

The Burden of Liver Cirrhosis in Mortality: Results from the Global Burden of Disease Study 2017

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Research

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Abstract

Background: Liver cirrhosis related death is a serious threat worldwide. Rare study explored the mortality trend of liver cirrhosis caused by specific etiologies. This study aimed to demonstrated the pattern and trend based on GBD data.

Methods: The liver cirrhosis mortality data was collected from GBD 2017. The ASR and EAPC were used to estimate the temporal trend of liver cirrhosis mortality by etiologies, regions, SDI and sexes.

Results: Globally, mortality cases of liver cirrhosis increased 47.15%. Though the global ASR of liver cirrhosis mortality reminded stable during the period, the temporal trend varied in etiologies. The ASR of liver cirrhosis mortality caused by HCV, alcohol consumption and NASH increased with an EPAC of 0.17 (95% CI 0.14–0.20), 0.20 (95% CI 0.16–0.24), 1.00 (95% CI 0.97–1.04), respectively. A decrease trend of ASR was found in etiologies for HBV and other causes. The increase pattern was heterogeneous worldwide. The most pronounced increase trend was found in middle-high SDI regions and Eastern Europe. In contrary, the most pronounced decrease trend was found in low SDI regions and Western Sub-Saharan Africa.

Conclusion: Liver cirrhosis is still a public health problem. The growth trend of liver cirrhosis mortality caused by HCV has been slowed by promoting direct-acting antiviral therapy. Unfortunately, we observed an unfavorable trend in etiologies for alcohol consumption and NASH, suggesting that more targeted and specific strategies should be established to limit alcohol consumption and promote healthy lifestyles in high risk countries, especially in middle-high SDI regions and Eastern Europe.

Background

Liver cirrhosis has emerged as the end-stage of chronic liver disease[1]. It became one of the top ten causes of death [2]. More than 160 million people suffered liver cirrhosis in 2017 throughout the world and more than 0.8 million patients with liver cirrhosis died each year [3, 4]. Among the etiologies, more than half of the patients can be attributed to hepatitis B (HBV) and hepatitis C virus (HCV) [5, 6]. Though the antiviral therapy has been continuously improved, the burden of liver cirrhosis caused by hepatitis has remained considerable. Additionally, the rate of decompensation and survival is also affected by the underlying etiologies of liver cirrhosis [7].

Nowadays, the epidemiological distribution of the liver cirrhosis etiologies varies worldwide because of socioeconomic development and antivirus therapy application. However, the availability of detailed information remains poorly described. Previous studies indicated that HCV and alcohol were the major causes of liver cirrhosis in United States, most European countries and Japan. HBV caused liver cirrhosis was mainly found in Asian-Pacific and African countries [5, 8–10]. With the rising morbidity and mortality of liver cirrhosis, it is important to study the epidemiological distribution of liver cirrhosis. Thus, more targeted prevention strategies could be implemented by public health department.

The Global Burden of Disease (GBD) is the most comprehensive worldwide observational epidemiological study to date. By exploring the trends from 1990 to 2017 via GBD, it helps us to study the changing health challenges in 21st century. Since the burden of liver cirrhosis from 1980 to 2010 studied in 2014 by Mokdad [6], there has been no comprehensive global assessment of liver cirrhosis mortality. Due to data additions, improvements and methodological refinements made by GBD study 2017, it is now possible and timely to study the burden of liver cirrhosis in mortality and underlying etiologies. In the study, we used the GBD 2017 to explored the mortality and the

burden of liver cirrhosis all over the world from 1990 to 2017. For the first time, we demonstrated the trends of liver cirrhosis mortality rates and provided estimates of annual sexual, geographical, and social liver cirrhosis rates for 195 countries and territories.

Methods

Study data

The data of liver cirrhosis were collected from GBD 2017. The 195 countries and territories were divided into low socio-demographic index (SDI) region, low-middle SDI region, middle SDI region, high-middle SDI region and high SDI region. According to the geographical location, they were classified as 21 regions including East Asia, Central Europe, North America-high income, etc. The analysis and estimation methods for studying the trend and burden of liver cirrhosis was mentioned by Liu *et al*/study [3]. Additionally, human development index (HDI) was collected and used in the study to match GBD data.

Statistical analysis

The age-standardized mortality rate (ASR) and estimated annual percentage change (EAPC) are used to explore the trend of liver cirrhosis mortality from 1990 to 2017 [3, 11]. Using ASR, we can obtain the mortality of liver cirrhosis, changes in etiology. The EAPC was also used in our study to assess the changes of ASR during the period [12, 13]. To explore the trend in etiologies related with liver cirrhosis ASR of mortality, a hierarchy cluster analysis was conducted. The 195 countries and territories were group into 4 categories including significant increase, minor increase, remained stable or minor decrease and significant decrease. Additionally, a correlation analysis between EAPC and ASR, HDI was conducted to study the influential factors of EAPC. The R software (R 3.5.1, Institute for Statistics and Mathematics) and STATA/MP (STATA 13.1, StataCorp LLC) were used to analyze data obtained from GBD 2017. $p < 0.05$ was considered statistically significant.

Results

Mortality burden of global liver cirrhosis

Globally, the mortality of liver cirrhosis increased 47.15% from 1990 to 2017. In 1990, the highest mortality cases were found in China with 0.15 million patients. However, India became the country with the largest number of deaths in 2017 (Fig. 1A, Table S6). The highest growth of mortality was found in United Arab Emirates (UAE), followed by Qatar and Philippines. Contrarily, the highest decrease of mortality of liver cirrhosis was found Hungary with value of -45.67%. During the period, the growth rate of mortality of China was 2.02% (Fig. 1B, Table S6).

The ASR of liver cirrhosis mortality varied worldwide. The ASR was 16.66 per 100000 in 1990 and 17.31 per 100000 in 2017 (Fig. 2A-B, Table 1). In 1990, the ASR was higher in Western Sub-Saharan Africa and Central Europe, especially in Moldova (Fig. 2A). However, the Europe had higher ASR compared with other regions, for example Moldova, Romania and Ukraine (Fig. 2B). Globally, the ASR of liver cirrhosis mortality remained stable with an EAPC of 0.02 (95% CI -0.01-0.06). Additionally, The ASR increased in male patients and decreased in female patients all over the world (Table 1). Higher EAPCs were found in European countries, including Lithuania, Belarus and Russia. The country with the lowest EAPC value was Mali (Fig. 2C, Table S6). Based on the results of cluster analysis, 6 countries (3.08%) were grouped into significant increase group, such as Lithuania, Belarus and Armenia. 41 countries (21.03%) were grouped into minor increase group, such as United States, United Kingdom and Poland. In

contrast, 30 countries (15.38%) were grouped into significant decrease group, including South Korea, Spain, Italy and Qatar. Additionally, most of the 195 countries (60.51%) were grouped into the remained stable or minor decrease group, such as France, China and India (Fig. 3).

Table 1
The mortality cases, age-standardized mortality, and temporal trend of liver cirrhosis

Characteristics	1990		2017		1990–2017
	Mortality cases	ASR per 100,000	Mortality cases	ASR per 100,000	EAPC
	No. ×10 ³ (95% UI)	No. (95% UI)	No. ×10 ³ (95% UI)	No. (95% UI)	No. (95% CI)
Overall	898.99(828.93-948.21)	16.66(15.37–17.58)	1322.87(1268.20-1449.13)	17.31(16.60-18.97)	0.02(-0.01-0.06)
Sex					
Male	588.47(532.79-625.28)	21.65(19.61–23.01)	882.67(838.34-966.51)	23.02(21.86–25.21)	0.11(0.08–0.15)
Female	310.52(281.45-331.62)	11.60(10.51–12.39)	440.20(415.54-518.43)	11.57(10.92–13.62)	-0.14(-0.18–0.09)
Socio-demographic index					
Low	111.18(93.03-135.44)	15.94(13.34–19.42)	171.16(148.49-217.56)	13.27(11.51–16.87)	-0.74(-0.80–0.67)
Low-middle	223.58(187.05-249.36)	21.41(17.91–23.88)	363.70(329.01-404.22)	21.33(19.30–23.71)	-0.11(-0.16–0.07)
Middle	240.42(211.29-255.18)	15.50(13.62–16.45)	366.92(349.88-412.84)	17.55(16.74–19.75)	0.23(0.16–0.30)
Middle-high	144.08(137.48-150.39)	12.96(12.36–13.52)	215.78(205.55-245.43)	15.55(14.82–17.69)	0.56(0.41–0.72)
High	176.52(173.37-178.78)	18.27(17.95–18.51)	201.83(195.82-208.23)	17.71(17.18–18.27)	-0.13(-0.22–0.04)
Etiology					
Hepatitis B	287.01(251.68-318.06)	5.32(4.67–5.90)	383.97(349.07-441.67)	5.03(4.57–5.78)	-0.35(-0.41–0.29)
Hepatitis C	225.27(201.66-248.59)	4.18(3.74–4.61)	342.24(312.60-381.10)	4.48(4.09–4.99)	0.17(0.14–0.20)
Alcohol consumption	215.19(194.90-234.59)	3.99(3.61–4.35)	332.27(303.00-373.28)	4.35(3.97–4.89)	0.20(0.16–0.24)
NASH	61.88(55.40-67.98)	1.15(1.03–1.26)	118.03(108.62-128.58)	1.54(1.42–1.68)	1.00(0.97–1.04)
other causes	109.64(96.65-126.68)	2.03(1.79–2.35)	146.36(130.86-164.57)	1.92(1.71–2.15)	-0.33(-0.37–0.28)
Region					
Asia Pacific-high income	37.97(37.24–38.67)	21.88(21.45–22.28)	35.08(32.40-37.04)	18.75(17.32–19.80)	-0.68(-0.94–0.42)

Characteristics	1990		2017		1990–2017
	Mortality cases	ASR per 100,000	Mortality cases	ASR per 100,000	EAPC
	No. ×10 ³ (95% UI)	No. (95% UI)	No. ×10 ³ (95% UI)	No. (95% UI)	No. (95% CI)
Central Asia	13.06(12.78–13.48)	18.72(18.32–19.32)	30.86(28.66–32.91)	33.94(31.52–36.19)	2.17(1.87–2.48)
East Asia	161.53(132.16–174.09)	12.83(10.50–13.83)	167.64(154.66–215.37)	11.28(10.41–14.50)	-0.98(-1.17–0.78)
South Asia	159.40(143.50–184.96)	14.38(12.94–16.68)	295.61(268.24–378.26)	16.58(15.05–21.22)	0.47(0.40–0.54)
Southeast Asia	110.99(98.34–120.21)	23.78(21.07–25.75)	176.32(164.70–190.08)	26.70(24.94–28.78)	0.35(0.30–0.41)
Australasia	1.53(1.47–1.58)	7.57(7.24–7.79)	2.48(2.23–2.74)	8.73(7.87–9.67)	0.70(0.41–0.99)
Caribbean	5.45(5.00–5.98)	15.44(14.15–16.94)	7.29(6.49–8.62)	15.77(14.03–18.63)	-0.23(-0.44–0.02)
Central Europe	30.08(29.45–30.90)	24.24(23.73–24.89)	30.99(29.83–32.15)	26.99(25.98–28.00)	0.15(-0.10–0.41)
Eastern Europe	30.56(29.06–31.58)	13.47(12.80–13.92)	78.29(75.81–80.58)	37.24(36.07–38.33)	4.08(3.41–4.75)
Western Europe	81.43(80.03–82.97)	21.11(20.75–21.51)	74.23(70.80–78.16)	17.14(16.35–18.05)	-0.98(-1.04–0.91)
Andean Latin America	6.02(5.53–6.74)	15.70(14.42–17.58)	11.23(10.16–12.32)	18.28(16.54–20.05)	0.58(0.48–0.69)
Central Latin America	32.02(31.38–32.52)	19.51(19.12–19.81)	59.05(56.63–62.09)	23.11(22.16–24.30)	0.46(0.37–0.55)
Southern Latin America	9.59(9.33–9.88)	19.35(18.84–19.94)	12.82(11.69–14.02)	19.54(17.81–21.37)	0.19(0.04–0.33)
Tropical Latin America	22.46(21.88–23.02)	14.63(14.26–15.00)	36.94(35.69–38.04)	16.89(16.32–17.39)	0.31(0.22–0.39)
North Africa and Middle East	48.99(37.29–55.72)	14.37(10.94–16.35)	77.39(61.26–90.64)	12.89(10.21–15.10)	-0.39(-0.51–0.27)
North America–high income	38.76(37.54–39.46)	13.81(13.37–14.06)	67.35(65.13–69.62)	18.66(18.05–19.29)	1.50(1.25–1.76)
Oceania	0.94(0.81–1.10)	14.55(12.60–16.96)	1.73(1.44–2.11)	13.77(11.46–16.70)	-0.18(-0.27–0.10)
Central Sub-Saharan Africa	10.42(7.74–14.09)	18.94(14.06–25.61)	20.33(15.74–26.35)	16.71(12.94–21.66)	-0.52(-0.62–0.42)

Characteristics	1990		2017		1990–2017
	Mortality cases	ASR per 100,000	Mortality cases	ASR per 100,000	EAPC
	No. ×10 ³ (95% UI)	No. (95% UI)	No. ×10 ³ (95% UI)	No. (95% UI)	No. (95% CI)
Eastern Sub-Saharan Africa	38.73(32.17–46.35)	20.22(16.79–24.20)	57.85(44.09–69.97)	14.71(11.21–17.80)	-1.44(-1.57–1.31)
Southern Sub-Saharan Africa	5.79(4.63–6.51)	11.03(8.82–12.41)	6.78(5.63–7.91)	8.77(7.28–10.23)	-1.34(-1.93–0.75)
Western Sub-Saharan Africa	53.27(33.63–75.52)	27.71(17.49–39.28)	72.60(48.86–101.65)	16.73(11.26–23.43)	-1.99(-2.17–1.81)

For SDI regions, the number of liver cirrhosis mortality increased across the 5 SDI regions (Fig. 4). However, the ASR decreased in the low, low-middle and high SDI regions (Table 1). For geographical regions, absolute numbers of liver cirrhosis mortality increased in most of the regions except for Asia Pacific–high income and Western Europe (Fig. 5A). 11 of 21 regions demonstrated an increase trend of ASR during the period, especially in Eastern Europe with the EAPC of 4.08 (95% CI 3.41–4.75) (Fig. 6A). In contrast, the most significant decrease of ASR was found in Western Sub-Saharan Africa (Fig. 6A, Table 1).

For etiologies, HBV (29.03%) was the most important cause of death in patients with liver cirrhosis in 2017, followed by HCV (25.87%) (Fig. 5B). During the period, the proportion of HCV remained relatively stable worldwide. The proportion of HBV decreased from 31.93% in 1990 to 29.03% in 2017 (Fig. 5B), but it significant changed in some regions. For instance, in middle-high SDI region, the proportion of HBV decreased from 34.31–27.52% from 1990 to 2017. Additionally, the proportion of HBV decreased from 41.93–38.14% in North Africa and Middle East (Fig. 5B).

Influential factors for EAPC in mortality of liver cirrhosis

The ASR of liver cirrhosis in 1990 demonstrated the disease reservoir at baseline. The HDI of liver cirrhosis in 2017 demonstrated the level of available medical resources in each country. A significant negative association was found between EAPC and ASR in 1990 when the ASR was limited to below 45 per 100000 (Fig. 6B). In contrast, the association disappeared when the ASR in 1990 was greater than 45 per 100000 (Fig. 6B). Additionally, EAPC was positively correlated with HDI in 2017 when HDI was less than 0.77. Surprisingly, the relationship between EAPC and HDI disappeared when countries with higher HDI (Fig. 6B).

Mortality burden of liver cirrhosis due to HBV

Globally, approximately 29.03% of dead hepatitis patients were caused by HBV in 2017 (Fig. 5B). The proportion decrease from 31.93% in 1990 to 29.03% in 2017 (Fig. 5B, Table 1). The mortality caused by HBV increased 33.78% (Table S1). The highest mortality was found in India with the value of 75.60 thousand in 2017, followed by China with 75.16 thousand patients (Fig S1A). However, in 1990, China had the highest mortality with a value of 81.34

thousand (Table S6). United Arab Emirates had the highest increase mortality, and Hungary had the highest decrease of mortality, contrarily (Fig S1B, Table S6). The ASR of liver cirrhosis caused by HBV was significantly heterogeneous across the world with the highest ASR observed in Southeast Asia (Fig S2A-B, Table S1). Contrary to the increase trend of mortality, the ASR displayed a decrease trend with an EAPC of -0.35 (95% CI -0.41–0.29) during the period (Table S1). The highest EAPC was found in Lithuania, and the lowest EAPC was observed in Mali (Fig S2C). The mortality increased in 4 SDI regions except for high SDI region, while the ASR decreased in all 5 SDI regions (Fig. 4, Fig S2C, Table S1). For geographical regions, the mortality cases of liver cirrhosis caused by HBV increased in 16 regions, excepted for Asia Pacific–high income, East Asia, Central Europe, Western Europe and Southern Sub-Saharan Africa. In parallel, the greatest EAPC was found in Eastern Europe and the lowest EAPC was found in Southern Sub-Saharan Africa and Western Sub-Saharan Africa (Fig S2C, Table S1).

Mortality burden of liver cirrhosis due to HCV

In 2017, the mortality of liver cirrhosis caused by HCV was 0.34 million, and mortality increased 51.92% from 1990 to 2017 (Table S2, Fig S3A). The proportion of mortality due to liver cirrhosis caused by HCV remained stable during the period (Fig. 5). But the number of deaths increased dramatically in United Arab Emirates, followed by Qatar and Philippines (Fig S3B). In China, the mortality increased 9.20% during the period (Fig S3B). The mortality of liver cirrhosis caused by HCV was under 10 per 100000 in most countries in 1990 and in 2017 (Fig S4A-B). The highest ASR was found in Moldova in 2017, followed by Cambodia and Egypt (Fig S4A-B). The ASR indicated an increasing trend with the EAPC of 0.17 (95% CI 0.14–0.20) from 1990 to 2017 (Table S2). Among all countries, the highest EAPC was found in Lithuania, followed by Belarus and Armenia. Contrary, the lowest EAPC was found in Mali during the period (Fig S4C). For SDI regions, the decrease trend in mortality of liver cirrhosis caused by HCV was only observed in low SDI region with the EAPC of -0.65 (95% CI -0.72–0.59), and the most significant increase was found in middle-high SDI region (Table S2). Among the 21 geographical regions, 12 regions displayed an increase trend during the period, and the most significant increase was found in Eastern Europe, followed by Central Asia. Contrary, the most significant decrease was observed in Western Sub-Saharan Africa with the EAPC of -2.04 (95% CI -2.18–1.91) (Table S2).

Mortality burden of liver cirrhosis due to alcohol consumption

In 2017, approximately 25.12% of deaths caused by liver cirrhosis was ascribed to alcohol consumption (Fig S5A, Table 1). India had the greatest number of liver cirrhosis deaths caused by alcohol use in 2017 (Fig S5A). United Arab Emirates had the highest increase mortality (434.87%). During the period, China showed a 15.76% increase of mortality cases (Fig S5B). The ASR of liver cirrhosis caused by alcohol use minor increased from 1990 to 2017 (Fig S6A-B, Table S3). With respect to countries, the higher ASR were found in Moldova, Romania and Ukraine in 2017. The highest increase in ASR was found in Lithuania, followed by Belarus. Contrary, the highest decrease in ASR was found in Mali (Fig S6C). The ASR decreased in low and high SDI regions, while it increased in low-middle, middle and middle-high regions (Table S3). For geographical regions, 9 regions demonstrated an increase trend of ASR, especially in Eastern Europe, Central Asia and North America–high income. Contrary, 10 of 21 regions indicated a decrease trend of ASR (Fig S6C, Table S3).

Mortality burden of liver cirrhosis due to NASH

Globally, NASH precipitated nearly 8.92% of the total number of deaths from liver cirrhosis (Table 1). The proportion of NASH induced death patients with liver cirrhosis increased in all 5 SDI regions (Fig. 5B). In 2017, India had the largest number of deaths due to liver cirrhosis caused by NASH all over the world (Fig S7A). The mortality of United Arab Emirates increased most significantly, while the mortality of China increased 39.87% during the same period (Fig S7B). Similarly, Hungary demonstrated the highest decrease of mortality during the period (Fig S7B). The ASR significantly increased with the EAPC of 1.00 from 1990 to 2017 (95% CI 0.97–1.04) (Fig S8A-C, Table S4). The highest EAPC was found in Lithuania, followed by Belarus and Armenia. In contrast, the most pronounced decrease of ASR was detected in Afghanistan (Fig S8C). The ASR increased in 4 SDI regions, except for low SDI region (Table S4). Moreover, the significantly increased ASR was found in middle-high region with EAPC of 1.81 (95% CI 1.66–1.95) (Fig S8C, Table S4). For geographical regions, most of the region (66.67%) showed an increase trend of ASR, especially in Eastern Europe, followed by North America–high income and Central Asia. In contrast, Asia Pacific–high income and Sub-Saharan Africa demonstrated a decrease trend of ASR from 1990 to 2017 (Table S4).

Mortality burden of liver cirrhosis due to other causes

In 2017, deaths due to liver cirrhosis caused by other causes accounted for 11.06% (146.36 thousand) of total liver cirrhosis deaths (Fig S9A, Table S5). In North America–high income, the proportion exceeded 20%, albeit the ASR was at a relatively low level (Fig. 5B, Table S5). The absolute number increased by 33.49% at the global level, and the most pronounced increase was observed in United Arab Emirates (Fig S9B). The global ASR decreased by an average 0.33% (95% CI -0.37–0.28) per year from 1990 to 2017. The highest ASR was observed Sao Tome and Principe in 1990 and Moldova in 2017, while the highest increase of ASR was found in Armenia, followed by Lithuania (Fig S10A-C). The ASR decreased in low, low-middle and middle SDI regions. Contrary, an increase trend of ASR of deaths due to liver cirrhosis caused by other causes was observed in middle-high and high SDI regions (Fig S10C, Table S5). The most significant decrease in ASR was found Western Sub-Saharan Africa, followed by Eastern Sub-Saharan Africa and East Asia. Interestingly, Eastern Europe, North America–high income, central Asia and Australasia demonstrated higher increased ASR during the period (Table S5).

Discussion

Liver cirrhosis has been regarded as the major cause of global health burden. The number of deaths due to liver cirrhosis is increasing gradually [6]. However, because of the heterogeneous pattern in risk factor of different countries, the number of patients who died from liver cirrhosis markedly varies [14]. In the study, we demonstrated the key findings on liver cirrhosis mortality from GBD 2017. For the first time, we comprehensively estimated the trends of liver cirrhosis mortality for 195 countries and 5 SDI regions between 1990 to 2017. In general, mortality of liver cirrhosis increased 47.15%. The trends were mainly dominated by an increase of HCV caused liver cirrhosis, with a smaller contribution from alcohol use and NASH. Notably, the number of deaths from NASH induced liver cirrhosis has increased 90.74%, which was highest among all etiologies. Thus, the global health community should recognize the importance of controlling liver cirrhosis risk factors and pay more attention to the liver cirrhosis caused by alcohol consumption and NASH[6].

HBV caused liver cirrhosis was a major health burden worldwide. Previous study indicated that about 248 million people suffered with HBV infection in 2010 [15]. Our study showed that about 383.97 thousand people died from HBV caused liver cirrhosis in 2017. Additionally, the mortality of HBV caused liver cirrhosis widely varied between countries. In some countries, HBV is the leading cause of liver cirrhosis, especially in East Asia and south Asia [15].

Our study demonstrated that the ASR of Eastern Europe increased 3.69% per year. Contrary, the ASR of Western Sub-Saharan Africa decreased 2.02% per year. This amazing variation might be partly explained by varying risk factors and transmission routes across countries. Additionally, our study showed that India and China had the largest number of deaths due to HBV related liver cirrhosis. However, the mortality in India increased 102.6% from 1990 to 2017, while the mortality in China decreased 7.6%. This might be related with promoting HBV vaccine, screening of blood products and obtaining safe injection methods. Moreover, socioeconomic development and improvement in people's cognition might also be related to the number of deaths from liver cirrhosis caused by HBV. Unfortunately, 76 of 195 countries demonstrated an increase trend of ASR, although the availability of an effective vaccine and potent antiviral treatments. It might be related with national HBV prevention policy, national immigration policy, national medical insurance policy and national blood transfusion and blood donation policy [16–18]. Consequently, these countries should be recommended to reorient their HBV prevention strategies [19, 20]. Additionally, ensuring blood safety and medical device safety was also important for reducing mortality of liver cirrhosis caused by HBV [16, 21]. Finally, developing the anti-HBV drugs might provide another method to reduce mortality of liver cirrhosis [22].

Similar with previous studies, HCV still was the most important risk factors for liver cirrhosis [23, 24]. In contrast to liver cirrhosis mortality caused by HBV, the ASR of liver cirrhosis mortality caused by HCV increased and decreased only in low SDI region. It might be caused by absence of effective vaccine. Moreover, lack of treatment and poor efficacy were also closely related to the increase trend of mortality. Though the prevalence remained low in most European countries and America, but the ASR had a more significant increase in Eastern Europe, Central Asia and North America–high income [25–28]. Fortunately, direct-acting antiviral therapy had been on the market since 2014 and was effective in more than 90% of HCV patients [29, 30]. Moreover, ensuring the safety of blood transfusion, injection drug use and therapeutic injections were equally important for blocking HCV transmission [31]. Although the ASR has been increasing nowadays, the EAPC value was significantly lower than that of other causes, and negative growth of ASR is likely to occur in the future.

The overall ASR of liver cirrhosis mortality caused by alcohol has been minor increased, but has decreased in low and high SDI regions. In our study, the increase was more remarkable in Eastern Europe, Central Asia and North America–high income. This result was similar to those of previous global survey [32]. In our study, the ASR of liver mortality caused by alcohol decreased in Sub-Saharan Africa, though it increased in most regions. According to a previous global survey, the alcohol consumption was 17.1 liters per drinker in 2005, and the alcohol consumption was lowest in Africa by shown in the adult per capita consumption of alcohol by country [32]. This result obtained by Liu et al was consistent with our result [32]. It might be related to the living habits, beliefs and economic development of local people. Thus, developing policies to limit alcohol consumption was necessary for reducing mortality of liver cirrhosis caused by alcohol and improving population-health outcome. Moreover, we needed to pay more attention to the drinking problem of young people and formulated relevant policies [33, 34].

Although the mortality of liver cirrhosis caused by hepatitis decreased, the ever-increasing mortality of liver cirrhosis caused by NASH posed a continuing threat. In our study, the EAPC of liver cirrhosis mortality caused by NASH was highest among all etiologies. Moreover, the ASR increased in 4 SDI regions except for low SDI region, and significantly increased in Asia. The increase trend might be related with heavy and salty meat diet and westernized lifestyle [35]. Similar results also demonstrated that higher prevalence rate was found in China and other Asia countries in males and obese population [36]. Based on a research which indicated that the prevalence of NAFLD was higher in regions with a GDP less than 50000 yuan and more than 100000 yuan in China, the burden of liver cirrhosis mortality caused by NASH also might be closely related with national and personal economic levels [35].

Thus, systematic treatment of metabolic diseases and loss of weight might effectively reduce the liver cirrhosis mortality caused by NASH in patients. Additionally, we should closely monitor the patients who suffered with liver cirrhosis caused by multiple causes, especially those who suffered with NASH and hepatitis [37].

In addition, our study showed that EAPC was negatively correlated with baseline ASR ($< 45/100000$), and indicated that countries with lower ASR had a higher mortality of liver cirrhosis. It might be explained as follows. Firstly, the smaller the ASR, the more significant impact on the EAPC induced by ASR change. Secondly, the country with lower ASR might pay less attention to liver cirrhosis. Finally, with the focus on liver cirrhosis, EAPC increased with the increase of ASR, though there was no statistical significance. The HDI (< 0.77) was positively correlated with EAPC. This may be because with the improvement of living standards and medical technology, patients with liver cirrhosis who were missed in the past have been diagnosed. As the HDI gradually increased, people became more aware of liver cirrhosis, and invested more money and time in prevention and treatment, so the EAPC declined.

Although the GBD estimates demonstrated the burden of liver cirrhosis mortality, several limitations should be noted. First, some liver cirrhosis patients not included in the GBD database may affect the results. Second, due to the data scarcity of GBD data, multi-etiological liver cirrhosis was not considered in this study. The interaction of several etiologies might play a role in promoting liver cirrhosis. For instance, alcohol consumption could worsen liver cirrhosis caused by hepatitis [38, 39]. Additionally, obesity and diabetes also increased the risk of liver cirrhosis caused by HCV [40, 41].

In summary, liver cirrhosis remains a huge threat to public health. Though the ASR of liver cirrhosis mortality caused by HBV decreased, the number of patients who died from liver cirrhosis due to HBV was high, especially in developing countries. The ASR of liver cirrhosis mortality caused by HCV still increased, though the direct-acting antiviral therapy for HCV patients has been used since 2014. Additionally, liver cirrhosis due to alcohol consumption and NASH were a global health concern that cannot be ignored. Thus, developing policies to limit alcohol consumption and advocate healthy living was important to reduce the mortality and improve population-health outcome, especially in several "high-risk" regions. By conducting this study, we can roughly illustrate the disease burden of liver cirrhosis mortality worldwide and formulate more reasonable and effective prevention strategies.

Conclusions

The worldwide ASR of liver cirrhosis mortality remained stable from 1990 to 2017. The most pronounced increases were found in the middle-high SDI region and Eastern Europe. An unfavorable trend in etiologies for alcohol consumption and NASH was observed.

Abbreviations

GBD, Global burden of disease; HBV, hepatitis B virus; HCV, hepatitis C virus; SDI, socio-demographic index; HDI, human development index; ASR, Age standardized prevalence rate; EAPC, estimated annual percentage changes; CI, confidence interval; NASH, non-alcoholic steatohepatitis.

Declarations

Ethics approval and consent to participate

This research does not involve ethical issues, so ethical approval and informed consent are not needed.

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare no conflicts of interest.

Availability of data and materials

All original data is available at <http://www.healthdata.org/gbd>

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Authors' contributions

Study design: Ye F, Zhai MM and Liu SS. Data collection: Ye F, Long JH and Liu SS. Data analysis: Zhai MM, Long JH, Shu B and Liu C. Figures: Gong Y, Li L and Zhang D. Manuscript writing: Ye F, Zhai MM, Long JH and He C. Manuscript proofing: Zhai MM and Liu SS.

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Figures

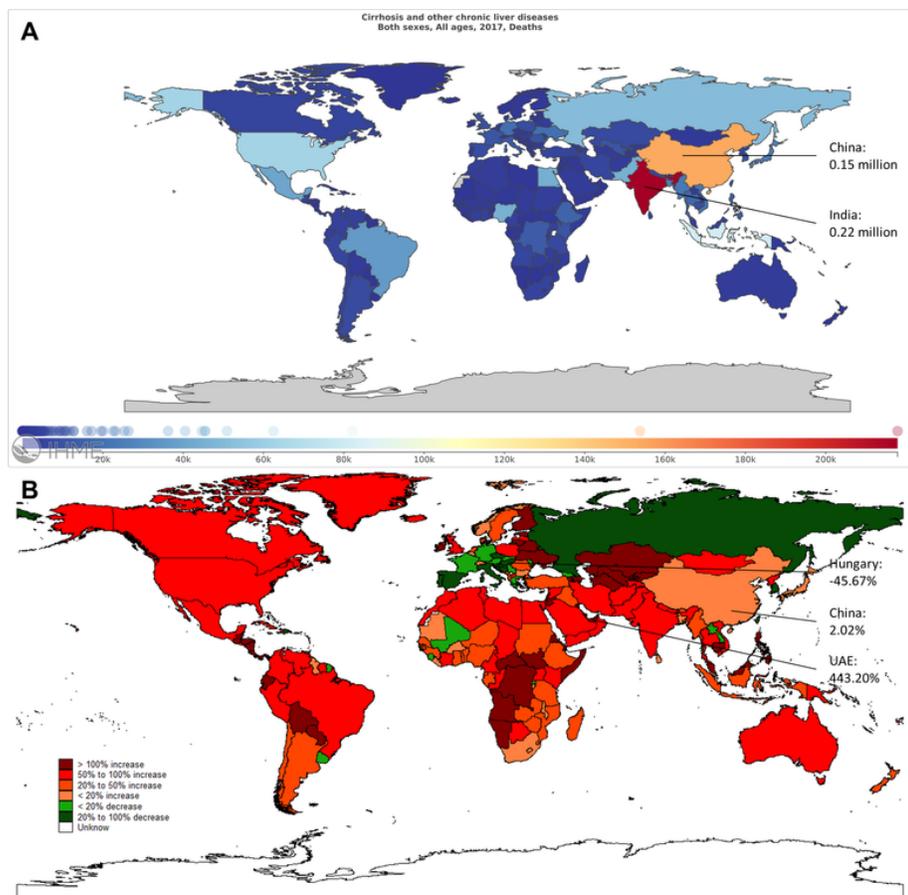


Figure 1

The overall mortality cases of liver cirrhosis in 195 countries and territories. (A) The mortality cases in 2017 across the world. (B) The change in mortality cases from 1990 to 2017 across the world. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part

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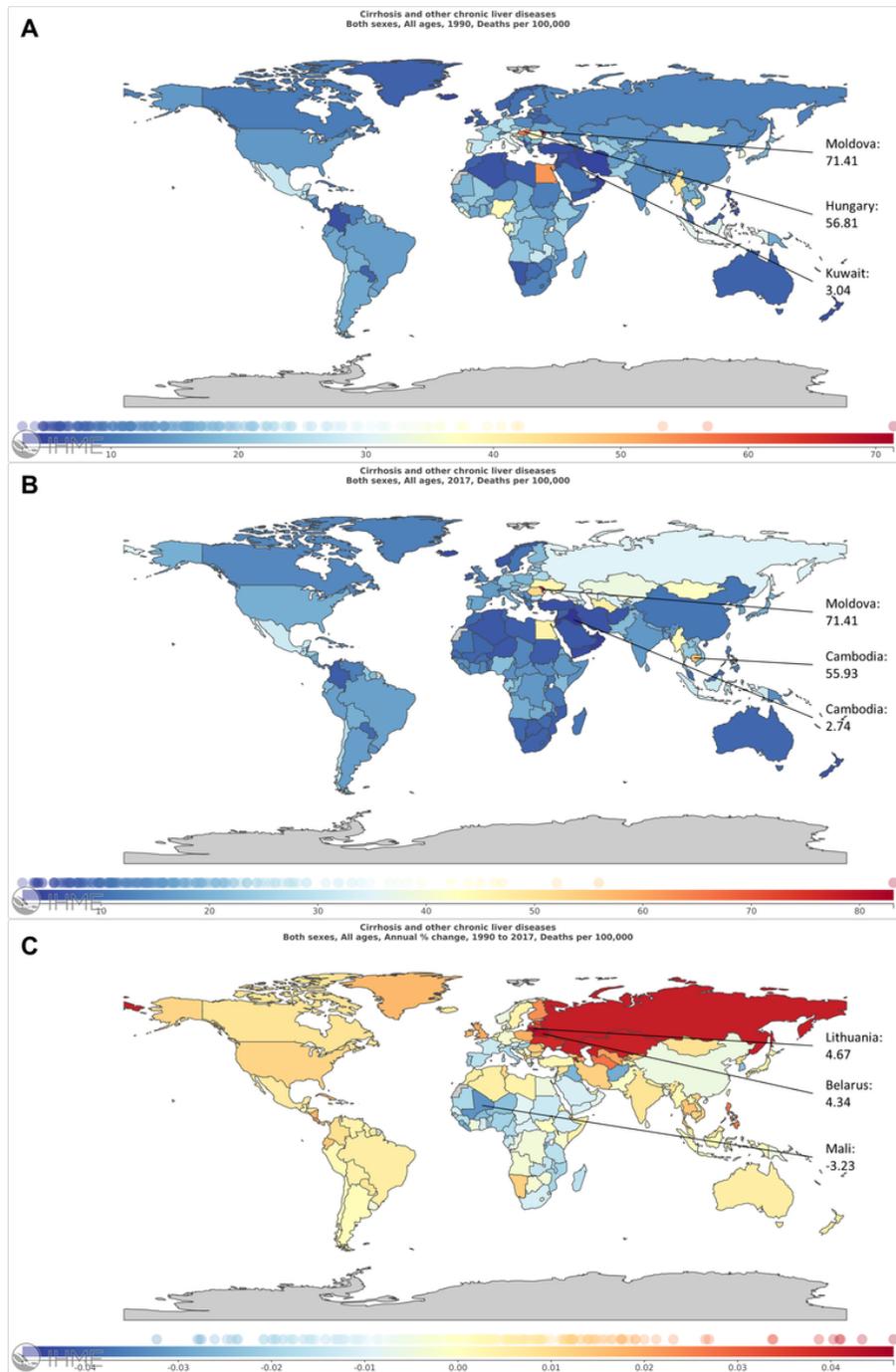


Figure 2

The global burden of liver cirrhosis mortality in 195 countries and territories. (A-B) The ASR of liver cirrhosis mortality in 1990 (A) and in 2017 (B). (C) The ASR trend of liver cirrhosis from 1990 to 2017. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

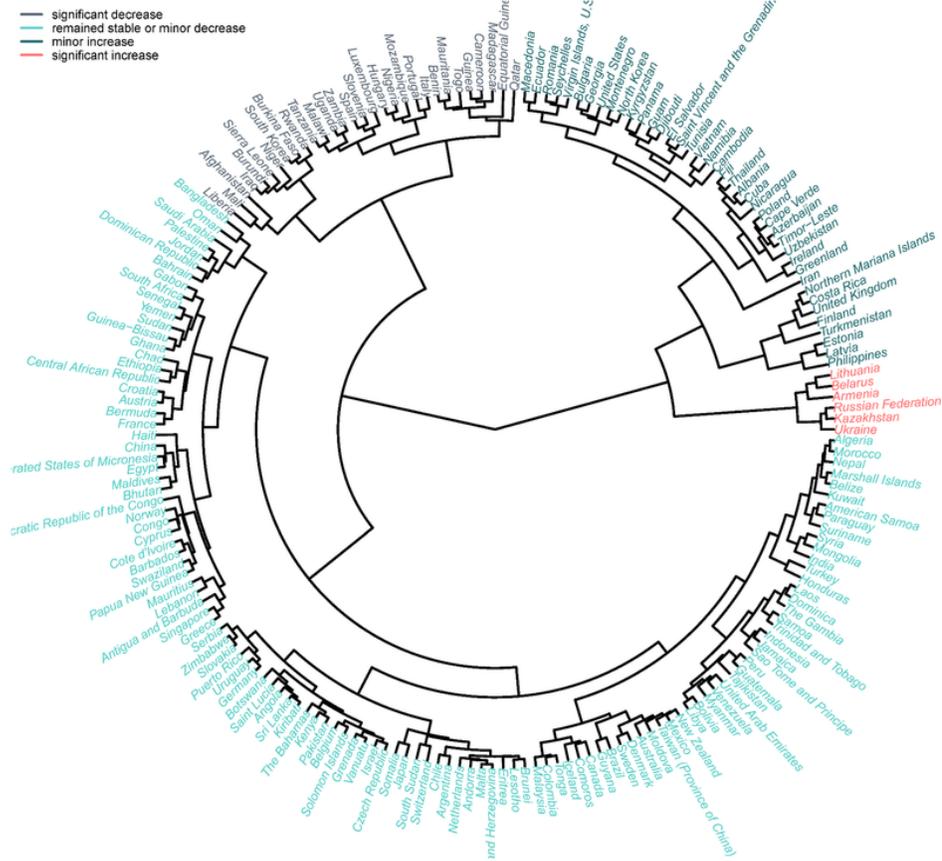


Figure 3

The temporal ASR trends clusters in etiologies related with liver cirrhosis for countries and territories.

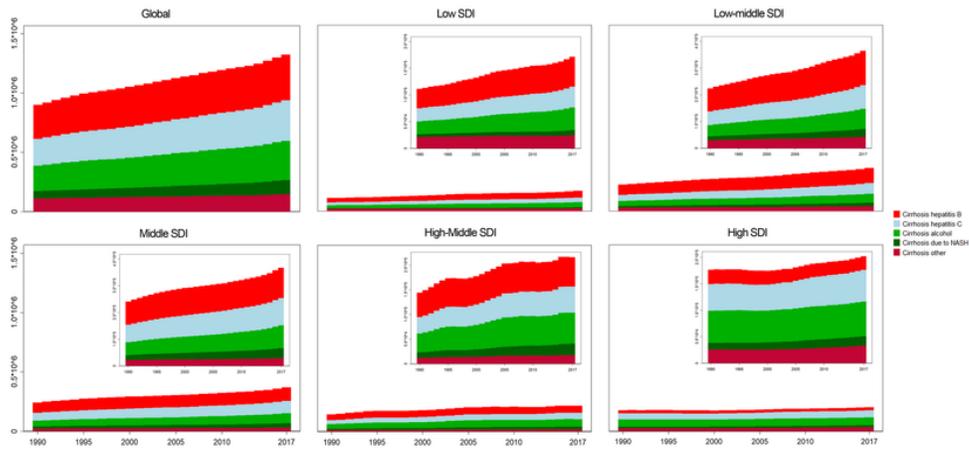


Figure 4

The liver cirrhosis mortality cases caused by different etiologies and SDI regions from 1990 to 2017.

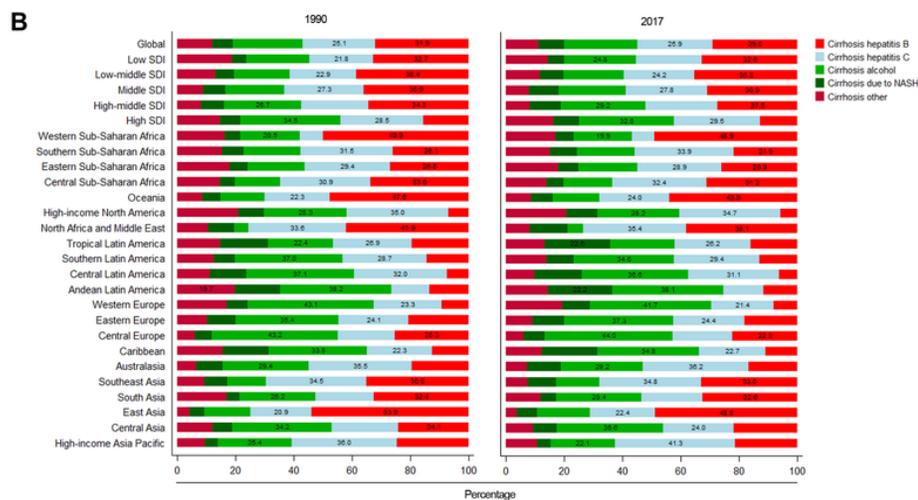
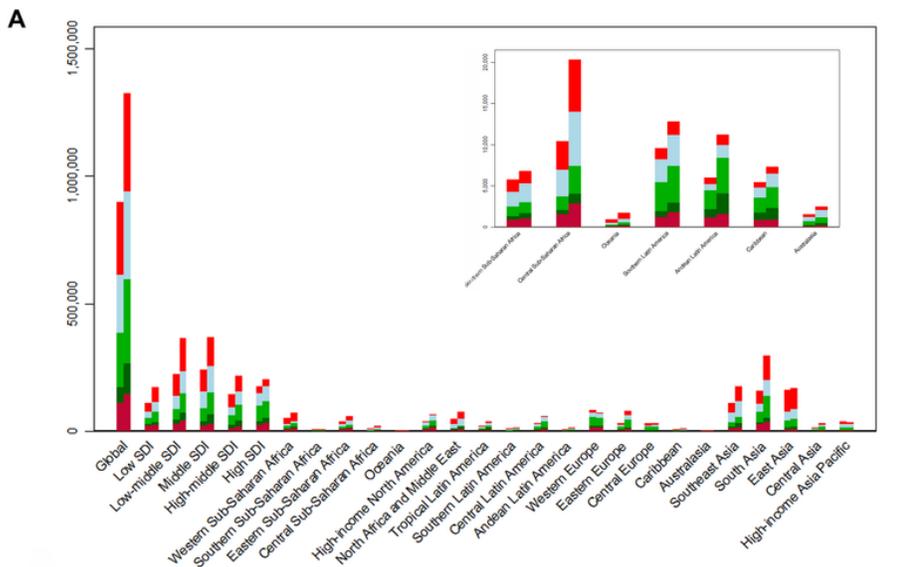


Figure 5

The liver cirrhosis mortality cases and its proportion in different countries and SDI regions by etiologies. (A) The mortality cases of liver cirrhosis in different SDI regions and geographical regions by different etiologies. (B) The proportion of liver cirrhosis mortality for different etiologies in different SDI regions and geographical regions.

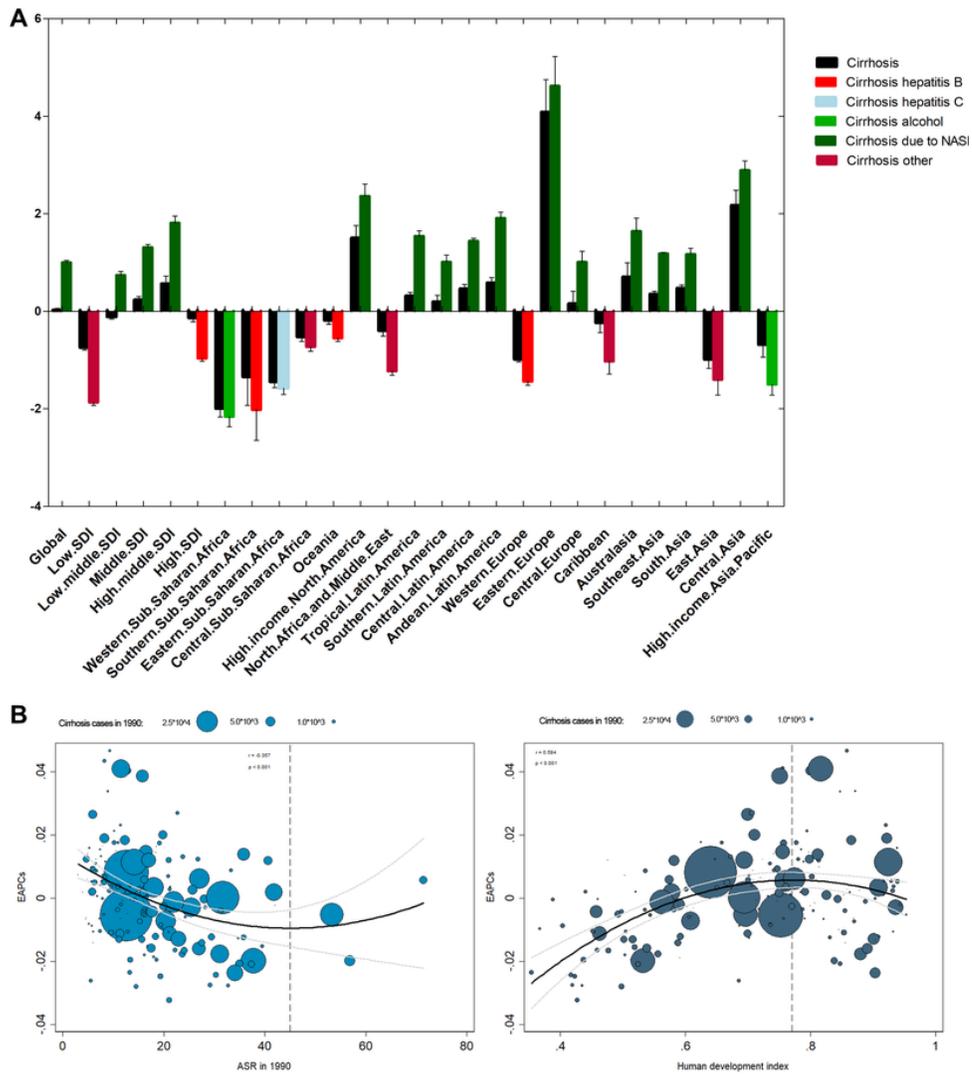


Figure 6

The EAPC of liver cirrhosis mortality at global and national level. (A) The EAPC of liver cirrhosis mortality by regions and etiologies from 1990 to 2017. (B) The correlation between EAPC and ASR in 1990 and HDI in 2017.

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