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Cost of illness of the non-alcoholic liver cirrhosis in Japan - a time trend analysis and future projections

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Abstract

Aim

Liver cirrhosis is a preneoplastic condition to hepatocellular carcinoma that is an important worldwide public health concern, and its economic burden has been estimated in some countries. The objective of this study was to estimate and predict the cost of illness (COI) associated with non-alcoholic liver cirrhosis in Japan.

Methods

Using a COI method on available data from government statistics, we estimated the economic burden in 3-year intervals from 1996–2014. We then predicted the COI in 3-year intervals from 2017–2029 using fixed and variable model estimation. With fixed model estimation, only estimated future population was used as a variable. Variable model estimation considered the time trends of health-related indicators throughout the past 18 years.

Results

The estimated COI of non-alcoholic liver cirrhosis was 208.1 billion yen in 2014. The COI of non-alcoholic liver cirrhosis had a downward trend from 1996 to 2014. The predicted future COI of non-alcoholic liver cirrhosis was 144.3–210.5, 106.0–213.8, 88.6–213.4, 76.7–215.5, and 66.4–214.3 billion yen in 2017, 2020, 2023, 2026, and 2029, respectively.

Conclusions

The results of this study suggest that the COI of non-alcoholic liver cirrhosis in Japan has steadily decreased and will continue to decrease in future. Treatment of HCV patients with newly introduced technologies has high therapeutic effectiveness, which will affect the future prevalence of non-alcoholic liver cirrhosis. Because the results

of this study were based on present conditions, it should be noted when interpreting the results of long-term estimation.

Keywords:
Cost of illness, non-alcoholic liver cirrhosis, health economics, health policy

Introduction

Liver cirrhosis is the end stage of chronic liver disease, and it is divided into alcoholic and non-alcoholic types. The pathogenesis of non-alcoholic liver cirrhosis includes viral hepatitis. In developed countries, the main cause of viral hepatitis is hepatitis C virus (HCV), but infection with hepatitis B virus (HBV) is the most common cause in sub-Saharan Africa and most parts of Asia [1]. Michitaka et al. estimated the etiological agents of liver cirrhosis in Japan [2]: the major etiology of liver cirrhosis in Japan remains HCV (60.9%), followed by HBV and alcohol, respectively. Therefore, we focus on non-alcoholic liver cirrhosis (ICD 10 code: K74.3-74.6) in this study. The definition of non-alcoholic liver cirrhosis was based on the condensed list of causes of death for Japan. This list was used in government statistics. According to this definition, “liver cirrhosis (excluding alcoholic liver cirrhosis)” includes the viral hepatitis related cirrhosis and other types of liver cirrhosis such as non-alcoholic steatohepatitis (NASH) related liver cirrhosis, but alcoholic liver cirrhosis is excluded. Although an increase of prevalence in NASH related liver cirrhosis, the occupancy rate is low (2.1% in 2008) [2]. Recently, management of chronic hepatitis C has greatly changed. Interferon-free treatment with direct acting antivirals (DAAs) could

lead to sustained virological response (SVR) in patients with chronic hepatitis C and compensated cirrhosis [3].

Some recent studies have estimated the economic burden of liver disease, including cirrhosis [4-8]. In Japan, estimates based on the Survey of Medical Care Activities in Public Health Insurance and the Patient Survey [9] have been reported [10]. However, those snapshot estimations were limited to direct costs.

Both direct and indirect costs should be taken into account in the analysis of comprehensive economic burden. Estimation of comprehensive economic burden could be used as a public health policy tool for the prioritization of healthcare and prevention policies. Indirect costs include productivity losses resulting from inability to work because of hospitalization, outpatient visits, or premature death resulting from illness. The human capital approach for estimation of productivity losses can estimate the impact of disease on patients' wages and salaries, which reflect individual contributions to society. The cost of illness (COI) method developed by Rice et al. [11-14] has been widely used to estimate the comprehensive economic burden of disease.

COI can be used for decision making in allocating limited resources for implementation of governmental health policies [15]. The purpose of this study was to estimate and predict the economic burden associated with non-alcoholic liver cirrhosis in Japan. In addition, the COI of viral hepatitis in 2014 was calculated for reference.

Methods

We used the COI method to examine the economic burden of non-alcoholic liver cirrhosis. The calculation method employed in this study was the same as that of our

previous study [16]. First, we calculated the COIs for 1996, 1999, 2002, 2005, 2008, 2011, and 2014. We then predicted future COIs [17-20] based on those results. We adapted a top-down approach to the COI method, employing published government office statistics (Table 1) and data on the prevalence of non-alcoholic liver cirrhosis.

Measurement and valuation

The components of COI, direct cost (DC) and indirect cost (IC), are shown in Table 2. IC comprises morbidity cost (MbC) and mortality cost (MtC). COI was calculated using the following equation:

$$COI = DC + MbC + MtC$$

The DC comprises hospitalization cost (HC) and outpatient cost (OC). DC is calculated using the following equation:

$$DC = HC + OC = iCd \times THD + oCd \times TOVy$$

HC was determined by multiplying inpatient cost per day (iCd) for non-alcoholic liver cirrhosis by total person-days of hospitalization (THD). OC was determined by multiplying OC per day (oCd) by total person-days of outpatient visits (TOVy).

MbC comprised that of inpatients (MbCi) and outpatients (MbCo). MbCi was calculated by multiplying 1-day labour value per person (LVd) by THD according to gender and 5-year age groups. MbCo was determined by multiplying the half of LVd by TOVy according to gender and 5-year age groups.

MtC was calculated as loss of human capital by multiplying the number of deaths (NDy) and the lifetime labour value per person (LVl). LVl was determined by summing the patients' potential income, which would have accrued in future had they not died, from the age of death to their life expectancy. MbC and MtC were calculated using the following equations:

$$MbC = MbCi + MbCo = THD \times LVd + TOVy \times LVd / 2$$

$$MtC = NDy \times LVl$$

Pensions were not included in MbC and MtC. Future labour value was adjusted to its present value using a 3% discount rate, because a 3% discount rate has been widely used in previous studies in developed countries, including Japan and the United States [21].

Statistical approach

To examine change over time, we first estimated the COIs for 1996–2014 in 3-year intervals using available data. Next, to make future predictions, we estimated the COIs for 2017–2029 in 3-year intervals using the two methods. We calculated the COI for the survey years of the Patient Survey, which was conducted every 3 years.

Future COI was estimated using two methods: fixed and variable model estimation [17-20]. Fixed model estimation assumed that health-related indicators (e.g., mortality rate, number of outpatient visits, and average length of stay) were unrelated to the time trend. Only an estimated future population was used as a variable. For fixed model estimation, we first calculated the mortality rate, number of outpatient visits per population, and number of hospitalizations per population

according to gender and 5-year age groups in 2014 as a baseline for estimation. Next, we multiplied these factors by future population estimates according to gender and 5-year age groups in 3-year intervals for 2017–2029 to calculate the predicted number of deaths, TOVy, and THD. We estimated MbC and MtC in 3-year intervals for 2017–2029 using 2014 data on average length of stay, life expectancy, labour value, iCd, and outpatient visits. The fixed model was the simplest method and could be regarded as a reference.

Variable model estimation consisted of linear, logarithmic, and mixed models depending on the formula selected for each health-related indicator. For variable model estimation, we drew a trend line for each health-related indicator by using a logarithmic or linear approximation with seven time points (i.e., 1996, 1999, 2002, 2005, 2008, 2011, and 2014). We then extended the trend line for each approximation to determine values for 2017, 2020, 2023, 2026, and 2029. Variable models assumed that every health-related indicator was a variable with its own trend line. Difference of time trend among indicators was reflected in calculation process by variables.

Estimated future health-related indicators were used in addition to future population estimates. Because the trend of each health-related indicator was different, the single model estimation (logarithmic and linear models) might not predict future COI precisely. Therefore, we developed a mixed model, which adopted the value with a higher coefficient of determination for each 5-year age groups. Our mixed model was an approximation using health-related indicators with a higher coefficient of determination in a logarithmic and linear approximation for each 5-year age groups. By mixing the optimal results of both logarithmic and linear model depending on the characteristics of each health-related indicator, getting more appropriate estimates could be possible. This is the reason why it was named mixed model for this approach.

This method was already employed in our previous study [17-20]. Because the mixed model was a combination of models with a higher coefficient of determination, we believed the mixed model to be the most valid for this study. The estimations using the logarithmic and linear models can be regarded as a sensitivity analysis to test the robustness of the mixed model.

Estimations using trend lines sometimes yielded future predicted values less than 0; that could not reflect actual conditions. Therefore, we set a "minimum value". For mortality rate, number of times of outpatient visit per population, and number of times of hospitalization per population, the minimum values were set as the values from the year prior to that in which the estimate was less than 0. We assumed that the value from the year prior to that when the estimate was less than 0 would be maintained thereafter; negative values were not used in the model. We set 9.2 days, the average length of stay of patients with liver disease (2014) in Organization for Economic Co-operation and Development countries, as the minimum value.

This study used only anonymous governmental data; no human or animal subjects were involved. The Institutional Ethics Committee at Toho University approved this study (No. A16019).

Results

Each health-related indicator had a downward trend in 1996–2014, and the health-related indicators used for the future estimates are presented in Table 3. The average age of death rose 62.5–69.9 years and 70.5–76.7 years in 1996–2014 among male and female individuals, respectively. Fixed model estimation showed a slight upward trend in the number of non-alcoholic liver cirrhosis deaths, outpatient visits,

hospitalizations, and total days of hospitalization. Meanwhile, linear and logarithmic model estimation showed decreasing trends of these indicators. The estimated COI of non-alcoholic liver cirrhosis was 443.7, 397.3, 371.6, 300.8, 272.1, 237.5, and 208.1 billion yen in 1996–2014, respectively (Table 4). MtC was the largest component of COI throughout the study period, accounting for 72.3% and 79.4% of total COI in 1996 and 2014, respectively. The future COI estimates appear in Table 5. The COI was predicted to decrease to 144.3 billion yen (linear model) or 210.5 billion yen (logarithmic model) in 2017; 106.0 billion yen (linear model) or 213.8 billion yen (fixed model) in 2020; 88.6 billion yen (linear model) or 213.4 billion yen (fixed model) in 2023; 76.7 billion yen (linear model) or 215.5 billion yen (fixed model) in 2026; and 66.4 billion yen (linear model) or 214.3 billion yen (fixed model) in 2029. For the mixed model, a logarithmic approximation was used for the numbers of outpatient visits, hospitalizations per population, and mortality, and a linear approximation was also employed for average length of stay. The mixed model predicted that the COI would decrease from 200.9 billion yen in 2017 to 126.5 billion yen in 2029.

MtC was the largest component of COI, accounting for 72.3% and 79.4% of the total in 1996 and 2014, respectively. Under the mixed model, MtC as a proportion of COI was expected to increase to 92.1% in 2029.

The pathogenesis of liver cirrhosis is closely related to chronic liver diseases, such as viral hepatitis. We also estimated the COI of viral hepatitis (ICD 10 code: B15- 19) in 2014 for reference, obtaining a result of 221.9 billion yen (DC: 102.8 billion yen; MbC: 31.5 billion yen; MtC: 87.6 billion yen).

Discussion

The COI of non-alcoholic liver cirrhosis in Japan was estimated as 208.1 billion yen in 2014 and is expected to continue decreasing. The current study found that this trend will continue until at least 2029. This COI reduction is predicted to be related to the downward trend in the number of patients with HCV in Japan.

HCV infection is the leading cause of non-alcoholic liver cirrhosis in Japan, and its prevalence is closely related to age. Tanaka et al. [22] reported the prevalence of HCV among first-time blood donors: the overall prevalence of anti-HCV antibody was 0.49% in Japan during 1995–2000. The infection rate was much higher in older adults: 3.45% in men and 3.33% in women aged 60–69 years compared with 0.11% in men and 0.14% in women aged 16–19 years. The main causes of HCV dissemination in Japan included past blood transfusions from paid blood donors and injections using contaminated syringes among methamphetamine abusers [23]. Paid blood donation was common in Japan until the beginning of the 1960's; this is a main reason that the proportion of HCV carriers increases with age. After the introduction of voluntary blood donation in 1964 and HBsAg screening in 1972, the risk of post-transfusion hepatitis dramatically decreased [23]. Screening tests for HCV antibodies in blood products, which were introduced in 1989, further decreased the risk of post-transfusion hepatitis. The screening tests were also updated in 1992, 1993, and 1999. The accuracy improvements to screening tests for donated blood decreased the incidence of transfusion-transmitted hepatitis in Japan from 50.9% in 1960 to 0.0007% in 2007 [24]. Additionally, nationwide health screening programs for HBsAg and HCV RNA in people aged over 40 years were performed in 2002–2006. From April 2002 to March 2003, this program examined 1,923,480 individuals, of whom 31,393 (1.6%) had ongoing HCV infection [25]. A total of 6,280,111 people

238 (26% of the target population) were tested for this program, and 99,950 (1.6%)
239 patients with HCV infection were newly detected [23]. In recent years, the Basic Act
240 on Hepatitis Measures (enacted in 2009) has provided opportunities for viral hepatitis
241 screening. These programs have significantly reduced the number of patients with
242 viral hepatitis. As a result, the number of patients with non-alcoholic liver cirrhosis
243 has decreased in Japan in recent years.

244 The majority of recent non-alcoholic liver cirrhosis cases in Japan have been
245 among older adults. According to the governmental Patient Survey [9], 72.2% of
246 patients with non-alcoholic liver cirrhosis were aged ≥65 years in 2014. The average
247 age of death from non-alcoholic liver cirrhosis in Japan in 2014 was 69.6 years and
248 76.7 years for male and female individuals, respectively, and these values have
249 trended upward. According to the human capital method, the labour value of older
250 adults is lower than that of younger people. Therefore, the increasing average age of
251 death has contributed to the reduction in MbC.

252 Related studies on medical expenditures on non-alcoholic liver cirrhosis have
253 been published in Japan. Toyokawa et al. [10] reported that the direct cost of non-
254 alcoholic liver cirrhosis in Japan was 97.0 billion yen in 2002, similar to the present
255 study's result (i.e., 75.0 billion yen in 2002). They used claim data from the Survey of
256 National Medical Care Insurance Services and the Patient Survey in Japan.
257 Unfortunately, no time trend analysis or future projections were performed.

258 The future COI of non-alcoholic liver cirrhosis showed a downward trend.
259 Screening of healthy people for viral hepatitis, which is now under discussion, may
260 temporarily increase the number of patients. The prevalence of anti-HCV antibody
261 among young people is very low, and the majority of newly diagnosed patients with

262 viral hepatitis would be older [22]. This increase would last for several years and
263 would be expected to abate.
264 The development and introduction of DAAs against HCV in clinical practice
265 has dramatically changed the management of chronic hepatitis C. DAAs have shown
266 potent activity against HCV and incrementally improved the rates of SVR, even in
267 patients with difficult-to-treat chronic hepatitis C [26]. The treatment of HCV patients
268 with DAAs has high therapeutic effectiveness and would affect the future prevalence
269 of non-alcoholic liver cirrhosis. On the other hand, nucleos(t)ide analogues (NAs)
270 against HBV also have remarkable antiviral effects [27]. The curative effects of NAs
271 were also contribute to reduce the prevalence of non-alcoholic liver cirrhosis caused
272 by HBV, and it might bring the decline of COI of non-alcoholic liver cirrhosis. Our
273 results of time trend analysis of COI of non-alcoholic liver cirrhosis took the
274 pharmacological treatments into account. Meanwhile, NASH accounted for only 2.1%
275 of liver cirrhosis in Japan [2]. One of the most serious complications of NASH is liver
276 cirrhosis, and it has recently become recognized as an important cause of liver
277 cirrhosis. Although the prevalence of NASH related liver cirrhosis increased [2], its
278 occupancy rate is low. Therefore, it seems that the increase of prevalence of NASH
279 related liver cirrhosis might not affect to downward trend of COI of non-alcoholic
280 liver cirrhosis. The future changes of the etiology of liver cirrhosis could affect future
281 COI estimates of non-alcoholic liver cirrhosis. Because the results of this study were
282 based on present conditions, long-term estimation results should be treated with
283 caution.
284 In recent years, the number of patients of non-alcoholic fatty liver disease
285 (NAFLD) has increased, and social burden of NAFLD is also expected to increase.
286 COI of NAFLD might also contribute to the policy making process. Because NAFLD

is categorized as "Other diseases of liver" in the condensed list of causes of death for Japan, the health related indicators of NAFLD is difficult to obtain. Limitations on the data availability of governmental statistics lead to restriction on calculation of COI. It is considered that expansion of health related indicators of NAFLD based on the national database of health insurance claims and specific health checkups of Japan might be useful for calculation of COI of NAFLD.

Estimating the future COI of non-alcoholic liver cirrhosis using data from present conditions makes it possible to measure the impact of social burden related to future advances in liver disease treatment.

Conclusions

The results of this study suggest that the COI of non-alcoholic liver cirrhosis in Japan has been decreasing and will continue to do so in the future. Newly introduced medical technology including DAAs for HCV patients will affect the future prevalence of non-alcoholic liver cirrhosis in Japan. This study is an estimation based on the current situation. The future number of patients and mortality of non-alcoholic liver cirrhosis may decrease more than estimated in this study because of the progress and dissemination of new medical technologies. Estimating the future COI of non-alcoholic liver cirrhosis using data from present conditions makes it possible to measure the impact of the social burden related to future advances in liver disease treatment.

Abbreviations

COI: Cost of illness, DAAs: Direct acting antiviral agents, DC: Direct cost, HC: Hospitalization cost, HBV: Hepatitis B virus, HCV: Hepatitis C virus, IC: Indirect cost, iCd: Inpatient cost per day, LVd: 1-day labour value per person, LVl: Lifetime labour value per person, MbC: Morbidity cost, MbCi: Morbidity cost of inpatients, MbCo: Morbidity cost of outpatients, MtC: Mortality cost, NAFLD: Non-alcoholic fatty liver disease, NASH: Non-alcoholic steatohepatitis, NDy: Number of deaths, OC: Outpatient cost, oCd: Outpatient cost per day, SVR: Sustained virological response, THD: Total person-days of hospitalization, TOVy: Total person-days of outpatient visits

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TK participated in the design of the study, performed the data collection and analysis, and drafted the manuscript. KM participated in the design of the study and performed the analysis. SF, KS, YW, and TH performed the data collection and analysis. TH

conceived the study, participated in its design, and helped draft the manuscript. All authors read and approved the final manuscript.

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408

409 **Tables**

410 **Table 1. Data sources**

Data sources	Issuer	Using purpose
Survey of Medical Care Activities in Public Health Insurance	Ministry of Health, Labour and Welfare	To determine the direct cost of non-alcoholic liver cirrhosis.
Basic Survey on Wage Structure	Ministry of Health, Labour and Welfare	To calculate labour value.
Labour Force Survey	Ministry of Internal Affairs and Communications	To calculate labour value.
Estimates of Monetary Valuation of Unpaid Work	Cabinet Office	To calculate labour value.
Vital Statistics	Ministry of Health, Labour and Welfare	To evaluate the number of deaths.
Patient Survey	Ministry of Health, Labour and Welfare	To distinguish the number of patients, total person-days of outpatient visits, and average length of stay.
Population Projections for Japan	National Institute of Population and Social Security Research in Japan	To refer future population.

411

412 **Table 2. Components of COI**

Components of COI				Formulas / Data sources
COI			Cost of illness	DC + MbC + MtC
DC			Direct cost	HC + OC
	HC		Hospitalization cost	iCd × THD
		iCd	Inpatient cost per day	Survey results of the Central Social Insurance Medical Council
		THD	Total person-days of hospitalization	Patient Survey
	OC		Outpatient cost	oCd × TOVy
		oCd	Outpatient cost per day	Survey of Medical Care Activities in Public Health Insurance
		TOVy	Total person-days of outpatient visits	Patient Survey
MbC			Morbidity cost	MbCi + MbCo
	MbCi		Morbidity cost of inpatients	THD × LVd
		THD	Total person-days of hospitalization	Patient Survey
		LVd	1-day labour value per person	Basic Survey on Wage Structure, Labour Force Survey, Estimates of Monetary Valuation of Unpaid Work
	MbCo		Morbidity cost of outpatients	TOVy × LVd/2
		TOVy	Total person-days of outpatient visits	Patient Survey
		LVd/2	1/2-day labour value per person	Basic Survey on Wage Structure, Labour Force Survey, Estimates of Monetary Valuation of Unpaid Work
MtC			Mortality cost	NDy × LVl
	NDy		Number of deaths	Vital Statistics
	LVl		Lifetime labour value per person	Basic Survey on Wage Structure, Labour Force Survey, Estimates of Monetary Valuation of Unpaid Work, Life table

413

414 **Table 3. Projected results of health-related indicators of non-alcoholic liver cirrhosis**

	2014 (base line)		Future estimates				
			2017	2020	2023	2026	2029
Number of death (person)	7,796	Fixed model	8,199	8,570	8,891	9,100	9,323
		Linear model	6,614	5,718	5,159	4,720	4,272
		Logarithmic model	8,232	8,103	7,936	7,698	7,476
Number of outpatient visit (person)	2,365,200	Fixed model	2,406,198	2,481,457	2,523,677	2,560,044	2,523,283
		Linear model	1,263,377	1,114,304	955,836	772,879	599,184
		Logarithmic model	1,899,878	1,678,165	1,527,741	1,367,805	1,217,578
Number of hospitalization (episodes)	2,500	Fixed model	2,589	2,658	2,712	2,745	2,778
		Linear model	662	311	169	95	18
		Logarithmic model	1,828	1,452	1,189	973	803
Total days of hospitalization (days)	984,960	Fixed model	1,033,135	1,069,917	1,110,179	1,129,821	1,167,722
		Linear model	302,329	142,026	69,488	32,292	4,696
		Logarithmic model	847,535	689,929	578,286	484,385	410,288

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Table 4. Estimated past COI of non-alcoholic liver cirrhosis (billion yen)

	1996	1999	2002	2005	2008	2011	2014
Direct cost	67.7	65.9	75.0	43.9	44.9	26.7	29.0
Mortality cost	320.6	281.7	266.4	235.2	210.9	196.1	165.3
Morbidity cost	55.4	49.7	30.2	21.7	16.2	14.8	13.8
COI	443.7	397.3	371.6	300.8	272.1	237.5	208.1

418 Table 5. Estimated future COI of non-alcoholic liver cirrhosis (billion yen)

		Future estimates				
		2017	2020	2023	2026	2029
Direct cost	Fixed model	30.1	31.1	32.1	32.6	33.2
	Linear model	23.2	20.6	18.1	15.5	13.2
	Logarithmic model	30.3	30.2	29.8	29.3	25.7
	Mixed model	21.5	17.0	13.9	11.2	6.3
Mortality cost	Fixed model	166.6	168.6	167.0	168.6	166.9
	Linear model	116.1	81.6	67.4	58.6	51.1
	Logarithmic model	170.6	157.1	143.3	129.9	116.5
	Mixed model	170.6	157.1	143.3	129.9	116.5
Morbidity cost	Fixed model	13.8	14.1	14.3	14.3	14.2
	Linear model	5.0	3.8	3.1	2.6	2.1
	Logarithmic model	9.6	7.5	6.3	5.4	4.4
	Mixed model	8.8	6.7	5.5	4.6	3.7
COI	Fixed model	210.5	213.8	213.4	215.5	214.3
	Linear model	144.3	106.0	88.6	76.7	66.4
	Logarithmic model	210.5	194.8	179.5	164.5	146.6
	Mixed model	200.9	180.8	162.8	145.7	126.5

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