



Original Article

Cost of illness of leukemia in Japan – Trend analysis and future projections

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Abstract

Background: Leukemia is a deadly hematological malignancy that usually affects all age groups and imposes significant burden on public funds and society. The objective of this study was to analyze the cost of illness (COI) of leukemia, and to mark out the underlying driving factors, in Japan.

Methods: COI method was applied to the data from government statistics. We first summed up the direct and indirect costs from 1996 to 2014; then future COI for the year 2017–2029 was projected.

Results: Calculated COI showed an upward trend with a 13% increase from 1996 to 2014 (270–305 billion yen). Increased COI was attributed to an increase in direct costs. Although mortality cost accounted for the largest proportion of COI, but followed a downward trend. Decreased mortality costs reflected the effects of aging. Mortality cost per person also decreased, however, the percentage of mortality cost for individuals ≥ 65 years of age increased consistently from 1996 to 2014. If a similar trend in health-related indicators continue, COI would remain stable from 2017 to 2029 regardless of models.

Conclusion: COI of leukemia increased from 1996 to 2014, but was projected to decrease in foreseeable future. With advancement of new therapies, leukemia has become potentially curable and require long-term care; so direct cost and morbidity cost will remain unchanged. This reveal the further continuing burden on public funds. Thus, the information obtained from this study can be regarded as beneficial to future policy making with respect to government policies in Japan.

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Keywords: Cost of illness (COI); Economics; Health policy; Japan; Leukemia; Medical

1. Introduction

Leukemia (ICD-10 code: C91–C95) is the 11th most common form of malignancy; its global prevalence is 2.5% of all cancers with around 352,000 new cases diagnosed in 2012.^{1,2} Incidence and mortality rates are 1.5–2 times higher in Western countries than in Japan.³ The age adjusted

incidence rate in Japan was 6.5 per 100,000 people in 2012.⁴ Leukemia occurs most often in older adults but it is also the most common form of malignancy in children. In Japan, the incidence of leukemia in children under 15 years of age has not changed much since 1975; accounting for 39.3% of all cancers in 2012.⁴ The crude mortality rate of leukemia is still increasing as the number of therapy resistant patients are increasing with aging.^{5,6}

Several studies from different countries have reported cost analysis of leukemia. For instance, Blankart et al. reported that, the cost of chronic lymphocytic leukemia amounted to 4946 € (\approx 601,059 yen) per person from payer's perspective in Germany, in 2008.⁷ In Japan, Matsumoto et al. reported that the cost of illness (COI) of leukemia followed an upward trend

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from 1996 to 2008, during which time direct costs increased by 100%.⁸

However, studies addressing both direct and indirect costs of leukemia are relatively sparse in the international literature. To the best of our knowledge, this is the first COI study of leukemia with future projections; that dealt with both direct and indirect costs, and included opportunity costs caused by disease and death.

The aim of the study was to evaluate and predict the future costs attributable to leukemia; and to identify the reasons in Japan, which will improve the informational basis for the allocation of scarce resources, while controlling costs and preserving quality.

2. Methods

The well-known COI method proposed by Rice DP in 1960, was used here to estimate the social burden of disease.^{9–16} The adapted top-down approach of the COI method used herein was the same as that described in our previous study.⁸ In the current study, future predictions were made for the years 2017–2029 to analyze the time trend, based on data from the COI calculated for 1996–2014. Details of the methodology are outlined in previously published COI studies.^{17–20}

2.1. Data sources

All calculations were performed using government statistical data. We used “Vital Statistics” to evaluate the number of deaths caused by leukemia according to sex and 5 years age group. We utilized data from “Basic Survey on Wage Structure,” “Labor Force Survey” and “Estimates of Monetary Valuation of Unpaid work” to calculate the labor value according to sex and 5 years age group. Future COI predictions for 2017–2029 were based on data from “Population Projection for Japan: 2011–2060 (January 2012)” by the National Institute of Population and Social Security Research in Japan. Survey results from the “National Medical Care Insurance Services” were used to determine the annual medical expenses. The “Patient Survey” was employed to identify the number of patients, total person-days of outpatient visits and average length of stay according to sex and 5 years age group.²¹

2.2. Calculation and analysis procedure

COI includes direct costs (DCs) and indirect costs (ICs), which further comprise morbidity costs (MbCs) and mortality costs (MtCs).

DCs are defined as medical expenses that originate directly from treatment costs, hospital charges, laboratory diagnostic costs and drug costs. In this study, we calculated annual medical costs derived from the total medical expense data collected in the Survey of National Medical Care Insurance Services. ICs are defined as opportunity costs lost due to disease or death. MbC was calculated by summing the costs related to inpatient and outpatient care. The MbC of inpatients

was calculated by multiplying total person days of hospitalization by the labor value per person for one day. MbC of outpatients was determined by multiplying the total person-days of outpatient visits by half of the one day labor value per person. MtC was measured as the loss of human capital (human capital approach) which we got by multiplying the number of deaths from leukemia by the lifetime labor value per person. Lifetime labor value was determined by summing the person's potential income (which might be the present value of their future earning if they had not died) from the time of death to average life expectancy.^{17–20}

We used a discount rate of 3% to present value to get the adjusted future labor value. Three percent is broadly accepted as discount rate in developed countries such as Japan and the United States where the COI method got applicability. We performed a sensitivity analysis of the discount rate using rates in the 0%–5% range.

2.3. COI projection over time

The year 2014 was determined as benchmark for the one day labor value by sex and 5 years age group. At first, we calculated COI for the years 1996–2014 using available past data to estimate the trend over time. Then, to make future projections, we calculated COI for the years 2017–2029 utilizing two methods described below.

The first method involved creating a “fixed model” in which health-related indicators (such as mortality rate, number of outpatient visits, number of hospitalization and average length of stay) were fixed at 2014 level by sex and 5 years age group, hence the term “fixed model”. However, this model did not fix the future population estimation of each age group.

The other one is the “variable model” which involved estimating changing trends in health-related indicators in addition to population and age structure, hereafter referred to accordingly. Future health-related indicators were grouped by sex and 5 years age group and obtained using three variable models according to approximation: 1. linear model (using linear regression), 2. logarithmic model (using logarithmic regression); and 3. mixed model (combination of the approximation with higher coefficient of determination). We found the mixed model to be most valid as it used the value from the higher coefficient of determination. The fixed model can be used as a reference due to its simple approach. The logarithmic and linear models can be considered as sensitivity analyses showing the robustness of the mixed model.

DCs, in case of fixed unit costs, were calculated by multiplying the rate of the increase in the number of outpatients and inpatients from 2014 to 2017, 2020, 2023, 2026 and 2029 by the outpatient and inpatient costs for 2014. DCs, taking changes in unit cost into account, was calculated by multiplying the number of outpatient visit by the DC of outpatients per visit and the number of hospitalizations by the DC of inpatients per day.

We received approval from the Institutional Review Board of Toho University School of medicine (no. A16019).

3. Results

3.1. Changes in health-related indicators over time (1996–2029)

Table 1 shows the number of leukemia deaths increased by 30.6% from 1996 to 2014 and were also expected to increase in all models. In gross, the number of deaths would increase by 18.7% from 2014 to 2029 in the mixed model.

Average age of death increased from 1996 to 2014, owing to the rapidly ageing Japanese population. This trend was found to continue and was projected to rise 6.1 years in the mixed model from 2014 to 2029 (Tables 1 and 2).

Our projections indicated that the number of outpatient visits and total number of hospitalizations and days of hospitalization would be fairly steady to some extent (Table 2).

3.2. Past estimated COI (1996–2014)

Table 1 shows the uneven upward trends of calculated COI from 1996 to 2014. COI showed increase of total 13.0% from 1996 to 2014.

DC increased 2.6-fold and MbC showed a steady 1.5-fold increase from 1996 to 2014. Although MtC was the largest contributor of total COI, but followed a downward trend.

3.3. Future projection of COI from 2017 to 2029 (fixed model)

In the fixed model, it was presumed that only demographic changes had an influence on COI outcomes, since health-related indicators were fixed at 2014 levels. In the fixed unit cost calculation, COI indicates a downward trend. Total COI was calculated to decrease by 2.9% from the benchmark year

(i.e. 2014) to 2029. On the other hand, where we considered the increase of unit cost, COI reflects an upward trend.

MtC remained the largest contributor of total COI; however, it followed a downward trend. DC rose negligibly until 2023, and then decreased gradually where we fixed the unit cost. As opposed to, DC showed a sharp increase where we considered the increase of unit cost.

MbC was projected to decrease continuously from 2014 to 2029. During this period, the rate of change for each component of COI was stable at less than 5% (Fig. 1, Table 2).

3.4. Future projection of COI from 2017 to 2029 (variable model)

According to the linear and logarithmic model estimation COIs were calculated to be decreased in both case; i.e. when unit cost was fixed and increase in unit cost was considered from 2017 to 2029.

DC was projected to remain unchanged in the linear model and decrease slightly in the logarithmic model, in case of fixed unit cost. Contrariwise, when increase in unit cost was considered, DC showed an increase in the linear and logarithmic from 2014 to 2029. MbC was calculated to remain almost unchanged in both the linear and logarithmic models.

The monotype estimation (linear or logarithmic model) might not have accurately forecasted future COI, as the trend of each health-related indicator was different. Therefore, we considered the mixed model to be the most integrated and valid for this study. According to the mixed model, COIs were predicted to decrease when unit cost was fixed and remain stable when considering increase in unit cost. DC was estimated to rise when unit cost was fixed; reversely, showed an increase from 2014 to 2029 when increase in unit cost was considered. In addition, MbC was projected to increase (Fig. 1, Table 2).

Table 1
Changes of health-related indicators and the COI (1996–2014).

		1996	1999	2002	2005	2008	2011	2014
Health-related indicators	Population (1000 person)	125,864	126,686	127,435	127,768	127,692	127,799	127,083
	[% of 65 years or older]	15.1%	16.7%	18.5%	20.2%	22.1%	23.1%	26.0%
	Number of leukemia deaths (person)	6255	6700	6969	7283	7675	8143	8194
	[% of 65 years or older]	51.9%	55.8%	63.0%	66.6%	72.1%	73.5%	78.3%
	Average age of death (years)	61.2	62.9	65.9	67.5	69.4	70.7	71.9
	Crude incidence rate (per 100,000)	6.4	6.6	6.8	7.7	8.7	9.6	NA
COI components	Crude mortality rate (per 100,000)	5.0	5.3	5.5	5.8	6.1	6.5	6.5
	Fatality rate (per 100,000)	0.8	0.8	0.8	0.8	0.7	0.7	NA
	Average length of stay (days)	55.8	66.7	64.1	59.9	53.3	48.9	46.8
	COI (billion yen)	269.7	291.8	282.0	304.1	287.9	308.0	304.6
	Direct cost (billion yen)	41.5	67.7	58.4	94.3	87.5	97.1	107.8
	Morbidity cost (billion yen)	10.4	11.9	13.7	14.5	13.9	12.9	15.5
	Mortality cost (billion yen)	217.8	212.2	209.9	195.4	186.5	198.0	181.4
	[% of 65 years or older]	12.1%	14.1%	21.2%	23.6%	29.0%	33.8%	37.9%
Mortality cost per person (million yen)	34.8	31.7	30.1	26.8	24.3	24.3	22.1	

Source of population: Ministry of Internal Affairs and Communications, Population Estimates.

Source of number of leukemia death: Vital statistics.

Average age of death: Calculated according to the number of deaths, sex and age (5 years age group) and cause of death in vital statistics.

Source of crude morbidity rate and mortality rate: Center for Cancer Control and information Services, National Cancer Center, Japan.

Fatality rate: Calculated by dividing the crude mortality rate by crude incidence rate.

COI = Cost of illness, NA = not available.

Table 2
Future estimation of health-related indicators and predicted COI (2017–2029).

Model	Item	2017	2020	2023	2026	2029	
Fixed model	Health-related indicators	Estimated population (1000 person)	125,738.7	124,099.9	122,122.1	119,891.4	117,464.6
		[% of 65 years or older]	28.0%	29.1%	29.8%	30.5%	31.2%
		Number of leukemia deaths (person)	8634.6	9018.0	9337.9	9539.3	9766.0
		[% of 65 years or older]	80.5%	81.6%	82.2%	82.6%	82.9%
		Average age of death (years)	72.7	73.4	74.0	74.5	75.1
		Average length of stay (days)	46.8	46.8	46.8	46.8	46.8
		Number of outpatient visits (person)	643,549.3	649,153.4	644,641.7	629,946.4	616,645.2
	COI components	Number of hospitalization (times)	3844.3	3866.8	3847.3	3809.0	3760.7
		Total days of hospital stay	2,074,529.8	2,087,650.5	2,086,344.8	2,076,020.1	2,057,458.7
		COI (billion yen)					
		Unit cost fixed at 2014	305.8	306.0	303.9	300.4	296.1
		Increase in unit cost	329.6	338.7	345.1	349.8	353.0
		Direct cost (billion yen)					
		Unit cost fixed at 2014	109.2	109.9	109.7	108.8	107.5
Variable model (Linear)	Health-related indicators	Increase in unit cost	133.0	142.6	150.9	158.1	164.5
		Morbidity cost (billion yen)	15.6	15.6	15.5	15.3	14.9
		Mortality cost (billion yen)	181.0	180.6	178.7	176.4	173.6
		[% of 65 years or older]	40.1%	41.0%	41.1%	41.1%	41.2%
		Mortality cost per person (million yen)	21.0	20.0	19.1	18.5	17.8
		Number of leukemia deaths (person)	8743.2	9061.2	9350.6	9560.4	9821.0
		[% of 65 years or older]	83.1%	85.9%	88.2%	90.0%	91.5%
	COI components	Average age of death (years)	73.8	75.1	76.4	77.5	78.5
		Average length of stay (days)	46.2	43.8	41.7	40.1	38.7
		Number of outpatient visits (person)	625,715.3	663,258.3	700,801.3	738,344.3	775,887.3
		Number of hospitalization (times)	3678.6	3946.4	4214.3	4482.2	4750.0
		Total days of hospital stay	1,875,122.4	1,862,879.9	1,848,799.5	1,823,960.9	1,785,738.3
		COI (billion yen)					
		Unit cost fixed at 2014	282.7	270.1	256.9	245.3	234.1
Variable model (Logarithm)	Health-related indicators	Increase in unit cost	307.9	304.0	299.5	296.5	293.5
		Direct cost (billion yen)					
		Unit cost fixed at 2014	100.1	100.9	101.5	101.7	101.4
		Increase in unit cost	125.3	134.7	144.1	152.9	160.8
		Morbidity cost (billion yen)	16.3	16.6	17.0	17.2	16.8
		Mortality cost (billion yen)	166.3	152.6	138.4	126.3	115.9
		[% of 65 years or older]	44.9%	49.8%	54.7%	59.6%	64.2%
	COI components	Mortality cost per person (million yen)	19.0	16.8	14.8	13.2	11.8
		Number of leukemia deaths (person)	8684.9	8982.3	9235.5	9393.0	9558.2
		[% of 65 years or older]	82.0%	84.1%	85.7%	86.8%	87.8%
		Average age of death (years)	73.3	74.3	75.3	76.1	77.0
		Average length of stay (days)	48.4	47.0	45.8	44.7	43.7
		Number of outpatient visits (person)	546,908.9	556,095.0	565,590.1	574,179.4	582,020.8
		Number of hospitalization (times)	3216.5	3299.8	3374.3	3441.7	3503.2
Variable model (Mixed)	Health-related indicators	Total days of hospital stay	1,726,790.6	1,698,921.7	1,669,286.6	1,639,161.2	1,609,377.4
		COI (billion yen)					
		Unit cost fixed at 2014	279.0	269.1	259.0	249.6	240.5
		Increase in unit cost	301.9	299.5	296.7	294.4	292.1
		Direct cost (billion yen)					
		Unit cost fixed at 2014	91.2	90.4	89.4	88.4	87.4
		Increase in unit cost	114.2	120.8	127.1	133.2	139.1
	COI components	Morbidity cost (billion yen)	14.9	14.9	14.9	14.9	14.8
		Mortality cost (billion yen)	172.8	163.9	154.7	146.3	138.2
		[% of 65 years or older]	42.7%	45.6%	47.8%	49.8%	51.7%
		Mortality cost per person (million yen)	19.9	18.2	16.8	15.6	14.5
		Number of leukemia deaths (person)	8718.9	9024.5	9298.6	9474.9	9724.1
		[% of 65 years or older]	82.0%	84.1%	85.1%	86.1%	86.1%
		Average age of death (years)	73.7	74.9	76.1	77.0	78.0
Health-related indicators	Average length of stay (days)	47.8	46.1	44.7	43.4	42.2	
	Number of outpatient visits (person)	614,407.5	642,550.1	671,532.1	700,037.6	728,149.4	
	Number of hospitalization (times)	3616.4	3853.1	4087.8	4320.9	4552.7	
	Total days of hospital stay	1,907,629.4	1,924,735.5	1,942,962.0	1,954,266.0	1,959,233.2	

(continued on next page)

Table 2 (continued)

Model	Item	2017	2020	2023	2026	2029
COI components	COI (billion yen)					
	Unit cost fixed at 2014	285.7	275.6	265.2	256.0	248.2
	Increase in unit cost	311.1	310.1	308.9	309.2	310.8
	Direct cost (billion yen)					
	Unit cost fixed at 2014	101.2	103.0	104.8	106.4	107.7
	Increase in unit cost	126.6	137.4	148.6	159.5	170.3
	Morbidity cost (billion yen)	16.4	16.8	17.2	17.5	17.8
	Mortality cost (billion yen)	168.1	155.9	143.2	132.1	122.7
	[% of 65 years or older]	44.1%	48.4%	52.3%	56.1%	59.7%
	Mortality cost per person (million yen)	19.3	17.3	15.4	13.9	12.6

Source of estimated population, 2014: Ministry of Internal Affairs and Communications. Population estimates 2017, 2020, 2023, 2026 and 2029: National Institute of Population and Social Security Research, Population Statistics of Japan.

COI = Cost of illness.

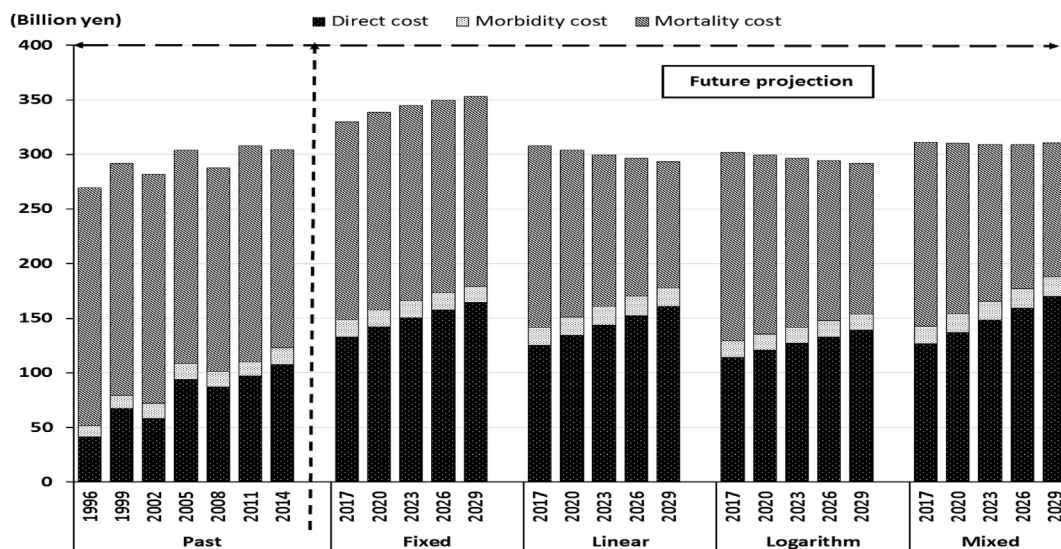


Fig. 1. Cost elements of past estimated and future projected COI (considering increase in unit cost).

COI (where DCs were calculated considering changes in unit cost into account) according to age group were shown in Fig. 2, which clarified the effects of ageing.

We performed a sensitivity analysis of the discount rate in the mixed model for future COI. Results showed variation of MtC from 2017 to 2029, ranging from 232.5 to 156.6 billion yen with a 0% discount rate and 143.2–108.2 billion yen with a 5% discount rate, illustrating similar downward trend.

3.5. Comparison with COI of stomach cancer, breast cancer and cervical cancer (fixed unit cost, mixed model)

Fig. 3 demonstrates the trend of future projected COI of stomach, breast and cervical cancers using the mixed model (when unit cost is fixed).^{17–19} It shows that the DC of leukemia was projected to sustain an almost static value suggesting that the burden on public medical funds associated with leukemia will continue.

4. Discussion

We found that, the COI of leukemia showed an upward trend from 1996 to 2014. The greatest contributor of the COI increase was the overall increase of DC in that time; but it showed a significant 1.6 fold increase from 2002 to 2005. This can be explained by the introduction of new medication; i.e. imatinib (Glivec[®]) for chronic myelogenous leukemia (CML) patients in 2001, which received approval in Japan in 2005 and contributed to the increase in DC. The annual cost of imatinib (Glivec[®]) in 2005 was 4.9 million yen per person (National Health Insurance Price Listing). Stem cell transplantation for leukemia was performed for the first time in 1993.²² In 2000, the annual number of allogeneic stem cell transplantation was less than 2,000, but this value increased to 3500 in 2010 (The Japanese Data Center for Hematopoietic Cell Transplantation). In Japan, the public health insurance system covers almost all medical services, and these efficacious yet costly procedures were applied widely within that brief period.

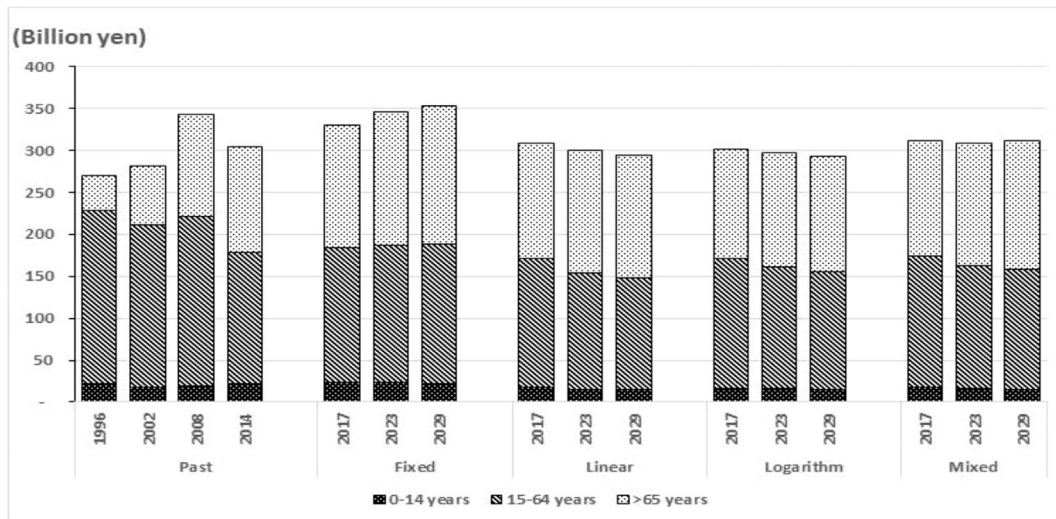


Fig. 2. COI for different age group; past estimation and future projections (considering increase in unit cost).

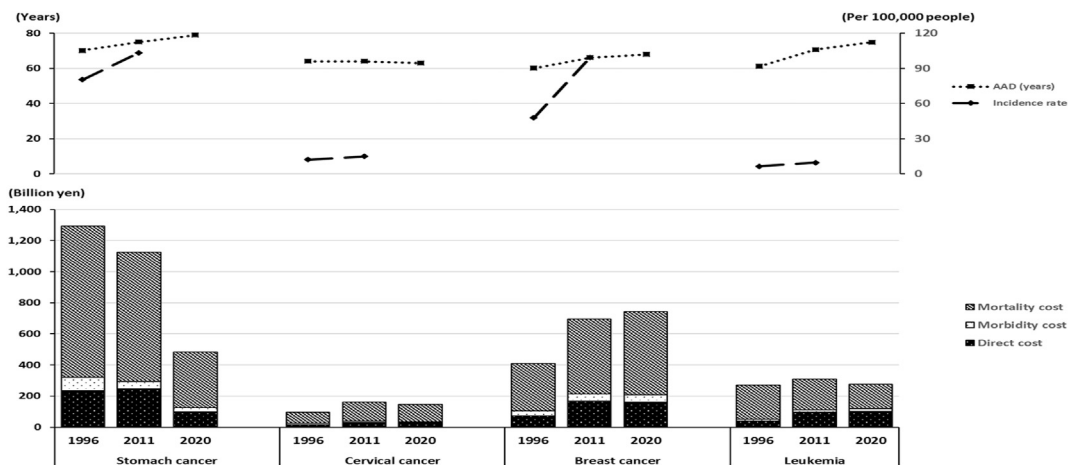


Fig. 3. COI components, Incidence rate and average age of death for stomach cancer, cervical cancer, breast cancer and leukemia over time (fixed cost, mixed model). Abbreviations: AAD-Average age of death.

These factors played a significant role in increasing DC, MbC and 5-year survival rate, thus reducing the MtC and MtC per person. The rapidly ageing society and increasing average age of death also influenced the downward trend of MtC, as elderly individuals holds relatively lower human capital value. A study conducted by Matsumoto et al. on the COI of major cancers in Japan from 1996 to 2008 also revealed a similar trend; showing a 14% decrease in the mortality costs of leukemia.⁸ The increase in the 5-year survival rate was 32.3%–39.2% from 1993 to 2008.²³

From the benchmark year 2014, it was predicted that COI would decrease consistently in all models in which unit cost was fixed. However, when we considered the increase in unit cost, COI showed a slight increase in mixed model and a significant increase in fixed model (Fig. 1). Amplification in future DC reflects the ongoing furtherance of technology and increase of expenditure in all sectors. Recent advancements in medical technology, newer and more effective drugs, bone marrow and stem cell transplantation might have a direct

impact on the slightly increasing trend in the number of outpatient visits, total number of hospitalizations and total length of hospital stays (Table 2). These, in turn, further influenced and counteracted the decline in DC and MbC. In contrast, MtC showed a consistent decreasing trend from 2014 to 2029 in all models, although it accounted for the major proportion of COI. On the other hand, increasing average age of death and percentage of deaths in individuals ≥ 65 years might be the reason, which will prevent the rise of MtC from increasing number of deaths.

Fig. 2 clarified the effects of ageing by showing COI of different age groups (where DCs were calculated considering changes in unit cost into account). 0–14 years and 15–64 years age group showed downward trend in both past estimation (1996–2014) and future projection (2017–2029); which might be due to more treatment availability and better therapeutic outcome for these age groups. On the other hand, both past and future estimation of COI for individuals ≥ 65 years of age showed increase. Increasing number of patients

and leukemia deaths in the ≥ 65 years age group would be more prominent with rapidly ageing society; which might be the reason (Table 1, Table 2).

Comparison of the COI of leukemia to that of other cancers revealed some beneficent information for prioritizing cancer control policies. Fig. 3 demonstrates future COI trends (in the case of fixed unit costs in the mixed model) in previous studies. Specifically, prostate and breast cancer shows the upward trend, whereas stomach cancer and leukemia shows reverse trend.^{17–19} However, the graph also shows that the DC of leukemia would hold almost static value in the near future, suggesting that the existent demand on public fund for leukemia treatment is going to continue. The future predicted COI of leukemia is much lower than those of other cancers because the average age of death owing to leukemia remains high. Further, leukemia is relatively rare compared to other cancers; indeed, it was 10.8 times lower than that of stomach cancer, 10.4 times lower than that of breast cancer and 1.6 times lower than that of cervical cancer in the year 2011 (Fig. 3).⁴ On the other hand, the DC of leukemia was only 2.5 times lower than that of stomach cancer, 1.7 times lower than that of breast cancer and 3.1 times higher than that of cervical cancer in the same year i.e. 2011.^{17–19} These trends can be attributed to treatment options, since stomach, breast and cervical cancer mainly involve surgical removal, whereas leukemic patients might undergo bone marrow or stem cell transplantation. In addition, patients must be in remission to receive transplants, and they are thus treated with immunotherapy and chemotherapy to gain the critical time required to find a suitable transplant donor. These factors might therefore contribute significantly to the larger amount of DC of leukemia compared to that of other cancers.

Haga et al. reported that the average transplant cost was 10.3 million yen for U-BMT (Bone Marrow Transplantation from unrelated donors) and 10.9 million yen for U-CBT (Cord Blood Transplantation from unrelated donors) in 2013.²⁴ Further, the self-burden of medical expenses among leukemia patients cannot be ignored. Kobayasahi reported that the amount of out-of-pocket payments in CML patients ranges from 0 to 1.4 million yen per year.²⁵ Fig. 3 illustrates that the projected future MtC is higher than that of prostate and cervical cancers. This might be due to childhood deaths by leukemia suggesting that further studies focusing on the structure and contributing factors of MtC are required.

In 2003, reduction of the length of hospital stays was encouraged by introduction of DPC/PDPS (Diagnosis procedure combination/Per diem payment system) which was part of the health sector reform implemented by the Japan Ministry of Health, Labor and Welfare.^{26,27} We observed a decreasing trend in the average length of hospital stays, although values remain higher compared with previous COI studies on other cancers.^{17–20}

Our study had certain limitations. Firstly, the data used for our analysis of health-related indicators were gathered over a relatively short period of time (1996–2014), and during that period, the healthcare system changed dramatically. As such, cautious interpretation of our results is recommended.

Secondly, we fixed the 2014 wage level because the growth rate of gross domestic product (GDP) growth rate was quite low before to that year. As a result, prediction of the future labor value per person was not possible, which is likely to rise, and might increase the total COI. Additionally, as the present study only made macroscopic cost estimates, we could not clarify the cost effectiveness of each therapeutic techniques, nor quality of life of patients relating to alternative treatment options. Furthermore, the present study dealt with the COI of leukemia without taking consideration of long-term care (LTC) insurance cost. LTC insurance was introduced in Japan in 2000 for chronic diseases, although the LTC cost accounts for only a small proportion of total COI.²⁸ Another contradictory fact is the COI method received criticism that it will only mislead and confuse policy makers.²⁹ We believe that COI studies can represent a starting point to identify areas for cost containment by providing reliable information to decision makers, acknowledging the effectiveness in policy-making are yet to be determined.¹⁶

Therefore, the information obtained from this study can be regarded as valid and projected future COI could be similarly beneficial to future policy making in Japan. However, future studies require the analysis of social burden considering each subtype of leukemia and analyzing data that spans longer time periods. Furthermore, concomitant cost analysis of specific treatment options should be performed by technology assessment teams.

Findings of the present study suggest that the COI of leukemia showed an overall increasing trend from 1996 to 2014. According to all models examined herein, if health-related indicators sustain the same trend, it was predicted that the COI of leukemia would decrease or remain nearly stable in the future. MtCs are expected to mitigate in the future; on the other hand, DC and MbC are presumed to remain stable. Thus, this result reflects the effect of ageing society, and the advancing treatment availability, respectively. While this may relieve the huge sense of frustration within the oncology community, but also reveal the further continuing burden on public funds in Japan, which has a universal public health insurance system.

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References

1. International Agency for Research on Cancer. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Available at http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed 25 May 2018.
2. Nasir M, Jabeen F, Hussain SM, Shaheen T, Samiullah K, Chaudhry AS. Impact of consanguinity, environment, socio-economic and other risk factors on epidemiology of leukemia. *Pakistan J Zool* 2015;47:1117–24.
3. IARC. Cancer incidence in five continents, Vol. IX. In: Curado MP, Edwards B, Shin HR, et al, editors. *IARC scientific publications No. 160*. Lyon: IARC; 2007. p. 703–6.

4. ganjoho.jp. Centre for Cancer Control and Information Services, National Cancer Centre. Available at [http://ganjoho.jp/data/reg_stat/statistics/dl/cancer_incidence\(1975-2013\).xls](http://ganjoho.jp/data/reg_stat/statistics/dl/cancer_incidence(1975-2013).xls). Accessed 25 May 2018.
5. ganjoho.jp. Centre for Cancer Control and Information Services, National Cancer Centre. Available at [https://ganjoho.jp/data/reg_stat/statistics/dl/cancer_mortality\(1958-2016\).xls](https://ganjoho.jp/data/reg_stat/statistics/dl/cancer_mortality(1958-2016).xls). Accessed 25 May 2018.
6. Endo T, Sakamoto J, Miyazawa M, Sumigawa K, Chiba Y, Hamano M, et al. Epidemiological feature of leukemia in Japan. *JPFNI* 2011;**21**:138–45.
7. Blankart CR, Koch T, Linder R, Verheyen F, Schreyögg J, Stargardt T. Cost of illness and economic burden of chronic lymphocytic leukemia. *Orphanet J Rare Dis* 2013;**8**:32.
8. Matsumoto K, Haga K, Hanaoka S, Kitazawa T, Hasegawa T. Costs of illness for major cancers in Japan. *Nihon Iryo Management Gakkai Zasshi* 2012;**13**:2–6 [in Japanese].
9. Crum GE, Rice DP, Hodgson TA. The priceless value of human life. *Am J Publ Health* 1982;**72**:1299–300.
10. Rice DP. Estimating the cost of illness. *Am J Publ Health Nations Health* 1967;**57**:424–40.
11. Rice DP, Hodgson TA. The value of human life revisited. *Am J Publ Health* 1982;**72**:536–8.
12. Rice DP, Hodgson TA, Kopstein AN. The economic costs of illness: a replication and update. *Health Care Financ Rev* 1985;**7**:61–80.
13. Rice DP. Cost-of-illness studies: fact or fiction? *Lancet* 1994;**344**:1519–20.
14. Rice DP. Cost of illness studies: what is good about them? *Inj Prev* 2000;**6**:177–9.
15. Hodgson TA, Meiners MR. Cost-of-illness methodology: a guide to current practices and procedures. *Milbank Mem Fund Q Health Soc* 1982;**60**:429–62.
16. Tarricone R. Cost-of-illness analysis. What room in health economics? *Health Pol* 2006;**77**:51–63.
17. Matsumoto K, Haga K, Kitazawa T, Seto K, Fujita S, Hasegawa T. Cost of illness of breast cancer in Japan: trends and future projections. *BMC Res Notes* 2015;**8**:539.
18. Hayata E, Seto K, Haga K, Kitazawa T, Matsumoto K, Morita M, et al. Cost of illness of the cervical cancer of the uterus in Japan—a time trend and future projections. *BMC Health Serv Res* 2015;**15**:104.
19. Haga K, Matsumoto K, Kitazawa T, Seto K, Fujita S, Hasegawa T. Cost of illness of the stomach cancer in Japan - a time trend and future projections. *BMC Health Serv Res* 2013;**13**:283.
20. Kitazawa T, Matsumoto K, Fujita S, Seto K, Hanaoka S, Hasegawa T. Cost of illness of the prostate cancer in Japan—a time-trend analysis and future projections. *BMC Health Serv Res* 2015;**15**:453.
21. e-stat.go.jp. Portal Site of Official Statistics of Japan, e-Stat. Available at <https://www.e-stat.go.jp/en/>. Accessed 25 May 2018.
22. Aversa F, Terenzi A, Felicini R, Carotti A, Falcinelli F, Tabilio A, et al. Haploidentical stem cell transplantation for acute leukemia. *Int J Hematol* 2002;**76**(Suppl. 1):165–8.
23. ganjoho.jp. Centre for Cancer Control and Information Services, National Cancer Centre. Available at [http://ganjoho.jp/data/reg_stat/statistics/dl/cancer_survival\(1993-2008\).xls](http://ganjoho.jp/data/reg_stat/statistics/dl/cancer_survival(1993-2008).xls). Accessed 25 May 2018.
24. Haga Y, Matsumoto K, Akira O, Saji T, Hasegawa T. Comparison of direct costs for allogenic bone marrow transplantation from unrelated donors and umbilical cord blood transplantation for childhood acute lymphoblastic leukemia in Japan. *J Med Soc Toho* 2013;**60**:76–84.
25. Kobayashi K. Elderly cancer care from the view point of health economics. *Geriatr Med* 2013;**51**:181–4 [in Japanese].
26. Wang K, Li P, Chen L, Kato K, Kobayashi M, Yamauchi K. Impact of the Japanese diagnosis procedure combination-based payment system in Japan. *J Med Syst* 2010;**34**:95–100.
27. Hashimoto H, Ikegami N, Shibuya K, Izumida NS, Noguchi H, Yasunaga H, et al. Cost containment and quality of care in Japan: is there a trade-off? *Lancet* 2011;**378**:1174–82.
28. Matsumoto K, Hanaoka S, Wu Y, Hasegawa T. Comprehensive cost of illness of three major diseases in Japan. *J Stroke Cerebrovasc Dis* 2017;**26**:1934–40.
29. Shiell A, Gerard K, Donaldson C. Cost of illness studies: an aid to decision making? *Health Pol* 1987;**8**:317–23.