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*Observational Study*

**Global trends in hepatitis C-related hepatocellular carcinoma mortality: A public database analysis (1999-2019)**

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**Abstract**

**BACKGROUND**

Hepatitis C is a leading cause of chronic liver disease worldwide and significantly contributes to the burden of hepatocellular carcinoma (HCC). However, there are marked variations in the incidence and mortality rates of HCC across different geographical regions. With the advent of new widely available treatment modalities, such as direct-acting antivirals, it is becoming increasingly imperative to understand the temporal and geographical trends in HCC mortality associated with Hepatitis C. Furthermore, gender disparities in HCC mortality related to Hepatitis C are a crucial yet underexplored aspect that adds to the disease's global impact. While some studies shed light on gender-specific trends, there is a lack of comprehensive data on global and regional mortality rates, particularly those highlighting gender disparities. This gap in knowledge hinders the development of targeted interventions and resource allocation strategies.

**AIM**

To understand the global and regional trends in Hepatitis C-related HCC mortality rates from 1990 to 2019, along with gender disparities.

## METHODS

We utilized the Global Burden of Disease database, a comprehensive repository for global health metrics to age-standardized mortality rates due to Hepatitis C-related HCC from 1999 to 2019. Rates were evaluated per 100000 population and assessed by World Bank-defined regions. Temporal trends were determined using Joinpoint software and the Average Annual Percent Change (AAPC) method, and results were reported with 95% confidence intervals (CI).

## RESULTS

From 1990 to 2019, overall, <sup>1</sup> there was a significant decline in HCC-related mortality rates with an AAPC of -0.80% [95%CI (-0.83 to -0.77)]. Females demonstrated a marked decrease in mortality with an AAPC of -1.06% [95%CI (-1.09 to -1.03)], whereas the male cohort had a lower AAPC of -0.52% [95%CI (-0.55 to -0.48)]. Regionally, East Asia and the Pacific demonstrated a significant decline with an AAPC of -2.05% [95%CI (-2.10 to -2.00)], whereas Europe and Central Asia observed an uptrend with an AAPC of 0.72% [95%CI (0.69 to 0.74)]. Latin America and the Caribbean also showed an uptrend with an AAPC of 0.06% [95%CI (0.02 to 0.11)]. In the Middle East and North Africa, the AAPC was non-significant at 0.02% [95%CI (-0.09 to 0.12)]. North America, in contrast, displayed a significant upward trend with an AAPC of 2.63% [95%CI (2.57 to 2.67)]. South Asia [AAPC -0.22%, 95%CI (-0.26 to -0.16)] and Sub-Saharan Africa [AAPC -0.14%, 95%CI (-0.15 to -0.12)] significantly declined over the study period.

## CONCLUSION

Our study reports disparities in Hepatitis C-related HCC mortality between 1999 to 2019, both regionally and between genders. While East Asia and the Pacific regions show a promising decline in mortality, North America has experienced a concerning

rise in mortality. These regional variations highlight the need for healthcare policymakers and practitioners to tailor public health strategies and interventions. The data serves as a call to action, particularly for regions where mortality rates are not improving, emphasizing the necessity for a nuanced, region-specific approach to combating the global challenge of HCC secondary to Hepatitis C.

## **INTRODUCTION**

In the late 20<sup>th</sup> century, there was a significant shift in the etiology of chronic liver disease due to the advent of Hepatitis C infection, which also contributed to a rising trend in the incidence of liver-related malignancies<sup>[1]</sup>. Data from the World Health Organization (WHO) indicates that globally, around 58 million individuals are infected with the hepatitis C virus (HCV). Each year, there are about 1.5 million new cases of HCV, and the virus is responsible for roughly 290000 fatalities annually<sup>[2]</sup>. Based on 2020 data, <sup>4</sup> hepatocellular carcinoma (HCC) ranks as the sixth most frequently diagnosed cancer globally and stands as the third leading cause of cancer-related deaths<sup>[3]</sup>. In Africa and East Asia, HBV infection is the predominant cause of HCC, responsible for up to 60% of cases. Conversely, in Western countries, chronic HCV infection emerges as the primary etiological factor for HCC, with about 34% of HCC cases in the United States (USA) attributed to it<sup>[4]</sup>.

The annual incidence of HCC in patients with hepatitis C ranges from about 1-8%, being the highest in Japan (4%-8%), followed by Italy (2%-4%), and USA (1.4%)<sup>[5]</sup>. Various studies suggest that HCC might be the first complication to develop and a more common cause of death in patients with HCV-associated cirrhosis<sup>[6]</sup>. Most cases of HCC manifest in individuals with cirrhosis, which serves as an independent risk factor for developing HCC, irrespective of the underlying cause of the liver disease. Data suggests that about one-third of patients with cirrhosis will develop liver cancer during their lifetimes<sup>[7]</sup>. The annual incidence of HCC among cirrhotic patients ranges between 1%-8%, with specific rates varying based on the type of liver disease, and estimates

indicate that patients infected with HCV face a 15 to 20 times higher risk of developing HCC. In those with cirrhosis, the annual incidence of HCC is projected to be between 1% and 4% over a period of 30 years<sup>[8]</sup>. In 2012, data indicated that around 170000 new cancer cases, which is approximately 7.8% of all newly diagnosed cancers, were attributed to the HCV<sup>[9]</sup>. Over the last ten years, deaths attributable to HCV-related HCC have increased by 21.1%; however, at the same time, deaths from HCC secondary to causes other than HCV and alcohol have remained stable<sup>[10]</sup>. Hence, this escalating global burden of HCV infection-related HCC has gained attention among clinicians, public health professionals, and researchers.

There has been variability in the incidence of HCV-related HCC, based on ethnicity and geographic location. HCV is recognized as the primary cause of HCC in regions including the USA, Europe, Japan, and South America<sup>[10]</sup>. Delving deeper into country-specific data, the prevalence of HCV in Japan has been estimated to be 3%, and an estimated 85% of patients with HCC are infected with HCV<sup>[11]</sup>. In the USA, where the prevalence of HCV is about 1.8% of the population, around 50%-60% of HCC patients are HCV-positive<sup>[12]</sup>. Analyzing the demographic distribution within the USA, there are distinct variations of HCC by ethnicity and age. Particularly, Hispanic individuals and those born between 1945 and 1965 are at the highest risk of HCC<sup>[13]</sup>. A comprehensive study involving 150000 HCV-infected USA veterans revealed that the Hispanic demographic reported the most substantial yearly HCC incidence at 7.8%. This heightened incidence is believed to correlate with the increased prevalence of nonalcoholic fatty liver disease within this group<sup>[14]</sup>. Another study from a comparable cohort highlighted a 2.5-fold surge in HCC incidence, with a threefold increase in mortality since 2001, even after the introduction of direct-acting antivirals (DAAs)<sup>[15]</sup>.

Despite the recent advancement in the development of antiviral therapies, including DAAs<sup>[16]</sup>, which have, to an extent, revolutionized the treatment of HCV, there persists an ongoing debate on the long-term impact of the virus on liver health. Adequate treatment helps cure the active infection, but the possibility of progression to cirrhosis leading to HCC persists in some patients. Hence, it makes understanding the

global mortality trends in HCV-related HCC of high academic interest and critical importance for public health policy and intervention strategies. In 2016, the World Health Assembly proposed eliminating viral hepatitis as a public health threat<sup>[17]</sup>. Still, most countries need to meet their expected goals by 2020 due to the impact of the coronavirus disease 2019 pandemic and various other factors<sup>[18]</sup>. Consequently, in 2021, the WHO established guidance featuring absolute incidence targets, specifying the number of new HCV infections per 100000 persons each year<sup>[19]</sup>.

In our analysis, we aim to examine the change in trends in regional and gender-specific variances in mortality rates due to HCC secondary to hepatitis C. We aim to identify disparities that inform targeted interventions for at-risk populations. Prior studies have mainly analyzed global liver cancer trends without focusing on specific etiologies such as HCV. To our knowledge, no prior study has estimated the risk of HCV-related HCC mortality and HCC trends over time, covering all World Bank regions. This article aims to provide a comprehensive review of current mortality trends in Hepatitis C-related HCC. It will provide a better understanding of the global mortality burden and facilitate designs for policymakers by providing targeted measures to mitigate the impact of the increasingly prevalent malignancy.

## **MATERIALS AND METHODS**

### ***Study population and data collection***

The primary data source for this study was the Global Burden of Disease (GBD) database, a comprehensive repository for global health metrics. Initiated in the early 1990s, the GBD database is continually updated to offer the most current insights into the global prevalence, incidence, and impact of diseases<sup>[20]</sup>. Compiled by the Institute for Health Metrics and Evaluation, the database strictly adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting. The GBD database encompasses data from numerous countries and territories, capturing various health-related metrics, including mortality. Our analysis was divided by World Bank-defined regions, including Sub-Saharan Africa, East Asia and Pacific, Europe and Central Asia, Latin

America and the Caribbean, Middle East and North Africa, and South Asia to provide a more comprehensive geographical perspective.

### *Measures of disease burden*

This study focused on mortality related to HCC due to Hepatitis C to comprehensively understand the disease's long-term trends and current status. Age-standardized estimates were employed to adjust for differences in the age distribution of different populations, aligning them to a standardized reference world population. This adjustment enabled the comparison of disease burdens across diverse populations. As in prior studies, rates were reported per 100000 population and were age-standardized to facilitate comparisons across different demographic structures<sup>[21]</sup>.

### *Data analysis*

We examined age-standardized mortality rates per 100000 population to analyze hepatitis C-related HCC mortality rates. Joinpoint software assessed temporal trends in the Average Percent Change (APC), representing the change in mortality during a specific period. Joinpoint identified time points where the trend changed significantly using a Monte Carlo permutation test and a *t*-test. Log-linear regression models were fitted to evaluate trends in age-standardized mortality rates. To enhance the reliability of our analysis, especially in the context of uncertain data distributions, we employed Joinpoint's Empirical Quantile Confidence Interval method. This approach provides robust and conservative 95% confidence intervals for APC, Average Annual Percent Change (AAPC), and the location of joinpoints ( $\tau$ ). Unlike traditional methods that yield *P* values, these confidence intervals directly reflect the measurement level of the data, offering a more intuitive understanding of result reliability and significance<sup>[22]</sup>. We limited our models to a maximum of three joinpoints to minimize bias. Statistical significance was determined based on these 95% confidence intervals, as the Empirical Quantile method does not compute traditional *p*-values but offers a more reliable measure of significance<sup>[23]</sup>.



## **RESULTS**

### ***World Bank regions***

The overall mortality rate declined from 2.25/100000 in 1999 to 1.78/100000 in 2019, with an AAPC of -0.80% (95%CI of -0.83 to -0.77). The mortality rate displayed five segments: An increase from 1990-1995 (APC: 2.29, 95%CI: 2.05 to 2.54), a slight rise from 1995-1999 (APC: 0.38, 95%CI: 0.11 to 0.68), followed by sharp declines from 1999-2004 (APC: -4.61, 95%CI: -4.76 to -4.45), 2004-2012 (APC: -1.14, 95%CI: -1.32 to -1.03), and 2012-2019 (APC: -0.46, 95%CI: -0.62 to -0.22) (Figure 1).

For females, the rate declined from 2.08/100000 in 1999 to 1.53/100000 in 2019, with an AAPC of -1.06% (95%CI: -1.09 to -1.03). The trends showed an increase from 1990-1995 (APC: 1.36, 95%CI: 1.11 to 1.65) with subsequent declines, notably from 1999-2004 (APC: -4.92, 95%CI: -5.07 to -4.75) (Figure 1).

For males, the rate declined from 2.42/100000 in 1999 to 2.08/100000 in 2019, with an AAPC of -0.52% (95%CI: -0.55 to -0.48). There was an initial rise from 1990-1996 (APC: 3.02, 95%CI: 2.85 to 3.22) followed by varied declines, most sharply from 1999-2004 (APC: -4.19, 95%CI: -4.40 to -4.00) (Figure 1).

### ***East Asia and the Pacific***

The rate declined from 4.54/100000 to 2.50/100000 with an AAPC of -2.05% with a 95%CI of -2.10 to -2.00. The mortality rate displayed five segments: An increase from 1990-1995 (APC: 2.31, 95%CI: 1.92 to 2.81), a slight drop from 1995-1999 (APC: -0.06, 95%CI: -0.62 to 0.42), followed by sharp declines from 1999-2004 (APC: -7.83, 95%CI: -8.08 to -7.57), 2004-2012 (APC: -3.16, 95%CI: -3.38 to -2.98), and 2012-2019 (APC: -0.69, 95%CI: -0.94 to -0.34) (Figure 2).

For females, the rate declined from 4.35/100000 in 1999 to 2.19/100000 in 2019, with an AAPC of -2.39 (95%CI: -2.43 to -2.35). The trends showed an increase from 1990-1996 (APC: 1.16, 95%CI: 0.91 to 1.40), a sharp decline from 1996-2000 (APC: -2.53,



95%CI: -2.86 to -2.20) followed by further declines, notably from 2000-2004 (APC: -9.17, 95%CI: -9.45 to -8.90) (Figure 2).

For males, the rate declined from 4.73/100000 in 1999 to 2.96/100000 in 2019, with an AAPC of -1.60 (95%CI: -1.64 to -1.55). The trends showed an initial rise from 1990-1996 (APC: 3.19, 95%CI: 2.95 to 3.52) followed by varied declines, most sharply from 1999-2004 (APC: -7.07, 95%CI: -7.33 to -6.82) (Figure 2).

### ***Europe and Central Asia***

The overall population's mortality rate increased from 1.16/100000 in 1999 to 1.43/100000 in 2019, with an AAPC of 0.72, with a 95%CI of 0.69 to 0.74. The mortality rate exhibited five distinct segments: An increase from 1990-1994 (APC: 2.58, 95%CI: 2.44 to 2.73), a steady rise from 1994-2005 (APC: 0.56, 95%CI: 0.50 to 0.61), a further increase from 2005-2012 (APC: 1.23, 95%CI: 1.12 to 1.38), a negligible decline from 2012-2015, and a drop from 2015-2019 (APC: -0.89, 95%CI: -1.19 to -0.72) (Figure 3).

For females, the rate increased from 0.98/100000 in 1999 to 1.17/100000 in 2019, with an AAPC of 0.60% (95%CI of 0.59 to 0.62). Mortality trends indicated an increase from 1990-1994 (APC: 1.22, 95%CI: 1.07 to 1.39) with subsequent varied changes, a notable rise from 1998-2005 (APC: 1.02, 95%CI: 0.90 to 1.10), a significant increase from 2005-2008 (APC: 1.60, 95%CI: 1.33 to 1.73), a steady rise from 2008-2013 (APC: 0.74, 95%CI: 0.59 to 0.82), and a decline from 2013-2019 (APC: -0.58, 95%CI: -0.65 to -0.50) (Figure 3).

For males, the rate increased from 1.41/100000 in 1999 to 1.76/100000 in 2019, with an AAPC of 0.77% (95%CI: 0.75 to 0.80). The segments displayed an initial rise from 1990-1994 (APC: 4.10, 95%CI: 3.91 to 4.30), growth from 1994-1999 (APC: 0.65, 95%CI: 0.50 to 0.86), a plateau from 1999-2006, an increase from 2006-2012 (APC: 1.33, 95%CI: 1.20 to 1.54), a slight drop from 2012-2015, and a decline from 2015-2019 (APC: -1.19, 95%CI: -1.50 to -1.01) (Figure 3).

### ***Latin America and the Caribbean***

For Latin America & Caribbean, a minor increase was noted from 1.06/100000 in 1999 to 1.09/100000 in 2019 with an AAPC of 0.06 with a 95%CI of 0.02 to 0.11. Mortality trends displayed six segments: An initial decline from 1990-1993 (APC: -0.91, 95%CI: -1.40 to -0.26), a further decrease from 1993-2000 (APC: -2.40, 95%CI: -2.56 to -2.26), an increase from 2000-2006 (APC: 1.11, 95%CI: 0.83 to 1.29), a pronounced rise from 2006-2012 (APC: 2.37, 95%CI: 2.11 to 2.81), a steady increase from 2012-2016 (APC: 0.66, 95%CI: 0.35 to 1.45), and a decline from 2016-2019 (APC: -0.59, 95%CI: -1.34 to -0.12) (Figure 4).

For females, the rate declined from 1.22/100000 in 1999 to 1.05/100000 in 2019, with an AAPC of -0.52% (95%CI of -0.56 to -0.48). The trends displayed six segments: A decline from 1990-1993 (APC: -1.31, 95%CI: -1.86 to -0.79), a sharp decrease from 1993-2000 (APC: -3.23, 95%CI: -3.36 to -3.10), a slight increase from 2000-2007 (APC: 0.47, 95%CI: 0.26 to 0.60), a significant rise from 2007-2010 (APC: 2.33, 95%CI: 1.76 to 2.63), a steady increase from 2010-2015 (APC: 0.77, 95%CI: 0.46 to 1.00), and a decline from 2015-2019 (APC: -0.56, 95%CI: -1.10 to -0.24) (Figure 4).

For males, the rate increased from 0.87/100000 in 1999 to 1.12/100000 in 2019, with an AAPC of 0.88% (95%CI: 0.82 to 0.94). Mortality trends highlighted an initial negligible change from 1990-1993, a decline from 1993-2000 (APC: -1.17, 95%CI: -1.66 to -0.97), a pronounced rise from 2000-2006 (APC: 2.06, 95%CI: 1.52 to 2.41), a further significant increase from 2006-2012 (APC: 3.24, 95%CI: 2.89 to 3.89), an increase from 2012-2016 (APC: 1.11, 95%CI: 0.70 to 2.08), and a slight decline from 2016-2019 (APC: -0.47) though it was not statistically significant (Figure 4).

### ***Middle East and North Africa***

In the Middle East & North Africa, the rate slightly decreased from 3.81/100000 to 3.74/100000 with an AAPC of 0.02 with a 95%CI of -0.09 to 0.12. The mortality rate presented three segments: An initial decline from 1990-1999 (APC: -1.10, 95%CI: -1.64 to -0.69), a substantial rise from 1999-2011 (APC: 2.10, 95%CI: 1.80 to 2.49), and a decrease from 2011-2019 (APC: -1.77, 95%CI: -2.35 to -1.27) (Figure 5).

For females, the rate declined from 2.36/100000 in 1999 to 2.12/100000 in 2019, with an AAPC of -0.38% (95%CI of -0.44 to -0.33). The trends indicated six segments: A decline from 1990-2000 (APC: -1.79, 95%CI: -2.11 to -1.61), a transient increase from 2000-2003 (APC: 2.58, not statistically significant), a mild rise from 2003-2006 (APC: 0.91, 95%CI: 0.29 to 1.88), a pronounced increase from 2006-2009 (APC: 4.14, 95%CI: 2.91 to 4.73), a decrease from 2009-2015 (APC: -0.87, 95%CI: -1.20 to -0.45), and a significant decline from 2015-2019 (APC: -2.51, 95%CI: -3.39 to -2.00) (Figure 5).

For males, the rate increased from 5.20/100000 in 1999 to 5.25/100000 in 2019, with an AAPC of 0.12% (95%CI: -0.02 to 0.24). The trends showed three segments: An initial decline from 1990-1998 (APC: -1.10, 95%CI: -2.02 to -0.49), a substantial increase from 1998-2011 (APC: 2.04, 95%CI: 1.74 to 2.51), and a decline from 2011-2019 (APC: -1.74, 95%CI: -2.42 to -1.18) (Figure 5).

### ***North America***

In North America, the mortality rate increased from 0.72/100000 to 1.53/100000 with an AAPC of 2.63, with a 95%CI of 2.57 to 2.67. The mortality trends showcased four distinct segments: A rise from 1990-1999 (APC: 4.02, 95%CI: 3.86 to 4.21), an increase from 1999-2010 (APC: 2.87, 95%CI: 2.74 to 3.01), an uptick from 2010-2015 (APC: 1.60, 95%CI: 1.20 to 2.10), and a minor rise from 2015-2019 (APC: 0.16, not statistically significant) (Figure 6).

For females, the rate increased from 0.61/100000 in 1999 to 1.17/100000 in 2019, with an AAPC of 2.21% (95%CI of 2.18 to 2.25). The mortality trends illustrated five segments: An increase from 1990-2000 (APC: 3.68, 95%CI: 3.58 to 3.79), a rise from 2000-2004 (APC: 1.50, 95%CI: 1.00 to 1.95), a pronounced growth from 2004-2009 (APC: 3.13, 95%CI: 2.83 to 3.69), an increase from 2009-2015 (APC: 1.32, 95%CI: 1.06 to 1.59), and a decline from 2015-2019 (APC: -0.48, 95%CI: -0.97 to -0.09) (Figure 6).

For males, the rate increased from 0.84/100000 in 1999 to 1.94/100000 in 2019, with an AAPC of 2.90% (95%CI: 2.84 to 2.95). The trends presented four segments: An initial rise from 1990-1998 (APC: 4.33, 95%CI: 4.12 to 4.61), growth from 1998-2008 (APC: 3.26,

95%CI: 3.10 to 3.47), an increase from 2008-2014 (APC: 2.20, 95%CI: 1.81 to 2.59), and an uptick from 2014-2019 (APC: 0.76, 95%CI: 0.17 to 1.10) (Figure 6).

### ***South Asia***

In South Asia, rates decreased from 0.86/100000 to 0.81/100000 with an AAPC of -0.22 with a 95%CI of -0.26 to -0.16. The mortality trends revealed four segments: An initial increase from 1990-2001 (APC: 0.27, 95%CI: 0.14 to 0.54), a decrease from 2001-2008 (APC: -0.37, 95%CI: -0.77 to -0.05), a sharp decline from 2008-2012 (APC: -1.82, 95%CI: -2.54 to -1.16), and a minor uptick from 2012-2019 (APC: 0.10, 95%CI: -0.17 to 0.57) (Figure 7).

For females, the rate declined from 0.98/100000 in 1999 to 0.88/100000 in 2019, with an AAPC of -0.37% (95%CI of -0.42 to -0.31). The mortality trends showcased four segments: A slight increase from 1990-2001 (APC: 0.13, 95%CI: -0.01 to 0.39), a decline from 2001-2008 (APC: -0.69, 95%CI: -1.07 to -0.29), a sharp drop from 2008-2012 (APC: -2.12, 95%CI: -2.94 to -1.40), and a mild rise from 2012-2019 (APC: 0.20, 95%CI: -0.11 to 0.67) (Figure 7).

For males, the rate declined from 0.75/100000 in 1999 to 0.72/100000 in 2019 with an AAPC of -0.09 (95%CI: -0.13 to -0.05). The trends indicated six segments: An initial minor decline from 1990-1994 (APC: -0.17, 95%CI: -0.89 to 0.14), a surge from 1994-1997 (APC: 1.19, 95%CI: 0.67 to 1.51), a stagnant phase from 1997-2008 (APC: 0.01, 95%CI: -0.31 to 0.11), a decline from 2008-2012 (APC: -1.41, 95%CI: -1.82 to 0.30), a decrease from 2012-2016 (APC: -0.37, 95%CI: -1.57 to 0.00), and an increase from 2016-2019 (APC: 0.54, 95%CI: -0.01 to 1.23) (Figure 7).

### ***Sub-Saharan Africa***

Sub-Saharan Africa mortality rates decreased from 1.30/100000 to 1.25/100000 with an AAPC of -0.14 with a 95%CI of -0.15 to -0.12. The mortality trends portrayed five segments: An initial surge from 1990-1998 (APC: 1.73, 95%CI: 1.65 to 1.79), a decline from 1998-2004 (APC: -0.91, 95%CI: -0.97 to 1.70), a sharper drop from 2004-2007 (APC: -

1.30, 95%CI: -1.44 to -0.99), followed by declines from 2007-2014 (APC: -0.47, 95%CI: -0.56 to -0.30), and 2014-2019 (APC: -1.00, 95%CI: -1.20 to -0.87) (Figure 8).

For females, the rate declined from 1.40/100000 in 1999 to 1.24/100000 in 2019, with an AAPC of -0.41% (95%CI of -0.43 to -0.38). The trends demonstrated four segments: An increase from 1990-1998 (APC: 0.70, 95%CI: 0.60 to 0.80), followed by declines from 1998-2007 (APC: -0.87, 95%CI: -1.05 to -0.79), 2007-2014 (APC: -0.45, 95%CI: -0.58 to -0.07), and 2014-2019 (APC: -1.27, 95%CI: -1.53 to -1.08) (Figure 8).

For males, the rate increased from 1.17/100000 in 1999 to 1.25/100000 in 2019, with an AAPC of 0.23% (95%CI: 0.21 to 0.26). The patterns illustrated four segments: A pronounced rise from 1990-1997 (APC: 3.26, 95%CI: 3.15 to 3.40), followed by minor growth from 1997-2000 (APC: 0.16, 95%CI: -0.23 to 0.48), a decline from 2000-2008 (APC: -1.23, 95%CI: -1.44 to -1.13), and another decrease from 2008-2019 (APC: -0.58, 95%CI: -0.65 to -0.49) (Figure 8).

## **DISCUSSION**

The results of our study show an overall decline in the mortality rates of patients with hepatitis C-related HCC over the last two decades. Notably, females exhibited a remarkable decrease in mortality compared to males. Regionally, East Asia and the Pacific displayed a significant decline in mortality, while Europe and Central Asia witnessed an upward trend. Latin America and the Caribbean also experienced an increase in mortality rates. However, no significant difference was observed in the Middle East and North Africa. North America exhibited a notable upward trend. South Asia and Sub-Saharan Africa significantly declined throughout the study period. This raises the hope of identifying areas for implementing more targeted resources. Despite some progress, multiple challenges remain in meeting the WHO 2030 goal of eliminating viral hepatitis<sup>[24]</sup>.

Globally, over 170 million people are affected by chronic HCV, with 50%-80% of these cases eventually leading to cirrhosis and HCC<sup>[25]</sup>. Despite ongoing challenges in creating and implementing preventive vaccines for HCV, recent advancements in

treatment using specific drugs have significantly lowered the morbidity and mortality associated with HCC<sup>[26-28]</sup>. The declining trends in deaths due to HCV-related HCC are likely influenced by the cumulative impact of hepatitis C viral suppression achieved through new-generation antiviral agents<sup>[29]</sup>. The most rapid decline in mortality occurred between 1999-2004. At the same time, the overall trends of death caused by HCC declined slowly, probably due to population growth and aging<sup>[30,31]</sup>.

Females demonstrated a marked decrease in mortality as compared to the male cohort. This finding has been reported previously, with most studies involving Western cohorts and two studies being in Asian cohorts<sup>[32-37]</sup>. In a large multi-ethnic Asian patient cohort, it was found that females with HCC were significantly more adherent to surveillance protocols. As a result, they often presented with less advanced stages of HCC, leading to correspondingly better overall survival rates compared to males<sup>[38]</sup>. A higher proportion of females had HCC diagnosed during regular surveillance, resulting in detection at an earlier BCLC stage, with significantly smaller tumor sizes and lower incidences of portal vein tumor invasion and extrahepatic involvement. Being diagnosed earlier allows for better therapeutic options, as seen by the trend of more women receiving curative treatments<sup>[38]</sup>. Studies have hypothesized that sex hormones may play a role in the pathogenesis of HCC, suggesting a protective effect of estrogen against the development of HCC and an increased risk associated with testosterone<sup>[39,40]</sup>. The male predominance in HCC mortality is traditionally attributed to factors such as a higher prevalence of HCV infection in males and gender differences in high-risk lifestyle behaviors, including heavier alcohol consumption and smoking among males<sup>[41]</sup>.

Decreasing mortality in Eastern Asia may be related to long-term vision, cost-effective interventions, and effective medical-care systems in high-risk countries (e.g., China)<sup>[42,43]</sup>. However, HCC-related mortality showed the largest increasing trend in Central Asia. Uzbekistan has high mortality due to HCC associated with the seroprevalence of HCV infections, and the transmission of HCV was standard in medical treatment and drug abusers<sup>[44]</sup>. In Europe, there is an increasing trend in



mortality, as patients successfully treated for HCV exhibit high rates of drug and liver-related mortality. Notably, <sup>7</sup> overall mortality rates in these patients are significantly higher than in the general population, including for those without cirrhosis at the time of successful HCV treatment<sup>[45]</sup>.

<sup>1</sup> Additionally, we did not observe a decreasing trend for HCC-related mortality in American countries. Data on the prevalence, incidence, and risk factors for HCC in Latin America is limited<sup>[46]</sup>. Mendez-Sanchez N. reported that in Mexico, the cause-specific mortality rate for this condition was 4.1 per 100000 in 2000, and it rose to 4.7 per 100000 by 2006<sup>[47]</sup>. The primary causes of liver cancer in Argentina or Brazil include HCV and HBV infection, alcohol abuse, cryptogenic cirrhosis, and schistosomiasis<sup>[48,49]</sup>. However, North America showed a significant uptrend in mortality, although the results of previous literature are conflicting. Ramani et al. noted a decline in the death rate from HCV-related HCC since 2011, attributing this to various factors: (1) the introduction of Direct-acting Antivirals (DAAs); (2) enhanced screening and better access to HCC therapies; (3) aging of the HCV-infected birth cohort alongside competing risks from other causes of death; and (4) inherent differences in the remaining HCV patients from the birth cohort, leading to a reduced risk of developing HCV cirrhosis and HCC<sup>[50-52]</sup>. However, Younossi *et al*<sup>[53]</sup> showed a statistically significant increase in in-hospital mortality for HCV admissions from 2005-2009.

The mortality trend decreased in South Asian countries; however, in the past twenty years, the incidence of HCC in India has increased, especially in Mumbai, Chennai, and Bangalore<sup>[54]</sup>. <sup>3</sup> Despite data showing that the incidence of HCV-related HCC in Asia has decreased since 2006, the potential risk of HCV infection cannot be ignored<sup>[55]</sup>. HCV cure is associated with a decreased risk of HCC in Sub-Saharan Africa; however, even after achieving a sustained virological response, patients with cirrhosis continue to face a risk for HCC, underscoring the necessity for ongoing surveillance<sup>[56]</sup>.

Prevention of HCV via vaccination is currently unfeasible due to its extreme genetic variability, the absence of small animal models, and the complexity of its glycoproteins<sup>[57]</sup>. Prevention of HCV can be achieved through measures such as



screening of blood products, using disposable needles, stringent sterilization of medical instruments, and strict measures against illegal drug use. While immediate medical intervention may not be necessary for new HCV infections, the WHO strongly recommends treatments such as pan-genotypic DAAs and interferon (IFN) for chronic cases. Sofosbuvir/velpatasvir has been shown to be effective and safe in a phase III trial for chronic HCV in the Asian population, and elbasvir/grazoprevir has also been proven effective in a phase III trial among Asia-Pacific/Russian participants<sup>[2,58,59]</sup>. These new medications offer a higher rate of sustained virological response, require shorter treatment durations, and cause fewer toxic side effects. It is widely recognized that while the risk of HCC occurrence decreases, it does not completely disappear after viral eradication achieved by either DAAs or IFN therapies<sup>[60]</sup>. Developing new therapies could minimize progress from chronic HCV infection to HCC. However, patients with advanced liver fibrosis still require regular surveillance after HCV eradication. <sup>6</sup> The use of DAAs for the management of HCV is relatively recent. More evidence is needed to show that effective treatment of HCV by DAAs can decrease the risk of developing HCV-related HCC. These medications can be costly; however, some DAAs are available at a much lower price in a few Asian countries than in the West<sup>[61]</sup>. Nevertheless, the cost may decrease as more pan-genotypic drugs are introduced, allowing for greater accessibility and a subsequent decrease in HCV-related mortality. One meta-analysis indicated no significant increase in HCC occurrence with DAA therapy compared to IFN-based treatment (RR 0.68)<sup>[62]</sup>. Another analysis showed similar risks for HCC occurrence and recurrence with DAAs and IFN-based treatments. These findings suggest comparable HCC risks between DAA and IFN therapies<sup>[63]</sup>.

While this study offers a comprehensive analysis of global mortality trends in Hepatitis C-related HCC across various demographics and regions, it has several limitations. The study relies on data from the GBD database, which may have inherent biases or inaccuracies. The study does not account for the impact of healthcare access, socioeconomic factors, or comorbidities on mortality rates, potentially affecting the interpretation of the results. The study focuses solely on mortality rates, not considering

other important clinical outcomes such as quality of life or disease progression. The study does not explore the potential impact of new therapeutic interventions on mortality trends. Lastly, the age-standardized estimates may only partially capture the complexities of age-related risk in different populations. These limitations should be considered when interpreting the findings and should guide future research in this area.

## **CONCLUSION**

In conclusion, we offer a comprehensive analysis of global mortality trends associated with hepatitis C-related HCC. The data reveals significant disparities in mortality rates across different regions and demographic groups, emphasizing the critical need for targeted interventions. Advances in hepatitis C treatment have shown promise, yet the persistently high mortality rates in certain areas and among specific populations call for a multi-faceted approach. This should encompass not only medical treatment but also broader strategies like improving healthcare access, raising public awareness, and promoting early diagnosis. The findings provide a robust foundation for future research and policy initiatives to mitigate the global impact of hepatitis C-related HCC.

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