

## Original Article

# Burden of Hepatitis C in Iran Between 1990 and 2010: findings from the Global Burden of Disease Study 2010

Hamid Mohaghegh Shalmani MD, PhD candidate<sup>1,2</sup>, Atefeh Noori MSc<sup>2,3</sup>, Mostafa Shokoohi MSc<sup>4</sup>, Alireza Khajavi MSc<sup>2,3</sup>, Mohammad Darvishi MD<sup>5</sup>, Alireza Delavari MD<sup>6</sup>, Hamid Reza Jamshidi PhD<sup>7</sup>, Shohreh Naderimaghham MPH PhD<sup>2,3</sup>

## Abstract

**Background:** Hepatitis C virus (HCV) is the foremost cause of deaths attributable to cirrhosis and hepatocellular carcinoma. The Global Burden of Disease study from 2010 (the GBD study 2010) quantifies and compares the degree of health loss as a result of diseases, injuries, and risk factors by age, sex, and geography overtime. This study aimed to present and critique the burden of hepatitis C and its trend in Iran between 1990 and 2010 by using the GBD study 2010.

**Methods:** We used results of the GBD study 2010 between 1990 and 2010 for Iran to measure rates and trends of mortality, causes of deaths, years of life lost (YLLs), years lived with disability (YLDs), and disability adjusted life years (DALYs) due to hepatitis C. Hepatitis C was defined as the presence of hepatitis C virus in the serum. Data were presented in three categories: acute hepatitis C, cirrhosis secondary to hepatitis C, and liver cancer secondary to hepatitis C.

**Results:** HCV infection (including the three categories of the study) led to 57.29, 59.92, and 66.45 DALYs (per 100,000 population) in 1990, 2000, and 2010, respectively. DALYs and death rates showed a slight decreasing trend for HCV cirrhosis; however, DALYs and death rates increased for acute hepatitis and liver cancer due to patients with HCV. The majority of deaths and DALYs were in individuals aged 70 years and above in all three categories of HCV. YLLs made the greatest contributions to DALYs.

**Conclusion:** DALYs due to HCV infection are increasing in Iran according to the GBD study 2010; however, the estimations of DALYs using the GBD study 2010 are mostly from model-based data and there are significant uncertainties for extrapolated data. In this regard, a comprehensive study such as the National and Subnational Burden of Diseases (NASBOD) study would be needed to estimate and calculate precisely prevalence and burden of HCV-related diseases at national and subnational levels.

**Key Words:** Global Burden of Disease, Hepatitis C, Iran

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## Introduction

Infection due to Hepatitis C Virus (HCV) is one of the leading causes of morbidity and mortality around the globe. Available data show 54,000 annual deaths and 955,000 annual disability adjusted life-years (DALYs) globally due to acute HCV infection.<sup>1</sup> Chronic hepatitis C infection is the main cause of death from cirrhosis and hepatocellular carcinoma.<sup>2</sup> Three to four million new infections occur each year and 170 million people are

chronically infected due to liver diseases including cirrhosis and liver cancer. 350,000 deaths occur each year due to all HCV-related disorders.<sup>3,4</sup> Therefore, chronic infection and HCV-related disorders such as cirrhosis and HCC are important issues in global health.

Prevalence studies for HCV have mostly been performed in particular groups such as blood donors and high-risk populations such as intravenous drug users or patients receiving hemodialysis. A systematic review of national studies between 2001 and 2008 showed a 0.16% seroprevalence of HCV infection in Iran.<sup>5</sup> The prevalence of HCV in high-risk groups such as intravenous drug users, patients with hemophilia or thalassemia, or those undergoing hemodialysis as high as 30%–90%.<sup>5,6</sup> In keeping with these ranges, a study on seroprevalence in Iran showed a high prevalence of HCV among patients with thalassemia (25%)<sup>7</sup> or hemophilia (71.3%)<sup>8</sup> and in those undergoing hemodialysis (14.4% in 1999 and 4.5% in 2006).<sup>9</sup> There is no available effective vaccine for HCV, and the combination of this and individuals with existing HCV risk factors causes the number of new positive cases of HCV to remain high.<sup>10</sup> Therefore, the determination of hepatitis C disease burden as well as its prevalence among different populations lead us to suggest best practices to implement to help lower HCV incidence and complications.

The burden of diseases, including those related to HCV, needs to be calculated for better planning and disease control. Due to this necessity, the Institute for Health Metrics and Evaluation (IHME)

**Authors' affiliations:** <sup>1</sup>Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. <sup>2</sup>Non-communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. <sup>3</sup>Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Research Institute, Tehran University of Medical Sciences, Tehran, Iran. <sup>4</sup>Regional Knowledge Hub, and WHO Collaborating Centre for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran. <sup>5</sup>Infectious Diseases and Tropical Medicine Research Center (IDTMRC), AJA University of Medical Sciences, Tehran, Iran. <sup>6</sup>Digestive Oncology Research Center, Digestive Disease Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. <sup>7</sup>School of Medicine, Department of Pharmacology, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

**Corresponding author and reprints:** Shohreh Naderimaghham MPH PhD, Non-communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. **Address:** 4<sup>th</sup> floor, No. 4, Ostad Nejatollahi St, Enqelab Ave., Tehran, Iran. Postal code: 1599666615, Tel: +98-21-88913543, Fax: +98-21-88913549; E-mail: shohrehnaderimaghham@ncdrc.info  
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team undertook the Global Burden of Disease study 2010 (the GBD study 2010) to quantify and compare the degree of health loss by age, sex, and geography over time as a result of diseases, injuries and risk factors. The first version of the GBD study was performed in 1990, and the study was rebuilt in 1999-2002, 2004, and 2010.<sup>11</sup> This study aimed to present the burden of hepatitis C and its trend by sex and age in Iran between 1990 and 2010 using the GBD study 2010. We also describe the methods and limitations of the GBD study 2010 while overviewing its calculations.

## Materials and Methods

The Global Burden of Disease study 2010 (the GBD study 2010) measured and reported metrics including rates and trends in mortality, causes of death, years of life lost (YLLs), years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy for 291 diseases and injuries as well as for 1160 sequelae and clinical outcomes related to specific diseases and injuries. One set of items evaluated by the GBD study 2010 was the prevalence and incidence of cirrhosis due to hepatitis C virus (HCV) infection among 187 countries, 20 age groups, and both sex; the period of time covered was 3 years. Prevalence, incidence, remission, and excess mortality for each disease were gathered by a systematic analysis of published and unpublished data sources. Estimates for causes of death were achieved from a comprehensive database of vital registration, verbal autopsy, surveillance, and other sources inclusive of the years 1980 to 2010.

Estimates were calculated using the database for all age-sex-country-year groups by means of DisMod-MR with a Bayesian meta-regression tool developed for the GBD study 2010.<sup>12</sup> A main part of the strategies of the GBD study 2010 to estimate cause-of-death was the enforcement of consistency between the sum of cause-specific mortality and independently assessed levels of all-cause mortality derived from demographic sources for each age-sex-country-year group. Uncertainty in every the GBD study 2010 cause of death model outcome had to be taken into account because some causes of death are known with much greater precision than others.<sup>13</sup> YLLs are years lost due to premature mortality. This index (YLL) is calculated by subtracting the age at death from the longest possible life expectancy for an individual at that defined age. On the other hand, YLLs are computed by multiplying the number of deaths in each age group by a reference life expectancy at that age. The life expectancy at birth in the reference life table is 86 years based on the lowest reported death rates for each age group across countries in 2010.<sup>11</sup> Years lived with disability are years lived in less than ideal health and calculated from the prevalence of a sequel multiplied by the disability weight for that sequel. Disability weights indicate the severity of different situations and are developed by the surveys of the general population.<sup>14</sup> DALYs is the sum of YLLs and YLDs.<sup>15,16</sup> In the GBD study 2010, uncertainty in DALYs by cause reflects uncertainty in YLLs and YLDs.<sup>17</sup> The entire measures have been reported with a 95% Uncertainty Interval (UI).

The GBD study 2010 presented burden of diseases associated with hepatitis C infection in Iran by sorting them into three categories: acute hepatitis C, cirrhosis secondary to hepatitis C, and liver cancer secondary to hepatitis C. As a lack of data sources exist in Iran related to HCV, the available data most often used by the GBD study 2010 team were data from blood donors and population-based studies obtained via systematic review.

## Results

### Death and DALYs rates due to acute hepatitis C

The reduced numbers of deaths and DALYs were related to acute hepatitis in comparison with cirrhosis and liver cancer due to HCV, for which these numbers increased from 1990 to 2010 according to the GBD study 2010. The trend of DALYs and death rates in the total population had a similar pattern, as there were slight increases in both parameters from 1990 to 2010 (Table 1). During this period, death rates for all ages increased from 0.13 (0.04–0.26) per 100,000 in 1990 to 0.20 (0.1–0.3) per 100,000 in 2010 (Table 1). The rate of DALYs in all ages also showed a rising trend from 3.86 (1.87–6.66) per 100,000 to 5.51 (3.59–7.97) per 100,000 during these years (Table 1). In women above the age of 70 years, the DALY rate in 1990 was 47 (8.15–128.8) per 100,000 and decreased to 35 (6.86–86.48) per 100,000 in 2010. For men in 1990, those older than 70 years had lower DALYs of 40 (8.78–108.99) per 100,000 and death rates of 2.79 (0.61–7.30) per 100,000 than did women of the same age range (Figure 1).

### Death and DALYs rates due to HCV-related cirrhosis

The largest number of deaths and DALYs occurred in the current category of HCV cirrhosis. Based on Table 1, the death rates for all ages in Iran increased marginally from 1.48 (1.16–1.82) per 100,000 in 1990 to 1.55 (1.25–1.87) per 100,000 in 1995 and continued to decrease slowly until 2010 (1.46 (1.18–1.87) per 100,000). Rates of DALYs in all ages demonstrated a decreasing trend from 1990 to 2010, from 43 (33.2–52.9) per 100,000 in 1990 to 35 (28.45–45.53) per 100,000 in 2010. In contrast to acute hepatitis, DALYs and death rates for HCV-related cirrhosis were higher in men older than 70 years than in women in the same age range in 2010 (Figure 2). In this age category, the trend of DALY and death rates between both sexes revealed a slight increase in 1995 and a dramatic decrease from 1995 to 2005 before leveling off in 2010. However, the decreasing trend was more significant in the DALYs rate as well as in male patients compared to the death rate and female patients (Figure 2).

### Death and DALYs rates due to HCV-related liver cancer

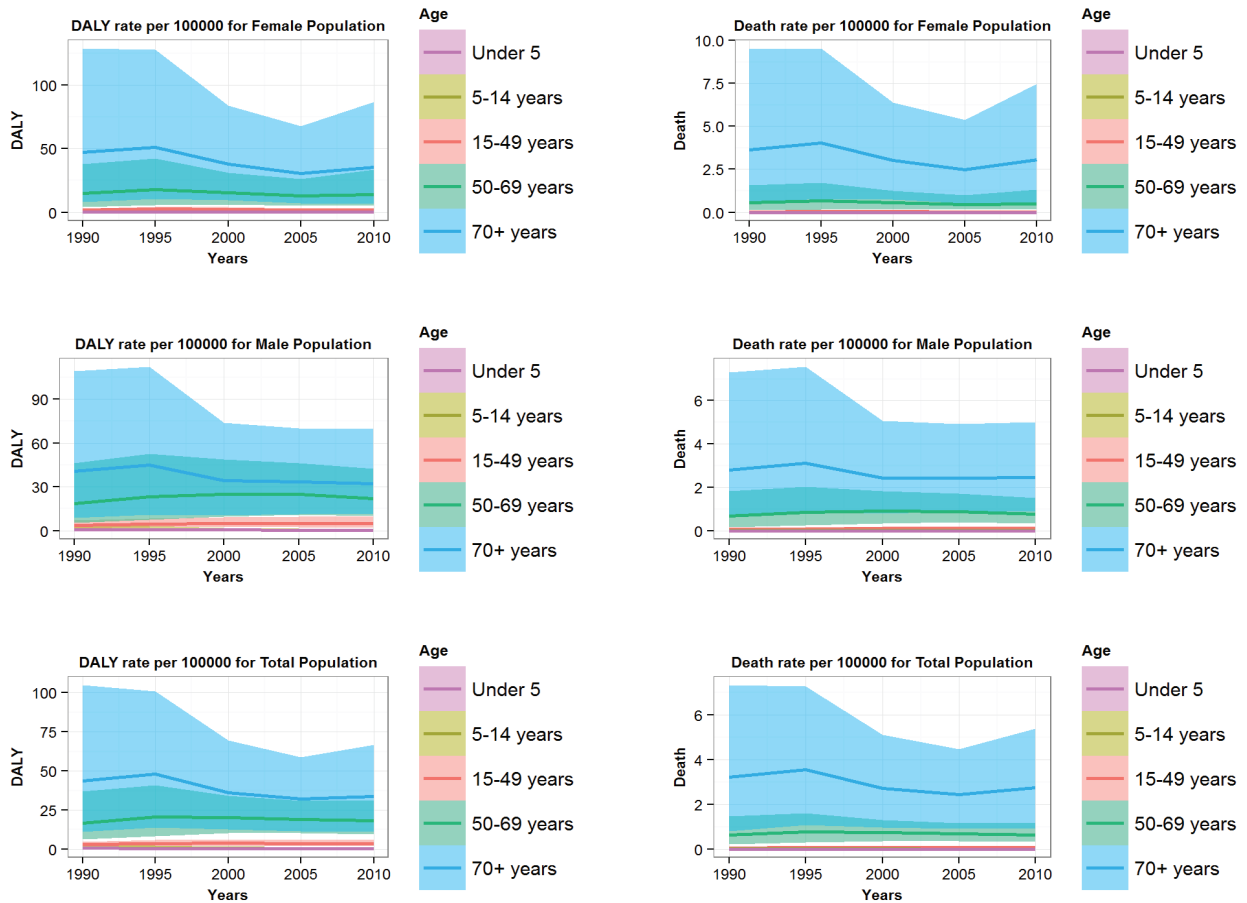
The rates of death and DALYs among patients with HCV-related liver cancer in Iran for all ages increased significantly from 0.42 (0.32–0.59) per 100,000 in 1990 to 1.23 (0.73–1.54) per 100,000 in 2010 for deaths and 10.32 (7.79–14.39) per 100,000 in 1990 to 25.67 (16.03–31.86) per 100,000 in 2010 for DALYs (Table 1). In individuals over the age of 70 years, the trend of DALYs and death rates in the total population was the inverse of the trend for patients with HCV-related cirrhosis, as rates declined in 1995, then increased until peaking in 2005 and declining slightly between 2005 and 2010 (Figure 3). As with the other 2 disease groups, in this category the death and DALYs rates were higher in men than in women (Figure 3).

The highest rates for deaths and DALYs were in individuals older than 70 years in all three HCV-related disease categories. Moreover, in all disease groups, the youngest patients (including under 5 years old and 5- to 14-years old) contributed the least to the death and DALYs rates.

Figures 4, 5, and 6 compare the YLLs and YLDs components of DALYs for acute hepatitis C, HCV-related cirrhosis, and liver cancer due to HCV. These figures show that YLLs had the highest proportion of estimated DALYs in all 3 groups. The rate of YLLs

**Table 1.** Hepatitis C Death rates, YLLs, YLDs, and DALYs (per 100000) in both sexes through 1990 to 2010 with 95% confidence interval in Iran.

	1990	1995	2000	2005	2010
<b>Acute hepatitis</b>					
Death rate	0.13 (0.04–0.26)	0.18 (0.07–0.32)	0.17 (0.27–0.09)	0.19(0.10–0.28)	0.21(0.11–0.33)
YLL	3.27 (1.39–6.07)	4.28 (2.11–7.14)	4.40 (2.78–6.26)	4.65(2.92–6.75)	4.97(3.04–7.29)
YLD	0.58(0.12–1.21)	0.56 (0.12–1.16)	0.54 (0.11–1.11)	0.51(0.11–1.08)	0.55(0.11–1.13)
DALY	3.86(1.87–6.66)	4.85 (2.63–7.74)	4.94 (3.22–6.90)	5.16(3.47–7.29)	5.52(3.59–7.97)
<b>Cirrhosis</b>					
Death rate	1.48 (1.17–1.82)	1.56 (1.26–1.88)	1.46 (1.22–1.86)	1.33(1.096–1.75)	1.47(1.18–1.87)
YLL	42.23 (32.38–52.07)	41.76 (33.78–50.37)	37.01 (30.89–48.12)	31.57(25.86–43.32)	34.31(27.41–44.72)
YLD	0.88 (0.42–1.55)	0.86 (0.42–1.51)	0.84 (0.41–1.48)	0.82(0.385–1.46)	0.95(0.47–1.67)
DALY	43.10 (33.20–52.98)	42.62 (34.56–50.88)	37.85 (31.72–49.12)	32.39(26.66–44.29)	35.26(28.45–45.53)
<b>Liver cancer</b>					
Death rate	0.43 (0.32–0.59)	0.487 (0.39–0.67)	0.78 (0.59-0.91)	1.19(0.69–1.43)	1.23(0.73–1.55)
YLL	10.26 (7.74–14.32)	11.40 (9.20–15.53)	17.008 (13.15–20.19)	24.54(14.89–29.32)	25.49(15.92–31.68)
YLD	0.07 (0.009–0.15)	0.091 (0.01–0.21)	0.13 (0.02–0.29)	0.17(0.07–0.33)	0.19(0.07–0.35)
DALY	10.33 (7.79 –14.39)	11.49 (9.27–15.66)	17.13 (13.32-20.28)	24.71(15.06–29.47)	25.68(16.03–31.86)



**Figure 1.** Death rate (per 100000 person) and DALY (per 100000) of acute hepatitis C through 1990 to 2010 with 95% confidence interval in Iran.

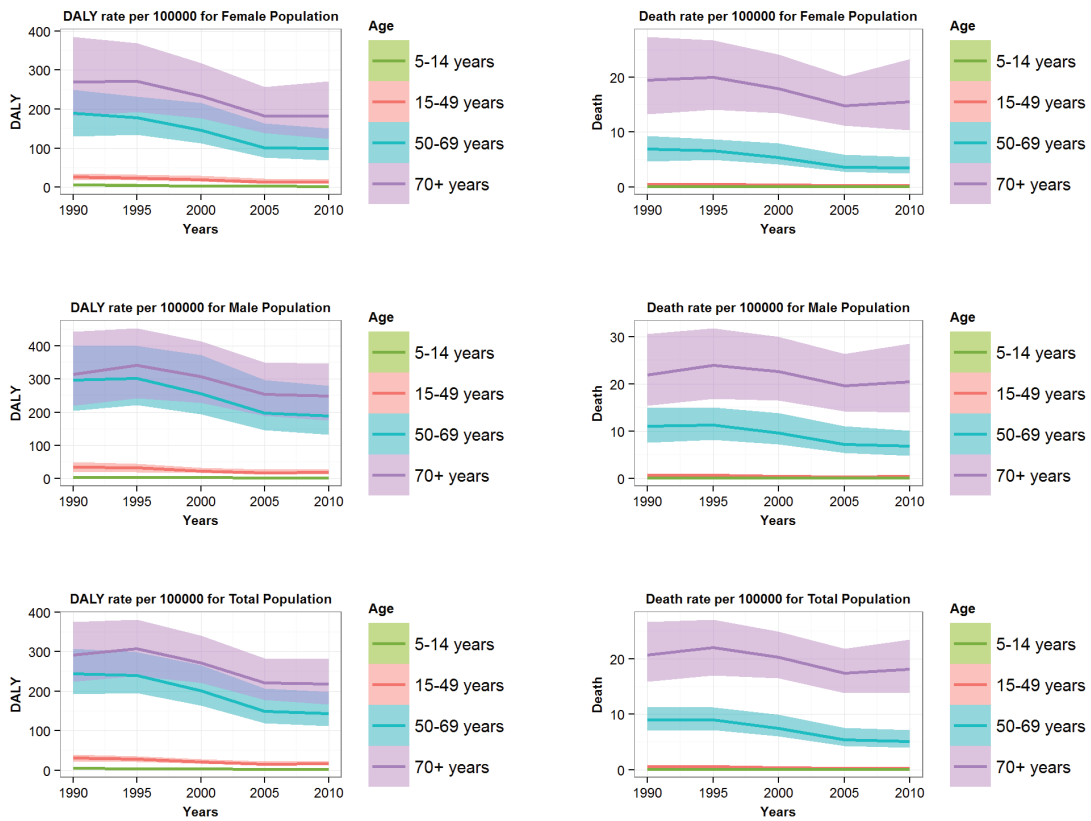


Figure 2. Death rate (per 100000) and DALY (per 100000) of HCV cirrhosis through 1990 to 2010 with 95% confidence interval in Iran.

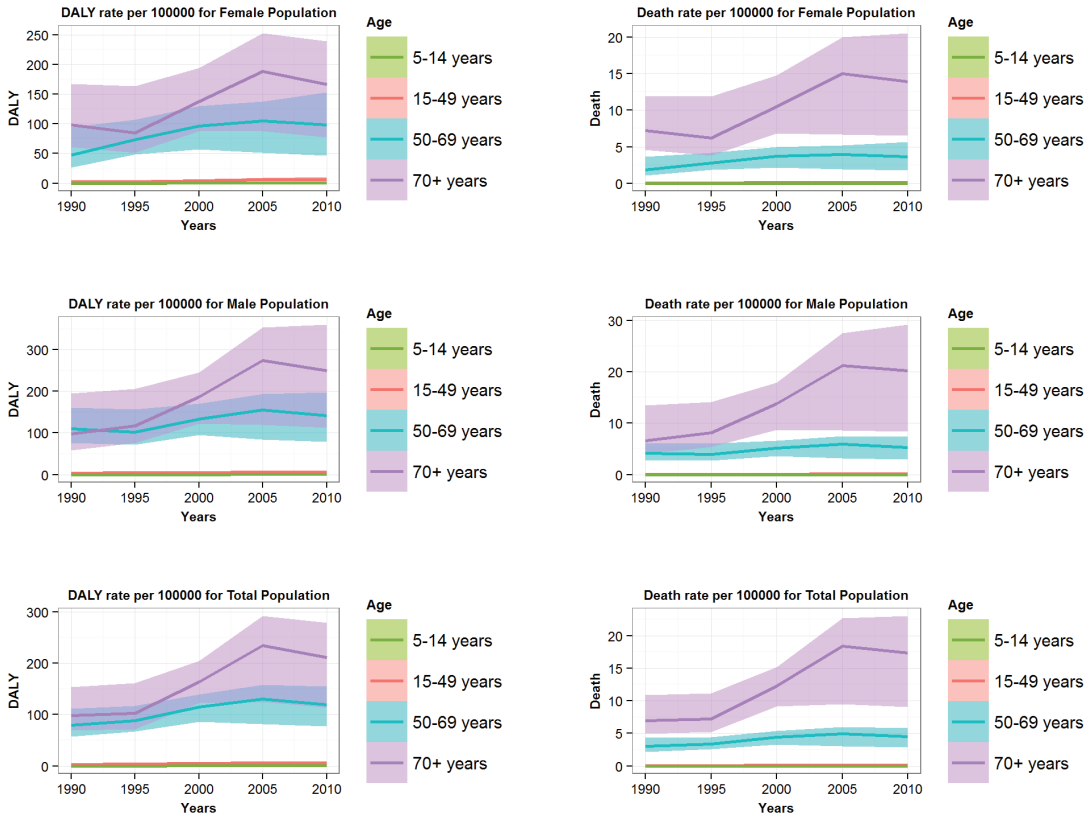
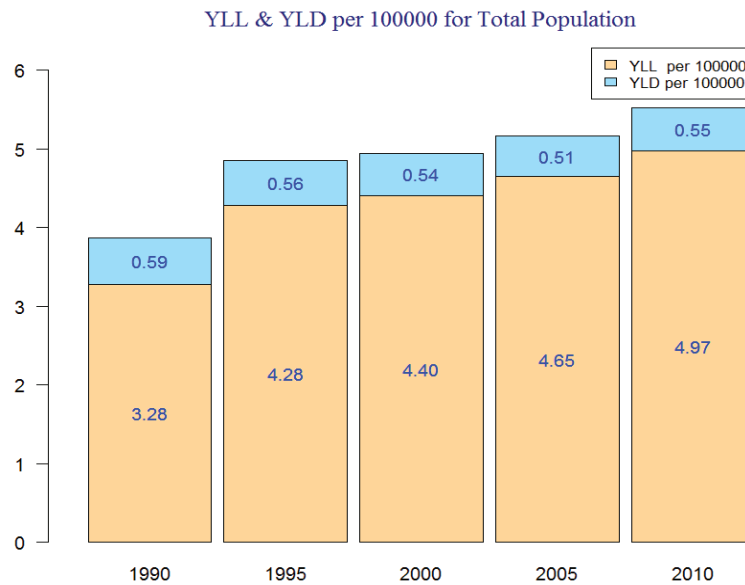
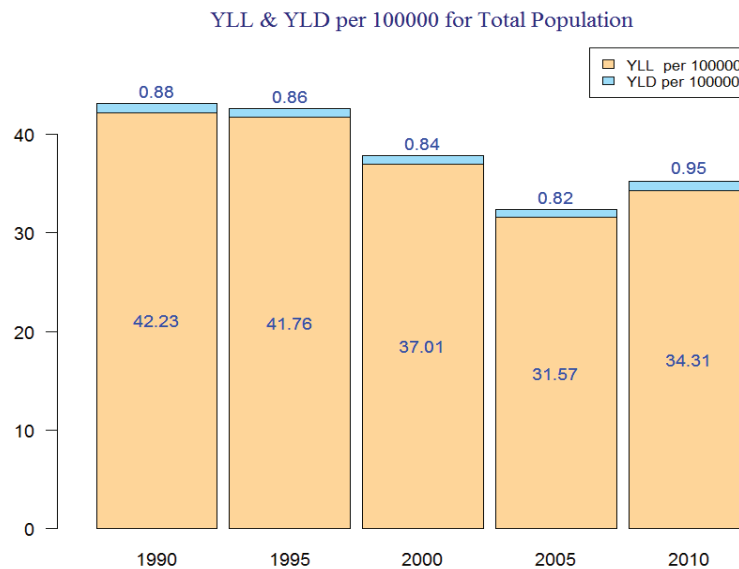


Figure 3. Death rate (per 100000) and DALY (per 100000) of liver cancer due to HCV through 1990 to 2010 with 95% confidence interval in Iran.



**Figure 4.** YLL and YLD components of estimated DALY for acute hepatitis C in total population through 1990 to 2010 in Iran.



**Figure 5.** YLL and YLD components of estimated DALY for HCV cirrhosis in total population through 1990 to 2010 in Iran.

increased from 1990 to 2010 for acute hepatitis and liver cancer due to hepatitis C, while it diminished gradually through these years in patients with HCV-related cirrhosis.

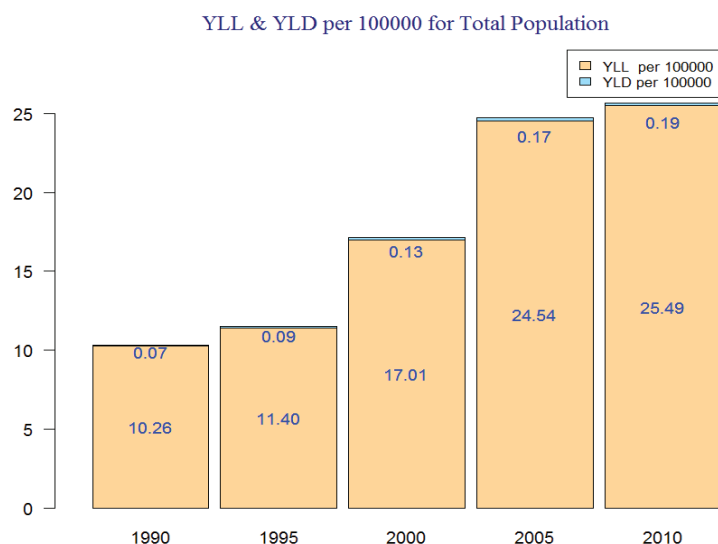
## Discussion

For the period of time measured using the GBD study 2010 (1990 to 2010), acute hepatitis and liver cancer due to HCV demonstrated an increasing trend with respect to DALYs and death. However, DALYs for HCV-related cirrhosis showed a slight decrease. The highest mortality rates were seen in individuals above 70 years of age for all 3 diseases. While there was an overall rise in the prevalence of acute hepatitis, DALYs and death rates in those over the age of 70 years declined between 1995 and 2010. Similarly, liver cancer due to HCV demonstrated a growth trend

with respect to DALYs and death rates from 1990 to 2010. HCV-related cirrhosis declined slightly in frequency in the general population and in those above 70 years of age over the duration of the study; in fact, the decreasing trend was more significant in those above 70 years of age than in other age groups for the period of time from 1990 to 2010. Years of life lost (YLL) due to premature mortality were the most significant contributors to DALYs for all three HCV-related illnesses.

The GBD study 2010 data showed that death rates due to HCV infection were largely attributable to cirrhosis followed by liver cancer and acute hepatitis. This is compatible with the findings of other studies that evaluated the burden of diseases attributed to HCV infection.<sup>18,19</sup> Mortality due to acute hepatitis C is very unusual and primary liver cancer because of HCV infection is less prevalent than is HCV cirrhosis.<sup>20</sup> It is estimated that cirrhosis and





**Figure 6.** YLL and YLD components of estimated DALY for liver cancer due to HCV in total population through 1990 to 2010 in Iran.

primary liver cancer are accountable for 2.5% of deaths worldwide and HCV infection has a primary role in developing cirrhosis and primary liver cancer.<sup>3</sup> More than 80% of cases of primary liver cancer occur in Sub-Saharan Africa and Eastern Asia. It is seldom diagnosed before the age of 50 years and is more often seen in men.<sup>21</sup> Iran isn't an endemic region for primary liver cancer and HCV cirrhosis is primarily responsible for the mortality and morbidity attributed to HCV infection.<sup>22</sup>

Death rates were highest in men above the age of 50 years. Similarly, DALYs for HCV infection are primarily due to cirrhosis and consistent with other reports of DALYs for HCV.<sup>18,23</sup> Regarding the natural history of hepatitis C, severe complications (including decompensated cirrhosis and primary liver cancer) occur after several years of HCV infection in those of older age.<sup>24</sup> This could explain the higher death rates and DALYs among patients above 70 years old and also the high contribution of YLLs in the estimated DALYs. As with the other studies, YLLs contributed the most in estimated DALYs,<sup>18,23</sup> providing the explanation for the similarity of death rates and DALYs.<sup>24</sup>

HCV infection in Iran led to 57.29, 59.92, and 66.45 DALYs (per 100,000) in 1990, 2000, and 2010, respectively. A study in Spain estimated a rate of 90.8 DALYs per 100,000 residents for HCV in 2006 using national Spanish data.<sup>18</sup> Some of this discrepancy could be explained by the different available data sources in Iran compared to Spain. In fact, there is a clear lack of data regarding HCV in Iran, leading to potential underestimations by the GBD study 2010 team.

The increasing trend for deaths and DALYs for liver cancer due to HCV infection could be related to the lack of effective treatment for liver cancer and also the improving death register system in Iran. Moreover, the improvement of patient care for acute hepatitis and cirrhosis could lead to some slight reductions in both DALYs and death rates in individuals above the age of 70 years.

Most prevalence data of Iran were gathered from blood donors, causing underestimation of HCV infection prevalence.<sup>4</sup> However, the GBD estimations are mostly based on non-population-based data, and there are significant uncertainties for extrapolated data. Data-driven studies are more valuable; with respect to this, in order to draw more accurate conclusions a national study was re-

cently conducted, the National and Subnational Burden of Diseases (NASBOD) study. This study aims to precisely estimate prevalence and burden of diseases, including communicable and non-communicable diseases such as hepatitis C, by using Iranian published and unpublished literature, national registry data, and population-based surveys.<sup>25,26</sup> This study is capable of estimating the burden of diseases accurately and in detail at the national and sub-national levels using two statistical models.<sup>27,28</sup>

In conclusion, the elimination of HCV infection in human beings is an optimal goal. Achieving this goal requires early detection of asymptomatic HCV carriers, delivery of proper care for all diagnosed patients, and administration of new antiviral agents. Meanwhile, comprehensive care and effective treatment for all patients promises to reduce the burden of diverse diseases and eventually eliminate HCV infection in the near future. Furthermore, conducting national and subnational studies in Iran in order to evaluate the prevalence of HCV infection would be an effective approach to the establishment of policies rooted in evidence-based medicine.

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## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

**General designing of paper:** Hamid Mohaghegh Shalmani, Atfeh Noori, Mostafa Shokoohi, Shohre Naderimaghani

**Designing of tables and graphs:** Alireza Khajavi, Hamid Mohaghegh Shalmani,

**Writing primary draft:** Hamid Mohaghegh Shalmani, Shohre Naderimaghani, Mohammad Darvishi, Alireza Delavari

**Manuscript revision:** Hamid Mohaghegh Shalmani, Shohre Naderimagham, Atefeh Noori, Mostafa Shokoohi, Hamid Reza Jamshidi

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