Hepatology International (2018) 12:269–276
https://doi.org/10.1007/s12072-018-9850-5

ORIGINAL ARTICLE

Liver cirrhosis and cancer: comparison of mortality

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Received: 9 November 2017 / Accepted: 14 February 2018 / Published online: 1 March 2018

Abstract

Background Liver cirrhosis is known to have low survival rate, and its assessment in relation with other fatal diseases will help us design appropriate health interventions. This study compares the mortality of liver cirrhosis with that of five major cancers (lung, colorectal, stomach, liver, and breast cancers).

Methods and results We used the National Health Insurance Service–National Sample Cohort (NHIS–NSC) which provides data for 1,025,340 representative samples of the 46,605,433 people in Korea from 2002 to 2010. During the 8 years, 800 out of 2609 liver cirrhosis patients died and 1316 out of 4852 patients with the five major cancers died. When we estimated the mortality between liver cirrhosis and five major cancers, the relative mortality for liver cirrhosis was greater [hazard ratio 1.47 (95% CI 1.28–1.67) after age, gender, area of residence, type of insurance, insurance premium level (proxy for income level), and comorbidities were adjusted for]. When a sensitivity analysis was performed by excluding patients with both liver cirrhosis and one of the five cancers, the relative mortality was still greater for liver cirrhosis [hazard ratio 1.27 (95% CI 1.10–1.47)]. Furthermore, when we limited liver cirrhosis patients to those with decompensated liver cirrhosis, the relative mortality of decompensated liver cirrhosis was even greater than that of the five cancers [hazard ratio 1.82 (95% CI 1.51–2.20)].

Conclusions The mortality of liver cirrhosis is greater than that of the five major cancers. This implies the need to prioritize appropriate health interventions for liver cirrhosis.

Keywords Liver cirrhosis · Cancer · Mortality

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Introduction

Accurate data regarding the burden of diseases are necessary to inform health-care policy, prioritize appropriate research and interventions, and allocate resources. Although there are substantial differences across different income group of countries, liver cirrhosis (13th, 2013 mean rank) and cancer (lung cancer, 15th; liver cancer, 21st; stomach cancer, 25th; colorectal cancer, 27th; breast cancer, 30th) are major causes of global years of life lost [1–3].

The natural history of liver cirrhosis is characterized by initial compensated stage followed by decompensated stage, defined clinically as the development of ascites, jaundice, variceal bleeding, or hepatic encephalopathy [4, 5]. For example, D'Amico et al. proposed clinically recognizable four stages with different prognosis and mortality: stage 1 (no esophageal varix, compensated), stages 2 (with varices, compensated), stage 3 (with ascites, decompensated), and stage 4 (with variceal bleeding, decompensated) with estimated annual mortality rates of 1, 3.4, 20, and 57%, respectively [6, 7]. Compensated cirrhosis eventually carries 4.7 times greater risk of death than that of general population and decompensated cirrhosis carries 9.7 times greater risk [8].

The prevalence of liver cirrhosis is probably higher than reported, since the initial compensated liver cirrhosis is frequently asymptomatic and often undiagnosed [5]. Similarly, liver-related mortality is claimed to be underestimated partly by incomplete determination of liver-related deaths. These pitfalls indicate that the burden of chronic liver disease should incorporate deaths due to hepatobiliary cancers and viral hepatitis in the determination of liver-related deaths accurately [9–12].

Meanwhile, cancer is the second leading cause of death worldwide. Its cases increased by 33% from 2005 to 2015 and the ‘war on cancer’ continues. Lung, colorectal, stomach, liver, and breast cancers are the top five cancers by number of deaths in the 50 most populous countries and by absolute years of life lost globally [13, 14].

When comparing the disease burden, it is imperative to deliberate on the age at death and the degree of disability of people affected by each disease. Different metrics, such as deaths, years of life lost, and years lived with disability, highlight different aspects of a population’s health status, and survival may be the most important of those [15–17].

Although the survival rate of liver cirrhosis is known to be low, few studies have directly compared the mortality of liver cirrhosis with that of other fatal diseases. It is important to estimate the relative mortality of fatal diseases for efficient and rational allocation of limited health-care resources, especially under ever increasing use of economic evaluation in the medical sector. We have carefully defined liver cirrhosis and estimated its mortality to compare it with that of five cancers (lung, colorectal, stomach, liver, and breast cancers). We conducted another analysis by limiting the liver cirrhosis patients to those with decompensated liver cirrhosis and examining their causes of death. Obviously, better understanding of the relative mortality burden by diseases is essential to prioritize appropriate health interventions for liver cirrhosis.

Methods

Data sources

This prospective cohort study used the National Health Insurance Service–National Sample Cohort (NHIS–NSC) database, which used a stratified random sampling method to select a representative sample of 1,025,340 from the non-institutionalized civilian Korean population of 46,605,433 in 2002 [18]. The NHIS–NSC is a population-based cohort established by the NHIS in Korea, which maintains and stores national records for health-care utilization and prescriptions. All data from the NHIS–NSC were obtained in a fully anonymized and de-identified manner (data serial number: NHIS-2014-2-070), and this study was approved by the Hallym University Institutional Review Board (HIRB-2014-98).

Study subjects

After consulting the Korean Association for the Study of the Liver, we defined liver cirrhosis using ICD-10 codes (K702, K703, K704, K717, K720, K721, K729, K740–K746, K761, K766–K767, R18, I850, I859, I864, I868, I982, and I983) among liver diseases (K70–K77). Similarly, the five major cancers were defined as lung (C33–C34), colorectal (C18–21), stomach (C16), liver (C22), and breast (C50) cancers.

After selecting two groups of patients in 2002, one for liver cirrhosis and the other for the five major cancers, we followed them for 8 years (from 2002 to 2010) to study their relative mortalities. It is notable that there are patients with both liver cirrhosis and one or more of the five major cancers. We classified these patients as liver cirrhosis patients in consideration of the fact that approximately 89% of them had liver cancer. However, we conducted another analysis that excluded these patients from the study sample. In total, the study subjects comprised 7461 patients, 2609 with liver cirrhosis (2173 patients with liver cirrhosis only plus 436 patients with both liver cirrhosis and at least one of five cancers), and 4852 patients with at least one of the five cancers.

Data analysis

Stata version 12 was used for data analysis. For descriptive analysis, means with the standard deviations and frequencies with percentages were used. Cox-proportional hazards models were adopted to study the relative mortality between the two groups of patients with and without adjustment for other mortality-related factors. The mortality-related factors used in our estimation were age [one dummy for age 0, 17 dummies for 5-year-age intervals from (ages 1–4) to (ages 80–84), and one dummy for (age over 85)], gender, area of residence (16 dummies for metropolitan cities and large administrative districts), insurance type (6 dummies for the employee-insured, the dependents of the employee-insured, the household head of the self-employed insured, other household members of the self-employed insured, the household head of the poor insured, and other household members of the poor insured), and insurance premium (one dummy for the poorest group exempt from insurance premium contribution and ten dummies for each decile of insurance premium contributions as income or wealth proxies). The categories for the reference groups were the youngest age group (0), the area of Seoul, the poorest group exempt from health insurance premium contributions, and the household head of the self-employed insured.

Health insurance premiums (income is not directly available from the NHIS–NSC database) were calculated based on the monthly income for the employed workers and based on income, standard of living, and property for the self-employed workers. When the household yearly income was 5 million won or less for the self-employed workers, the premium was calculated based on the living standard and economic activity, property value, and motor vehicle value. When the yearly income was greater than 5 million won, the premium was calculated based on income, property value, and motor vehicle value. Premium reductions were 50% for those living on islands or in remote rural areas, 22% for those living in rural areas, and 10–30% for those living with the elderly or disabled or who were single parents (http://www.nhis.or.kr). We also used Elixhauser comorbidities to control for any confounding effects of comorbidities [19]. All statistical tests were two-tailed ones and had a type 1 error of 5%.

Results

The summary statistics for the 7461 patients are presented in Table 1. There were 2609 liver cirrhosis patients and 4852 patients with the five cancers (17.2% had lung cancer, 20.9% had colorectal cancer, 31.2% had stomach cancer, 16.5% had liver cancer, and 17.8% had breast cancer; the sum is greater than 100%, because some patients had more than one type of cancer). There were 31,995 person-years of follow-up for the five cancers group (4664 for lung, 6621 for colorectal, 9849 for stomach, 5396 for liver, and 6422 for breast cancer) and 17,074 person-years of follow-up for the liver cirrhosis group (12,560 for compensated cirrhosis and 4514 for decompensated cirrhosis).

Out of 2609 patients of liver cirrhosis, 31.5% were female. On an average, they were hospitalized for 11.4 days and spent 932,542 won on medical expenses (1.00 USD = 1186.2 Korean won in 2002). During the 8 years of follow-up from 2002 to 2010, 800 liver cirrhosis patients (30.7%) died. However, of the 1316 cancer patients, a smaller proportion (27.1%) died during the 8-year follow-up period. The cancer patients (4852 patients) were more likely to be female (49.8%), were hospitalized longer (13.8 days), and spent more on medical expenses (1,661,534 won). When tests were performed, the two groups of patients were significantly different from each other by 1% or more for each of these variables.

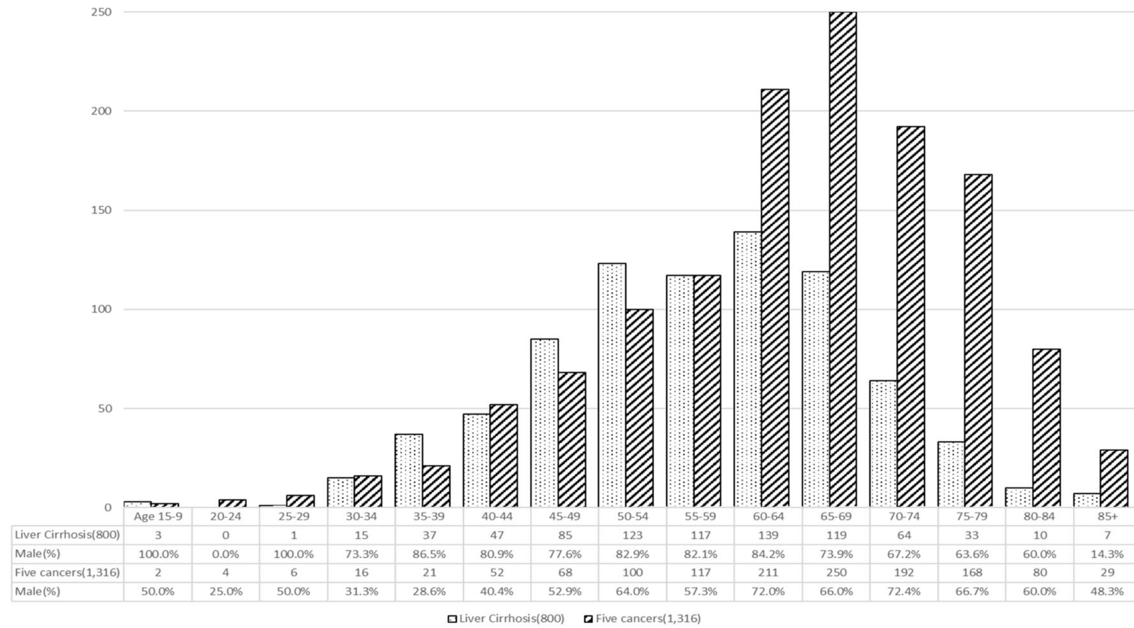
When we further divided the liver cirrhosis patients into two groups, one for liver cirrhosis only (2173 patients) and the other for both liver cirrhosis and at least one of the five cancers (436 patients), the latter group had more days of hospitalization and greater medical expenses. In addition, as expected, a significantly high proportion of the latter group (54.8%) died during the 8-year follow-up. Most of them were patients with liver cancer (89%) and stomach cancer (5%).

Figure 1 shows the age and gender distribution for the liver cirrhosis and cancer patients who died during the 8-year follow-up. Consistent with well-known findings, more males and younger patients died from liver cirrhosis than from cancers. Of the 800 patients who died from liver cirrhosis, 625 (78.13%) were male, and 62.3% were in the 50–69-year age group. However, of 1316 patients who died from the five cancers, 834 (63.37%) were male, and 62.4% were in the 60–79-year age group. Tests indicated that the two groups of patients differed significantly by 1% or more for each of these variables.

Table 1 Summary statistics of the study sample (year = 2002)

	Liver cirrhosis			The five cancers only
		Liver cirrhosis only	Both liver cirrhosis and the five cancers	
No. of patients	2609			4852
		2173	436	
Female	31.5%	31.9%	29.6%	49.8%
Days of hospitalization	11.4 (sd. 17.8)	8.9 (sd. 14.3)	23.7 (sd. 26.6)	13.8 (sd. 22.4)
Medical cost	932,542 (sd. 2436163)	545,193 (sd. 1,488,483)	2,863,067 (sd. 4,475,982)	1,661,534 (sd. 3,309,450)
Deaths within 8 years (2002–2010)	800 (30.7%)	561 (25.8%)	239 (54.8%)	1316 (27.1%)

Korean won: 1.00 USD = 1186.2 won in 2002



	Age 15-9	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
Liver Cirrhosis(800)	3	0	1	15	37	47	85	123	117	139	119	64	33	10	7
Male(%)	100.0%	0.0%	100.0%	73.3%	86.5%	80.9%	77.6%	82.9%	82.1%	84.2%	73.9%	67.2%	63.6%	60.0%	14.3%
Five cancers(1,316)	2	4	6	16	21	52	68	100	117	211	250	192	168	80	29
Male(%)	50.0%	25.0%	50.0%	31.3%	28.6%	40.4%	52.9%	64.0%	57.3%	72.0%	66.0%	72.4%	66.7%	60.0%	48.3%

Fig. 1 Age and gender distribution of decedents for liver cirrhosis and the five cancers. The five cancers were lung (C33–C34), colorectal (C18–21), stomach (C16), liver (C22), and breast (C50) cancers

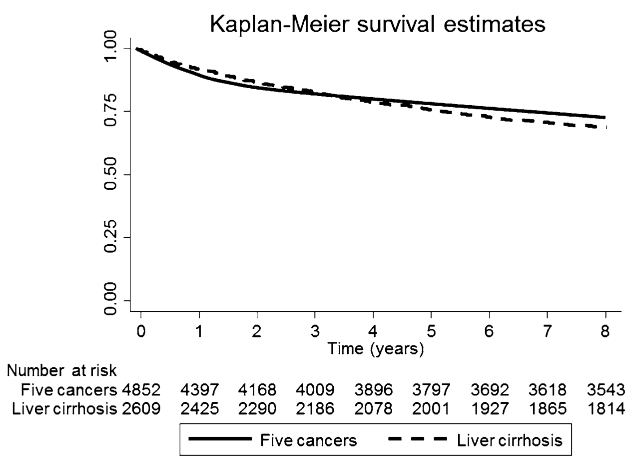


Fig. 2 Eight-year (2002–2010) mortality for the five cancers and liver cirrhosis. The five cancers were lung (C33–C34), colorectal (C18–21), stomach (C16), liver (C22), and breast (C50) cancers

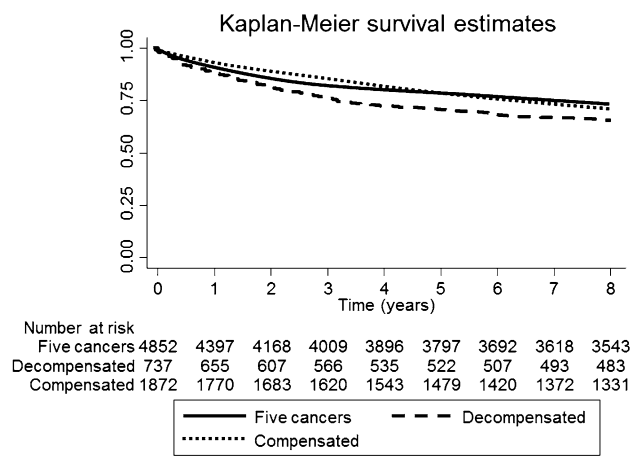


Fig. 3 Eight-year (2002–2010) mortality for the five cancers, decompensated cirrhosis, and compensated cirrhosis. The five cancers were lung (C33–C34), colorectal (C18–21), stomach (C16), liver (C22), and breast (C50) cancers

Figure 2 shows the Kaplan–Meier survival estimates for the two groups, and Fig. 3 shows the same survival estimates when the liver cirrhosis patients were divided into compensated and decompensated groups. The mortality rates per 1000 person-years were 41.1 (95% CI 39.0–43.4) for cancers and 46.9 (95% CI 43.7–50.2) for liver cirrhosis, which comprised 43.4 (95% CI 39.9–47.2) and 56.5 (95% CI 50.0–63.9) for compensated and decompensated liver cirrhosis, respectively. Results of the log rank tests showed that there were significant differences between the two survival curves in Fig. 2 (p value $= 0.0067$) and three curves in Fig. 3 (p value $= 0.0001$). As shown, the survival probability for compensated liver cirrhosis was higher initially but declined to be lower than that of the cancers, while the survival probability of decompensated liver cirrhosis was lower at all times. The overall survival rates at 8 years were 73% (95% CI 71.8–74.3) for the cancers and 69.5% (95% CI 67.7–71.3) for liver cirrhosis, which included 71.1% (95% CI 69.0–73.1) and 65.5% (95% CI 62.0–68.8) for compensated and decompensated liver cirrhosis, respectively.

Table 2 shows the estimated relative mortality for the liver cirrhosis patients and the five cancer patients using a Cox-proportional hazards model. Proportional hazards assumptions were examined using Schoenfeld residuals.

Table 2 Relative mortality of liver cirrhosis and five-cancer patients (years 2002–2010)

	Hazard ratio	95% CI
Liver cirrhosis		
Unadjusted ($n = 7461$)	1.13	1.03–1.23
Adjusted ($n = 7461$)	1.47	1.28–1.67
Compensated cirrhosis		
Unadjusted ($n = 6724$)	1.05	0.95–1.16
Adjusted ($n = 6724$)	1.41	1.22–1.63
Decompensated cirrhosis		
Unadjusted ($n = 5589$)	1.34	1.17–1.54
Adjusted ($n = 5589$)	1.82	1.51–2.20

Adjustment for age (19 groups), gender, area of residence (16 groups), type of insurance (6 groups for the employed, self-employed, poor etc.), insurance premium level (11 groups, proxy for income), and comorbidities

The hazard ratio was 1.13 (95% CI 1.03–1.23) for liver cirrhosis and increased to 1.47 (95% CI 1.28–1.67) when other mortality-related factors were adjusted for, such as age, gender, area of residence, insurance type, insurance premium, and comorbidities. Although not shown in Table 3, the hazard ratios for liver cirrhosis relative to lung, colorectal, stomach, liver, and breast cancers were 1.13 (95% CI 0.94–1.37, $n = 3443$), 1.61 (95% CI 1.32–1.96, $n = 3623$), 1.68 (95% CI 1.41–2.00, $n = 4121$), 1.17 (95% CI 0.95–1.42, $n = 3411$), and 1.87 (95% CI 1.38–2.54, $n = 3474$), respectively.

It is notable that 436 of the liver cirrhosis patients had at least one of the five cancers, primarily liver cancer. Furthermore, a significantly high proportion of them (54.8%) died during the 8-year follow-up, as shown in Table 1. For a sensitivity analysis, we excluded these patients from the analyzed sample. For the remaining patients ($n = 7025$), the hazard ratio for liver cirrhosis was 1.27 (95% CI 1.10–1.47) when other mortality-related factors were adjusted for. Alternatively, when we kept the 388 patients with both liver cirrhosis and liver cancer in the liver cirrhosis group, the hazard ratio for liver cirrhosis increased to 1.44 (95% CI 1.26–1.65, $n = 7413$) when other mortality-related factors were adjusted for.

We conducted another analysis by limiting the liver cirrhosis patients to those with decompensated liver cirrhosis (ICD-10 codes; K720, K721, K729, R18, I850, and I983). The relative mortality for decompensated liver cirrhosis was still greater than that for the five cancers. The hazard ratios were 1.34 (95% CI 1.17–1.54) and 1.82 (95% CI 1.51–2.20) for decompensated liver cirrhosis, without and with adjusting for other mortality-related factors, respectively.

While we carefully selected patients with liver cirrhosis and five cancers, their relative mortality could be subject to miscoding or misclassification errors. Therefore, we examined their respective causes of death, as shown in Table 3. The examination showed that while 70.6% of the five cancer patients died from the five cancers, only 39.3% of the liver cirrhosis patients died from the five cancers, mainly liver cancer (34%). Similarly, while 0.5% of the former group died from liver diseases, 35% of the latter

Table 3 Death causes of the liver cirrhosis and five-cancer patients

Causes	Liver cirrhosis (800) Proportion	Five cancers only (1316) Proportion
Four cancers (lung, colorectal, stomach and breast)	0.053	0.602
Liver cancer	0.340	0.104
Other cancers	0.055	0.096
Liver diseases (including viral hepatitis of B15–B19)	0.350	0.005
Infections, including tuberculosis	0.008	0.009
Diabetes	0.021	0.010
CNS diseases	0.003	0.010
Cardiovascular diseases	0.049	0.055
Pulmonary diseases	0.009	0.027
Gastrointestinal diseases	0.000	0.005
Kidney diseases	0.001	0.004
Senility	0.014	0.016
Transportation accidents	0.013	0.008
Intentional self-harm	0.016	0.011
Other	0.070	0.040
Total	1	1

National Health Insurance Service–National Sample Cohort (NHIS–NSC) database, Korea group died from liver diseases (including 5.5% of deaths caused by viral hepatitis). Therefore, examination of causes of death validated the reliability of our case definition. Nonetheless, when we limited the decedents to those who died from either the five cancers or liver diseases (excluding viral hepatitis), the hazard ratio for liver cirrhosis was 1.39 (95% CI 1.19–1.63) when other mortality-related factors were adjusted for.

Discussion

Liver cirrhosis causes 1,221,000 deaths yearly worldwide, ranking as the 14th and 10th leading cause of death in the world and in most developed countries, respectively [1]. The estimated worldwide mortality from the disease has increased to 14.4 per 100,000 population and 1.8% of all deaths worldwide in 2012, according to the Global Burden of Disease study by the WHO. The same source shows that liver cirrhosis caused 6169 deaths in 2012 in Korea [15, 20]. According to the Cause of Death Statistics of Korea, the number of deaths caused by liver cancer (C22) was 11,405, and the number of deaths caused by other liver disease (K70–K76) was 6665 in 2013; these diseases were the 5th and 12th leading causes of death, respectively, out of 103 disease categories. Even worse, the number of deaths due to liver disease (K70–K76) was higher for male (5186 male vs. 1479 female) and the economically active population: 1087 (25.1 per 100,000 people) among 50–54 years and 963 (44 per 100,000 people) among male aged 50–54 years in 2013 [21].

Our results showed that the relative mortality was higher for liver cirrhosis than for the five major cancers with and without adjusting for other mortality-related factors. During the 8 years from 2002 to 2010, the probability of survival approached 69.5% for liver cirrhosis patients compared with 73% for cancer patients. This difference in mortality was mainly due to patients with both liver cirrhosis and cancers, who were more likely to be sicker and die during the 8-year follow-up. It is notable, however, that mortality was still higher for liver cirrhosis patients, even when they were excluded from the analyzed sample. We conducted another analysis by limiting the liver cirrhosis patients to those with decompensated liver cirrhosis (ICD-10 codes; K720, K721, K729, R18, I850, and I983) and found that the relative mortality for decompensated liver cirrhosis was even greater than that for the five cancers. When we excluded colorectal cancer from the analysis, which can be higher in cirrhotic patients, the hazard ratios declined slightly but main results remained unchanged. This finding might help to adequately allocate health resources and the proper implementation of health policies. More importantly, 70.9% of liver cirrhosis patients died before the age of 65 years, while 54.6% of the five-cancer patients died after the age of 65 years, as shown in Fig. 1. Therefore, the socioeconomic burden of liver cirrhosis outweighs that of cancers.

D'Amico et al. estimated the 1-year mortality of patients with compensated and decompensated cirrhosis according to clinical stage as 1–3.4 and 20–57%, respectively [6, 7]. In a cohort study from the UK, the overall survival rates at 1 and 5 years were 87.3% (95% CI 86.1–88.4) and 66.5% (95% CI 64.5–68.5), respectively, between 1987 and 2002 for patients with compensated disease. They were much lower for patients with decompensated cirrhosis: 75.0% (95% CI 72.5–77.3) at 1 year and 45.4% (95% CI 42.1–48.7) at 5 years [8]. Using data from a nationwide Danish population-based hospital registry between 1995 and 2006, Jepsen et al. reported an overall 1-year survival rate of 65.5% and a 10-year survival rate of 21.5% among patients with liver cirrhosis. Interestingly, comorbidity increased the risk of cirrhosis-related death [22, 23]. Another large, population-based study from the UK that included the full spectrum of cirrhosis between 1998 and 2009 showed that the average survival rates at 1 and 5 years were 0.84 (95% CI 0.83–0.86) and 0.66 (95% CI 0.63–0.68) for the ambulatory group and 0.55 (95% CI 0.53–0.57) and 0.31 (95% CI 0.29–0.33) for the hospitalized group, respectively [24].

Our results showed that the survival rates were 93% (95% CI 91.9–93.9) at 1 year and 76.7% (95% CI 75–78.3) at 5 years for the cirrhosis patients and 88.9% (95% CI 86.4–90.9) at 1 year and 70.8% (95% CI 67.4–74) at 5 years for the decompensated cirrhosis patients. According to a well-cited paper on the natural history of liver cirrhosis, which followed 1455 chronic hepatitis and 1236 liver cirrhosis patients in Korea, 5-year survival rate of overall liver cirrhosis patients was 68%. The 5-year survival rate of Child–Pugh class A (compensated stage) patients was 89% and that of Child–Pugh class B&C (decompensated stage) patients were 60 and 50%, respectively [25].

We speculate that our somewhat higher survival is because our population came from the National Health Insurance System which may be more representative of the entire spectrum of disease than a university hospital-based selection of severely ill patients and improved treatment in the intervening years. The mortality attributable to liver disease in Korea has decreased over decades, mainly due to the implementation of universal hepatitis B vaccination program and advancement of management including widespread use of antiviral treatment for hepatitis B and C, band ligation for variceal bleeding, appropriate treatment of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome, availability of liver transplantation, etc. According to the Korean Network for Organ Sharing, Korea Centers for Disease Control and Prevention, number of liver transplantation increased steadily during our study period from 364 in 2002–1066 in 2010. It is also possible that the high prevalence of hepatitis B virus, affecting around 57–73% of the cases in Korea, had a better prognosis than alcoholic cirrhosis [24].

In comparison, Jung et al. analyzed the Korea National Cancer Incidence Database data on 626,506 adult patients aged ≥ 20 years, who were diagnosed between 2006 and 2010 with lung, colorectal, stomach, and liver and breast cancers. The 5-year relative survival rates were 19.7% for lung cancer, 72.7% for colorectal cancer, 67% for stomach cancer, 26.7% for liver cancer, and 91% for breast cancer [26].

Our results also showed that the hazard ratios for liver cirrhosis relative to lung, colorectal, stomach, liver, and breast cancers were 1.13 (95% CI 0.94–1.37), 1.61 (95% CI 1.32–1.96), 1.68 (95% CI 1.41–2.00), 1.17 (95% CI 0.95–1.42), and 1.87 (95% CI 1.38–2.54), respectively. However, based on the WHO database, Blachier et al. [27] reported that for the male population, the age-standardized mortality rate of liver cirrhosis was slightly lower than that of lung cancer, but was significantly higher than that of other major cancers, such as liver, stomach, and colon cancers. Any differences in mortality might have come from differences in disease stage, improved disease management in the intervening years, etiologies, etc. It is a limitation of our study that we did not have information on the disease stage at the time of diagnosis and had to assume that each patient population is more representative of the entire spectrum of disease.

Not only level of mortality, but also distribution of mortality across different age and gender groups is important for the relative economic burden of disease [21]. Similar to the results on general liver disease (K70–K76) from the Cause of Death Statistics of Korea, our results in Fig. 1 showed that more males and younger patients died during the 8-year follow-up from liver cirrhosis than from cancers. This high mortality of liver cirrhosis among the economically active population means the economic burden can be immense for individuals and society.

It is widely acknowledged that there is great potential for utilizing health-care data produced from routine application of modern health-care systems. However, three issues have dominated the concerns and critiques regarding the use of large databases for epidemiological research: selection bias, the accuracy of the data, and the retrospective nature of the data [28, 29]. This study used a nationally representative sample (NHIS–NSC) to compare the relative mortality of liver cirrhosis and the five cancers (lung, colon, stomach, liver, and breast cancers). The NHIS–NSC is a population-based cohort established by the NHIS in Korea, and a single insurer that provides universal coverage and maintains and stores national records for health-care utilization and prescriptions [18, 30]. The NHIS–NSC data allowed us to take a population-based approach to the study of relative mortality.

The results should be interpreted with caution due to other following limitations. First, even though the NHIS–NSC cohort is nationally representative, 'as-a-whole' comparisons between cirrhosis and cancer without information about severity (such as Child–Pugh scores or cancer staging) or etiology may be misleading, requiring more studies to generalize the results to other populations. Second, due to the Act on the Protection of Personal Information, we could not retrieve sampled patients to validate their diagnoses. Third, we may have missed other unmeasured mortality-related factors with a potential confounding effect.

Although the survival rate for liver cirrhosis is known to be low, few studies have compared the mortality of liver cirrhosis with that of other fatal diseases. Our results show that the mortality of liver cirrhosis is greater than that of five major cancers. Furthermore, the socioeconomic impacts could be greater when considering that more males and younger patients are subject to death from liver cirrhosis than from cancers. This implies that we need to prioritize the development of appropriate health interventions for liver cirrhosis just as we have done for cancer.

Acknowledgements This study was presented at the annual conference of the American Association for the Study of Liver Diseases (AASLD) [Hepatology 2017;66(Suppl 1):95A]. We would like to thank for the help of Ki Tae Suk, M.D., and Sang Hyun Choi, M.D., in preparation of the presentation at The Liver Meeting 2017.

Funding This study was supported by the Korean Association for the Study of the Liver (KASL) and the Korean Liver Foundation. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Compliance with ethical standards

Conflict of interest Wankyo Chung, Changik Jo, Woo Jin Chung, and Dong Joon Kim have declared that no competing interests exist.

References

1. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385:117–171
2. Ge PS, Runyon BA. Treatment of patients with cirrhosis. N Engl J Med 2016;375:767–777
3. Kochanek KD, Murphy SL, Xu J, Tejada-Vera B. Division of vital statistics. deaths: final data for 2014. Natl Vital Stat Rep 2016;65:1–122

4. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis. Hepatology 2010;51:1445–1449
5. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383:1749–1761
6. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217–231
7. D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39:1180–1193
8. Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. Liver Int 2012;32:79–84
9. Asrani SK, Larson JJ, Yawn B, Therneau TM, Kim WR. Underestimation of liver-related mortality in the United States. Gastroenterology 2013;145:375–382
10. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60:715–735
11. Runyon BA. Introduction to the revised American Association for the Study of the Liver Diseases practice guideline: management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013;57:1651–1653
12. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010;53:397–417
13. Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015. A systematic analysis for the Global Burden of Disease Study. JAMA Oncol 2017;3:524–548
14. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359–E386
15. Murray CJL, Lopez AD. Measuring the global burden of disease. N Engl J Med 2013;369:448–457
16. Murray CJL, Ezzati M, Flaxman AD, et al. GBD 2010: design, definitions, and metrics. Lancet 2012;380:2063–2066
17. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095–2128
18. Lee J, Lee JS, Park SH, Shin SA, Kim K. Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2016. https://doi.org/10.1093/ije/dyv319
19. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi J, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–1139
20. WHO. WHO methods and data sources for country-level causes of death 2000–2015. Global Health Estimates Technical Paper WHO/HIS/IER/GHE/2016.3
21. Chung W. The cost of liver disease in Korea: methodology, data, and evidence. Clin Mol Hepatol 2015;21:14–21
22. Jepsen P, Vilstrup H, Andersen PK, Lash TL, Sørensen HT. Comorbidity and survival of Danish cirrhosis patients: a nationwide population-based cohort study. Hepatology 2008;48:214–220
23. Jepsen P, Vilstrup H, Lash TL. Development and validation of a comorbidity scoring system for patients with cirrhosis. Gastroenterology 2014;146:147–156
24. Ratib S, Fleming KM, Crooks CJ, Aithal GP, West J. 1 and 5 year survival estimates for people with cirrhosis of the liver in England, 1998–2009: a large population study. J Hepatol 2014;60:282–289
25. Kim CY, Kim JW, Lee HS, Yoon YB, Song IS. Natural history and survival rate of chronic liver diseases in Korea—20 years prospective analysis. Korean J Med 1994;46:168–180
26. Jung KW, Won YJ, Kong HJ, Oh CM, Shin A, Lee JS. Survival of Korean adult cancer patients by stage at diagnosis, 2006–2010: national cancer registry study. Cancer Res Treat 2013;45(3):162–171
27. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013;58:593–608
28. Schneeweiss S. Learning from big health care data. N Engl J Med 2014;370:2161–2163
29. Genta RM, Sonnenberg A. Big data in gastroenterology research. Nat Rev Gastroenterol Hepatol 2014;11:386–390
30. Song SO, Jung CH, Song YD, Park CY, Kwon HS, Cha BS, et al. Background and data configuration process of a nationwide population-based study using the Korean National Health Insurance System. Diabetes Metab J 2014;38:395–403