advanced diseases. Broad implementation of these guidelines is crucial to reduce and prevent the high HBV-related mortality currently observed in mainland China.

DECLARATIONS

Authors' contributions

Design: Clifford GM, Chen W
Literature research: Lin C, Liu Z, Wei F
Data analysis: Lin C, Liu Z
Manuscript writing: Lin C
Manuscript editing: Clifford GM, de Martel C, Lin C, Wei F
Manuscript revision: Clifford GM, de Martel C, Chen W, Lin C, Liu Z

Data source and availability

Data used in this study were extracted from published articles and theses. Data are available from the corresponding author upon reasonable request.

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Conflicts of interest

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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