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Trends in survival of leukemia among children, adolescents, and young adults: A population-based study in Osaka, Japan

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Abstract

This study focused on children as well as adolescents and young adults (AYAs) and aimed to examine trends in survival of leukemia over time using population-based cancer registry data from Osaka, Japan. The study subjects comprised 2254 children (0-14 years) and 2,905 AYAs (15-39 years) who were diagnosed with leukemia during 1975-2011. Leukemia was divided into four types: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and other leukemias. We analyzed 5-year overall survival probability (5y-OS), using the Kaplan-Meier method and expressed time trends using the joinpoint regression model. For recently diagnosed (2006-2011) patients, a Cox proportional hazards model was applied to determine predictors of 5y-OS, using age group, gender, and treatment hospital as covariates. Over the 37-year period, 5y-OS greatly improved among both children and AYAs, for each leukemia type. Among AYAs, 5y-OS of ALL improved, especially after 2000 (65% in 2006-2011), when the pediatric regimen was introduced but was still lower than that among children (87% in 2006-2011, $P < .001$). Survival improvement was most remarkable in CML, and its 5y-OS was over 90% among both children and AYAs after the introduction of molecularly targeted therapy with tyrosine kinase inhibitors. Among patients with recently diagnosed AML, the risk of death was significantly higher for patients treated at nondesignated hospitals than those treated at designated cancer care hospitals. The changes in survival improvement coincided with the introduction of treatment regimens or molecularly targeted therapies. Patient centralization might be one option which would improve survival.

KEYWORDS
adolescents and young adults, children, epidemiology, leukemia, survival

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1 | INTRODUCTION

According to national cancer registry data that began in 2016, approximately 2000 children (age 0-14 years) and 20 000 adolescents and young adults (AYAs, age 15-39 years) are newly diagnosed with cancer each year in Japan.[1] Improvements in treatment and care for children and AYAs with cancer are included in the 3rd Basic Plan to Promote Cancer Control Programs in Japan.[2]

Previous reports revealed that survival of leukemia among children dramatically improved in Japan, and 5-year overall survival probability (5y-OS) was over 80% after the 2000s,[3] while among AYAs (age 15-29 years), 5y-OS of leukemia was lower (56.9%) than that among children.[4] It was noticeably lower among young adults with acute lymphoblastic leukemia (ALL) (age 20-29 years, 5y-OS was 29% in 2001-2005).[5] The reasons for this difference may include differences in cancer biology and chemotherapy pharmacokinetics, together with barriers to access to specialized centers, a lack of specialist care guidelines, treatment regimens, and clinical trials relevant to AYAs.[5-9] Regarding the treatment regimens, several clinical studies, including a Japanese trial, have confirmed the superiority of pediatric regimens in AYAs with ALL over adult regimens,[10-13] and survival in AYAs after the introduction of pediatric regimens is expected to improve. In Europe and the United States, long-term trends in survival of ALL among children (age 0-14 years), adolescents (age 15-19 years), and young adults (age 20-39 years) since the 1970s were examined and showed that the 5y-OS has improved in all generations, but survival in AYAs has still lagged behind that in children.[14] Regarding acute myeloid leukemia (AML), several studies have shown improved procedures for hematopoietic stem cell transplantation (HSCT) and clinical outcomes among both children and AYAs since the 2000s.[15,16] Regarding chronic myeloid leukemia (CML), the introduction of molecularly targeted therapy with tyrosine kinase inhibitors (TKIs), which inhibits BCR/ABL tyrosine kinase activity, has revolutionized treatment and prognosis among children and adults in recent decades.[17] However, in Japan, the long-term trends in survival of each type of leukemia among children and AYAs has never been reported.

The National Cancer Control Act in Japan was established in 2006, initially focusing on major adult cancers.[18] Based on the first Basic Plan to Promote Cancer Control Programs, a total of nearly 400 hospitals that meet the national criteria for the number of cancer patients, physician expertise, and availability of support programs for cancer patients have been designated as specialized cancer care hospitals across the country by the Ministry of Health, Labor, and Welfare (MHLW).[18,19] In 2012, the second Basic Plan to Promote Cancer Control Programs raised, for the first time, the issue of care for children, and fifteen hospitals were designated as childhood cancer care hospitals by the MHLW.[18] In the United States, the impact of care at specialized cancer centers on survival was assessed, and AYAs with ALL treated at nonspecialized centers had lower survival than those treated at specialized centers[9]; however, no such investigation has been reported in Japan.

This study focused on children (age 0-14 years) and AYAs (age 15-39 years) and aimed to examine the survival trends of each type of leukemia over time and clarify whether there is still a "survival gap" between children and AYAs, using population-based cancer registry data from Osaka, Japan. We also examined the impact of age, gender, and type of treatment hospital on prognosis among recently diagnosed patients.

2 | MATERIALS AND METHODS

2.1 | Data

We identified 5221 children and AYAs diagnosed with leukemia (International Classification of Disease 10th edition: C91-95) at the age of 0-39 years during 1975-2011 from the database of the Osaka Cancer Registry (OCR). The OCR is a population-based cancer registry which has been operating since 1962 and covers all residents in Osaka prefecture which has a population of 8.8 million (2015 census).[20] Patient data from the OCR include sex, age, date of cancer diagnosis, tumor sequence (ie, the numerical order of occurrence of the neoplasm), site, morphology, behavior, summary of treatment, vital status, treatment hospital, and date of death or the last follow-up for vital status. If more than one hospital submits the same cancer record, one hospital is selected as the "treatment hospital," and priority is given according to the order in which treatment was performed; surgery, radiation, chemotherapy, or other treatment (including HSCT). If the same treatment is performed at more than one hospital, the hospital with the earliest date of diagnosis is defined as the treatment hospital. Follow-up for vital status is routinely performed using death certificates. In addition, patients diagnosed with cancer were followed up using official resident registries to verify vital status by 3, 5, 10-years after diagnosis.[21] Of these, patients who were registered by death certificate only (34 patients, 0.7%) or registered as multiple primary malignancies (28 patients, 0.5%) were excluded; the remaining 5159 patients were analyzed. Extracted leukemia cases were divided into four leukemia types using the International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes: ALL (ICD-O-3 morphology codes: 9835, 9836, 9837), AML (ICD-O-3 morphology codes: 9840, 9861, 9866, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9931, 9988), CML (ICD-O-3 morphology codes: 9863, 9875, 9876), and other leukemias (the rest of the leukemia cases). Based on the designation of 18 hospitals, including two childhood cancer care hospitals, as specialized cancer care hospitals by the MLHW as of March 2019 in Osaka, we divided cases into two categories: those treated at designated cancer care hospitals and those treated at nondesignated hospitals, using information on treatment hospital.

2.2 | Statistical analysis

We used the chi-square test to compare the distribution of categorical variables between children (age 0-14 years) and AYAs (age 15-39 years).

	Children (age 0-14 years)		AYAs (age 15-39 years)		P-value[a]
	N	%	N	%	
Total number of patients	2,254	100.0	2,905	100.0	
Sex					
Male	1,232	54.7	1,719	59.2	.001
Female	1,022	45.3	1,186	40.8	
Histological type					
Acute lymphoblastic leukemia	1,429	63.4	648	22.3	<.001
Acute myeloid leukemia	557	24.7	1,337	46.0	
Chronic myeloid leukemia	77	3.4	611	21.0	
Other leukemias	191	8.5	309	10.6	
Period at diagnosis					
1975-1981	540	24.0	638	22.0	.023
1982-1987	434	19.3	484	16.7	
1988-1993	349	15.5	480	16.5	
1994-1999	319	14.2	450	15.5	
2000-2005	320	14.2	418	14.4	
2006-2011	292	13.0	435	15.0	
Treatment hospital					
Designated cancer care hospitals	1,369	60.7	1,626	56.0	<.001
Nondesignated hospitals	885	39.3	1,279	44.0	

TABLE 1 Characteristics of study subjects

Abbreviation: AYAs, adolescents and young adults.

[a]Comparisons between children and AYAs using chi-square test.

Evaluation of survival trends was conducted in three ways. (1) 5y-OS was estimated for leukemia (all types) and by each leukemia type among children (age 0-14 years) and AYAs (age 15-39 years) with 95% confidence interval (CI), using the Kaplan-Meier method, and compared between children and AYAs using the log-rank test by each 6- or 7-year period (1975-1981, 1982-1987, 1988-1993, 1994-1999, 2000-2005, and 2006-2011). (2) For the analyses of survival trends, the Joinpoint Regression Program, Version 4.7.0.0, February 2019, was used to obtain joinpoint regressions and inflection points via the logarithmic function and final selection models provided by the program.[14,22] We input the 5y-OS of leukemia (all types) in children (age 0-14 years) and AYAs (age 15-39 years) for each year calculated using the Kaplan-Meier method. Regarding each leukemia type, due to the small number of cases, we input the 5y-OS over a 3-year period for ALL and AML and over a 6-year period for CML. (3) We examined the Kaplan-Meier curves of each leukemia type over the three decades (1982-1991, 1992-2001, 2002-2011) by three age groups (age 0-14 years, age 15-24 years, age 25-39 years) to assess survival before and after the introduction of pediatric regimens for

ALL in 15-24-year-olds in 2002,[12] or before and after the introduction of TKIs for CML in 2001.[23]

Focusing on recently diagnosed (2006-2011) ALL and AML patients, we applied the Cox proportional hazards regression model using age group, gender, and type of treatment hospital as covariates to determine the predictors of 5y-OS.

For all analyses, a two-sided $P < .05$ was considered statistically significant. All analyses except for trend analysis were carried out using Stata 14. This study was approved by the institutional review board of Osaka International Cancer Institute (approval number: 19143).

3 | RESULTS

3.1 | Characteristics of study subjects

We identified 5192 leukemia cases in the period 1975-2011. Table 1 shows the differences in patient characteristics between children

(age 0-14 years) and AYAs (age 15-39 years). Male patients represented a slightly larger proportion of cases than female among both children (54.7%) and AYAs (59.2%). ALL was the most common leukemia in children (63.4%), while AML was the most common in AYAs (46.0%). The number and proportion of CML patients were smaller in children (n = 77) than AYAs (n = 611). Most patients (children: 60.7%, AYAs: 56.0%) were treated in the designated cancer care hospitals. We checked the number of cases by treatment hospital by each 6- or 7-year period (Figure 1). During the most recent period (2006-2011), over 90% (274 out of 292) of children with leukemia were treated in designated cancer care hospitals compared with 56.3% (245 out of 435) of AYAs with leukemia.

3.2 | Time trends in 5-y-OS for each leukemia type

We included 4323 (84%) patients in the survival analysis, excluding 836 patients (16%) without follow-up information. Table 2 shows 5y-OS and results of the log-rank test for children (age 0-14 years) and AYAs (age 15-39 years) by each leukemia type, by 6- or 7-year period. Overall, 5y-OS of leukemia (all types) improved in both children (from 22.0% [95% CI = 18.4-25.9] to 83.7% [95% CI = 78.9-87.5]) and AYAs (from 7.2% [95% CI = 4.9-9.9] to 71.8% [95% CI = 67.1-75.9]) between 1975 and 2011. Five-year OS of ALL improved from 30.2% (95% CI = 24.9-35.5) to 86.7% (95% CI = 80.7-91.0) in children and from 4.2% (95% CI = 0.8-12.0) to 64.5% (95% CI = 53.8-73.3) in AYAs between 1975 and 2011. Among AYAs, 5y-OS of ALL improved recently (64.5% [95% CI = 53.8-73.3] in 2006-2011), but this was still significantly lower than that in children (86.7% [95% CI = 80.7-91.0], P < .01). Regarding AML, 5y-OS improved from 7.0% (95% CI = 3.5-12.3) to 77.0% (95% CI = 66.6-84.5) in children and from 5.2% (95% CI = 2.8-8.8) to 66.5% (95% CI = 59.1-72.9) in AYAs between 1975 and 2011. The difference

in 5y-OS of AML between children and AYAs became nonsignificant in the most recent period (2006-2011) (P = .09). Regarding CML, 5y-OS improved from 6.3% (95% CI = 0.4-24.7) in children and 14.1% (95% CI = 8.0-22.0) in AYAs during 1975-1981 to over 90% in both children and AYAs during 2006-2011, and there has been no survival difference between children and AYAs since 1988.

Using the joinpoint model, we examined trends in survival of each leukemia type among children (age 0-14 years) and AYAs (age 15-39 years) during 1975-2011 (Figure 2A-D). Visually, improvement in 5y-OS was remarkable among both children and AYAs for all leukemia types. For ALL, 5y-OS among children improved rapidly during 1975-1994 and after that it plateaued. Among AYAs, 5y-OS improved rapidly during 1975-1991, plateaued, and then improved after 2000. For AML, during 1975-1978, the 5y-OS had been under 10% in both children and AYAs but improved rapidly until the 1990s and has been gradually improving recently. Survival improvement in CML was remarkable during the total study period, and 5y-OS reached 90% after 2006 in both children and AYAs.

Figure 3 shows the Kaplan-Meier survival curves of each leukemia type by three age groups (0-14 years, 15-24 years, 25-39 years) over three decades. For ALL, Kaplan-Meier survival curves among AYAs aged both 15-24 years and 25-39 years improved similarly in the period after the introduction of the pediatric regimen (2002-2011) (5y-OS during 1992-2001: age 0-14 years: 77.1%, age 15-24 years: 37.1%, age 25-39 years: 33.4%; 5y-OS during 2002-2011: age 0-14 years: 87.6%, age 15-24 years: 59.4%, age 25-39 years: 57.0%). For AML, Kaplan-Meier survival curves in all three age groups improved between the period 1982-1991 and 1992-2001 by over 20%, and 5y-OS reached over 60% in the period 2002-2011. For CML, survival curves in all age groups improved between the period 1982-1991 and 1992-2001 by over 30%, and 5y-OS reached over 80% in the period of 2002-2011.
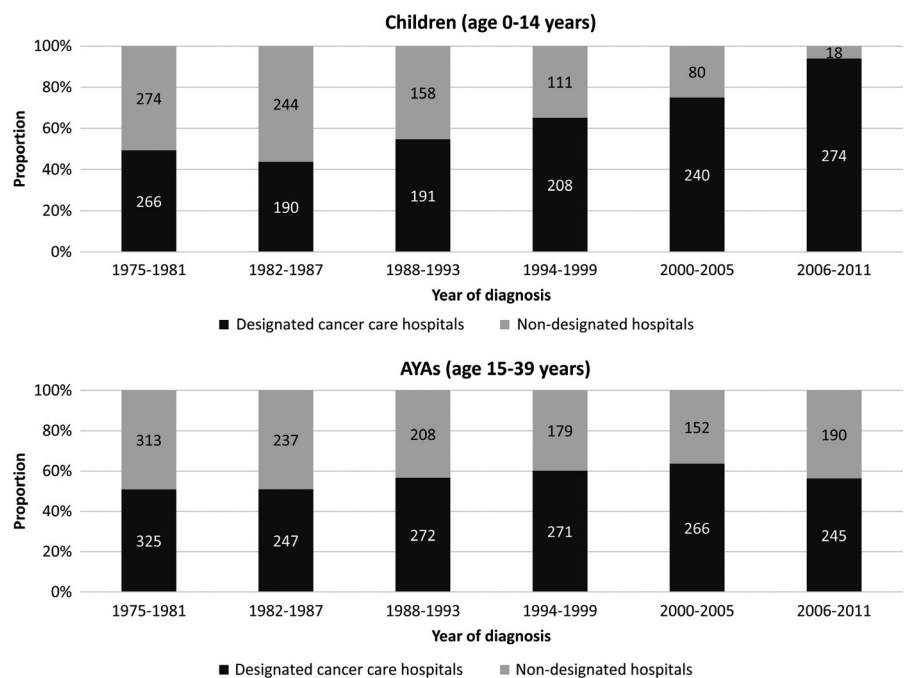
FIGURE 1 Trends in type of treatment hospital among children (age 0-14 y) and adolescents and young adults (AYAs; age 15-39 y)

TABLE 2 Five-year overall survival probability among children as well as adolescents and young adults by period at diagnosis and leukemia type, 1975-2011

Period at diagnosis	Children (age 0-14 y)			AYAs (age 15-39 y)			
	N at risk	5-y OS(%)	95%CI	N at risk	5-y OS(%)	95%CI	P-value[a]
Leukemia (all types)[b]	2059			2264			
1975-1981	477	22.0	(18.4-25.9)	404	7.2	(4.9-9.9)	<.01
1982-1987	387	45.2	(40.1-50.0)	373	16.1	(12.6-20.0)	<.01
1988-1993	301	56.8	(51.0-62.2)	360	29.2	(24.6-34.0)	<.01
1994-1999	305	75.4	(70.2-79.9)	368	46.9	(41.7-51.9)	<.01
2000-2005	306	81.6	(76.8-85.5)	350	52.5	(47.1-57.6)	<.01
2006-2011	283	83.7	(78.9-87.5)	409	71.8	(67.1-75.9)	<.01
Acute lymphoblastic leukemia	1318			515			
1975-1981	289	30.2	(24.9-35.5)	60	4.2	(0.8-12.0)	<.01
1982-1987	263	53.9	(47.7-59.7)	83	13.3	(7.0-21.5)	<.01
1988-1993	202	58.4	(51.3-64.9)	101	25.7	(17.7-34.5)	<.01
1994-1999	190	83.2	(77.0-87.8)	89	38.7	(28.5-48.6)	<.01
2000-2005	200	84.9	(79.2-89.2)	89	41.6	(31.3-51.5)	<.01
2006-2011	174	86.7	(80.7-91.0)	93	64.5	(53.8-73.3)	<.01
Acute myeloid leukemia	511			1059			
1975-1981	128	7.0	(3.5-12.3)	210	5.2	(2.8-8.8)	.03
1982-1987	76	19.7	(11.7-29.3)	180	15.6	(10.7-21.2)	.16
1988-1993	61	50.8	(37.7-62.5)	163	25.2	(18.8-32.0)	<.01
1994-1999	76	59.1	(47.2-69.2)	168	41.7	(34.2-49.0)	.01
2000-2005	83	74.5	(63.6-82.6)	153	49.6	(41.4-57.2)	<.01
2006-2011	87	77.0	(66.6-84.5)	185	66.5	(59.1-72.9)	.09
Chronic myeloid leukemia	69			502			
1975-1981	16	6.3	(0.4-24.7)	92	14.1	(8.0-22.0)	.03
1982-1987	17	5.9	(0.4-23.5)	89	20.2	(12.6-29.1)	.01
1988-1993	12	50.0	(20.8-73.6)	77	40.7	(29.7-51.5)	.50
1994-1999	13	69.2	(37.3-87.2)	79	64.6	(53.0-74.0)	.73
2000-2005	5	80.0	(20.4-96.9)	73	76.7	(65.2-84.8)	.80
2006-2011	6	100.0	-	92	93.3	(85.8-97.0)	.52

Abbreviations: AYAs, adolescents and young adults; CI, confidence interval; OS, overall survival probability.

[a]Comparisons of survival functions between children and AYAs using the log-rank test.

[b]Leukemia represents all types of leukemia, including acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, and other leukemias.

3.3 | Predictors of survival in recent cases

Focusing on recently diagnosed cases with ALL or AML during 2006-2011, we applied the Cox proportional hazards regression model using age group, gender, and type of treatment hospital as covariates (Table 3). In the multivariate analysis, for ALL, AYAs aged 15-39 years were associated with an increased risk of death compared with children (hazard ratio, HR = 3.0 [95% CI = 1.7-5.4], $P < .001$). For AML, the risk of death was not significantly different by age group (HR = 1.2 [95% CI = 0.7-2.1], $P = .55$) but was significantly higher among patients treated in nondesignated hospitals than in the designated cancer care hospitals (HR = 1.9 [95% CI = 1.2-3.0], $P = .01$).
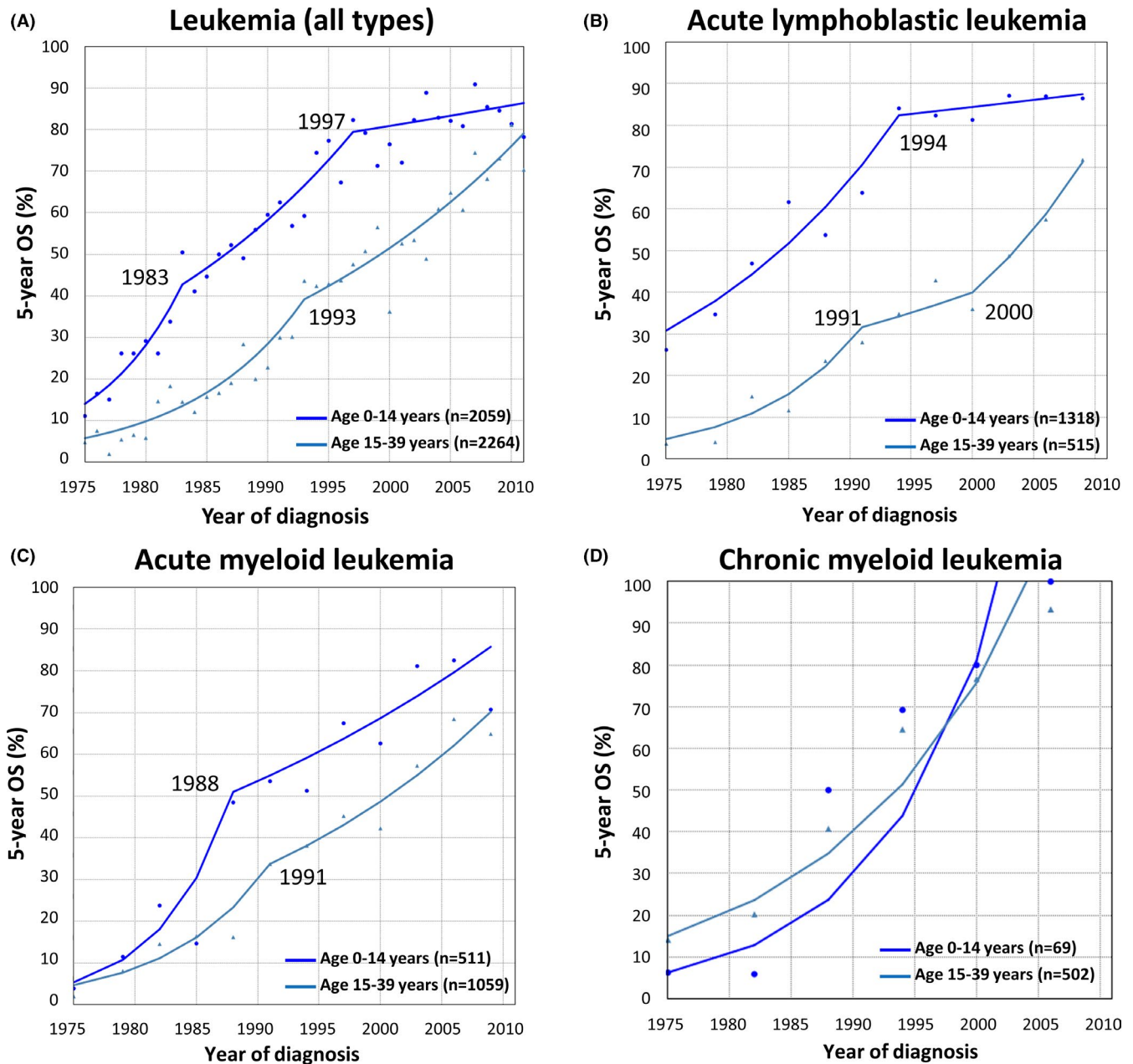
FIGURE 2 Trends in five-year overall survival (5y-OS) of leukemia and each leukemia type among children (age 0-14 y) and AYAs (age 15-39 y), 1975-2011. Leukemia represents all types of leukemia, including acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, and other leukemias

4 | DISCUSSION

In this study, we overviewed the trends in survival of each type of leukemia among children and AYAs over time and evaluated prognostic factors for recent cases.

4.1 | Acute lymphoblastic leukemia

We found that 5y-OS of ALL improved and after 1994 reached over 80% in children (Table 2 and Figure 2). Treatment for childhood

ALL started in 1948; almost all key drugs were approved before the 1980s, and the development of multidrug combination regimens and risk stratification was revised to maximize the antileukemia effect and to minimize toxicity within clinical trials.[24] In Japan, clinical study groups for leukemia in children were developed and followed these treatment modifications.[25-29] Our data may indicate these efforts contributed to an improvement in the survival of children with ALL at population level. Among AYAs, 5y-OS of ALL was especially improved after 2000 (65% in 2006-2011) when the pediatric regimen was introduced, but was still lower than that in children (87% in 2006-2011, P < .001) (Tables 2 and 3, Figure 2). The poor prognosis of ALL in AYAs compared with children was reported to
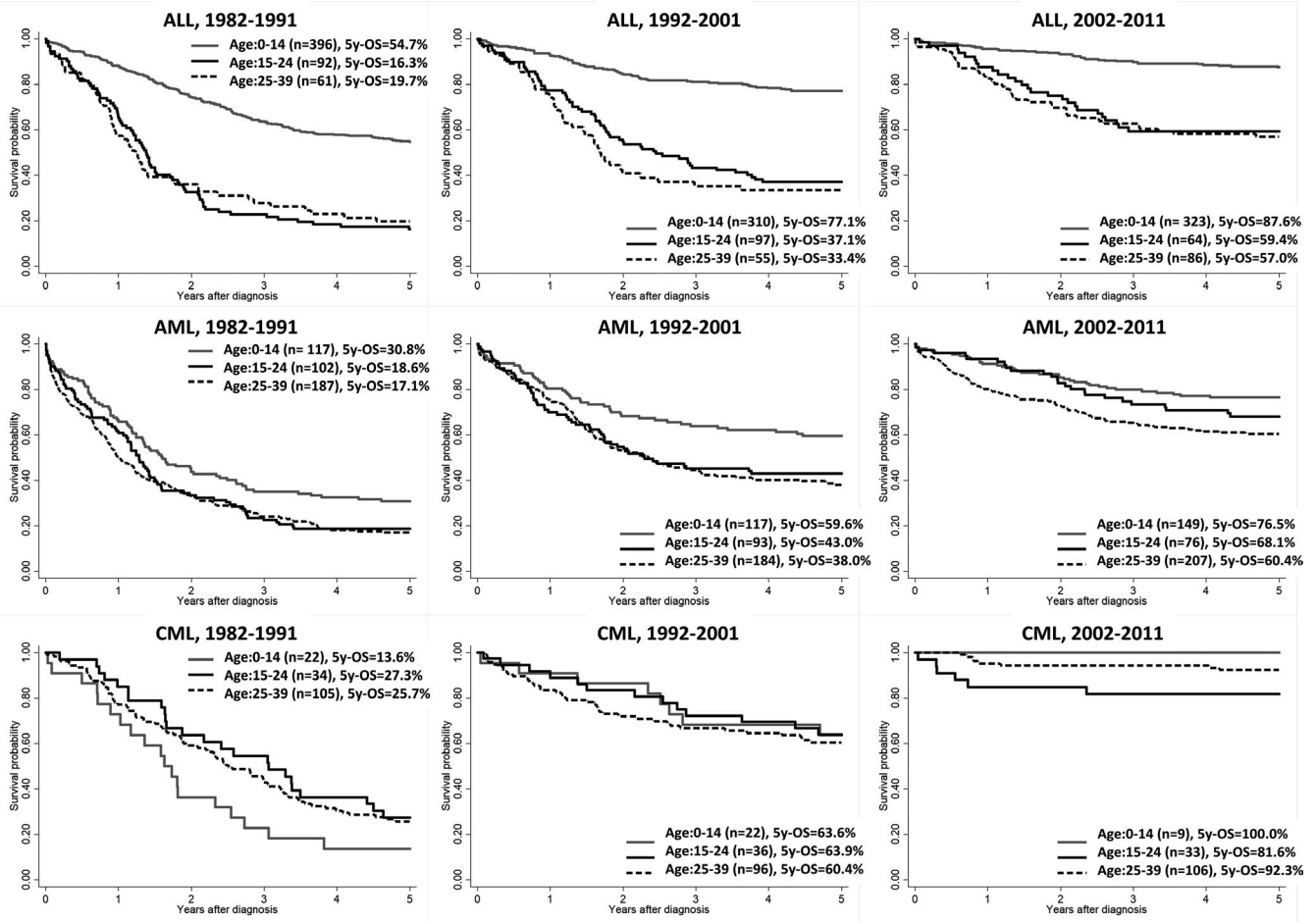
FIGURE 3 Kaplan-Meier estimates of survival probability of each leukemia type, by age group (0-14 y, 15-24 y, and 25-39 y), 1982-1991, 1992-2001, and 2002-2011. For acute lymphoblastic leukemia, a pediatric regimen was introduced for adolescents and young adults aged 15-24 y in 2002 in Japan, by the Japan Adult Leukemia Study Group (JALSG). Tyrosine kinase inhibitor (imatinib mesylate) was introduced as a molecularly targeted drug for chronic myeloid leukemia in all ages in Japan in 2001. 5y-OS; 5-year overall survival probability, ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia

be associated with several factors, including differences in biological characteristics; barriers to access to specialized centers; a lack of specialist care guidelines, treatment regimens, and clinical trials relevant to AYAs; and a lower proportion of participation in clinical trials.[5-13,30,31] Regarding biological differences, AYAs with ALL have been reported to have a higher proportion of poor prognostic features, including, hypodiploidy, T-cell immunophenotype, iAMP21, deletion of IKZF1, and Philadelphia chromosome–like ALL, and they are less likely to have favorable hyperdiploidy or t(12;21) translocation, than children with ALL.[6] As for the difference in treatment regimens, most pediatric regimens deliver higher doses of corticosteroids, vincristine, and asparaginase; more doses of intrathecal methotrexate; and lower doses of daunorubicin, cytarabine, and etoposide than conventional adult treatment regimens,[13] and have been confirmed to be superior to adult regimens in AYAs, as shown in clinical trials in several countries.[10-13] In Japan, a pediatric regimen was introduced for AYAs aged 15-24 years in 2002 by the Japan Adult Leukemia Study Group (JALSG).[12] In our

data, the inflection point of improvement of survival of ALL among AYAs coincided with the introduction of the pediatric regimen, and 5y-OS among patients aged 15-24 years, which is the target population of the pediatric regimen in the JALSG, improved after 2002 (Table 2, Figures 2 and 3). Surprisingly, the survival of older young adults aged 25-39 years has also improved recently (Figure 3); these young adults were not of eligible age for the clinical trials of the JALSG. To elucidate the reasons for this improvement, further investigation such as biology, treatment regimen, or information on HSCT will be needed. With respect to the type of treatment hospital, in the United States, AYAs with ALL treated at nonspecialized centers have been reported to have lower survival rates than those treated at specialized centers.[9] In our data, however, there was no significant difference in the risk of death between patients with ALL treated at the designated cancer care hospitals or nondesignated hospitals. To confirm this, further investigation to provide more information, such as the treatment regimen used in each hospital, is needed.

TABLE 3 Predictors of 5-year overall survival by Cox proportional hazards regression, among recently diagnosed patients (2006-2011)

	N at risk	Univariate analysis			Multivariate analysis		
		HR	95%CI	P-value	HR	95%CI	P-value
Acute lymphoblastic leukemia							
Age group							
Children (age 0-14 y)	174	Ref			Ref		
AYAs (age 15-39 y)	93	**3.2**	**(1.9-5.4)**	**<.001**	**3.0**	**(1.7-5.4)**	**<.001**
Treatment hospital							
Designated cancer care hospitals	224	Ref			Ref		
Nondesignated hospitals	43	**2.0**	**(1.1-3.6)**	**.03**	1.1	(0.6-2.1)	.76
Sex							
Male	153	Ref			Ref		
Female	114	0.8	(0.5-1.4)	.53	0.9	(0.5-1.5)	.71
Acute myeloid leukemia							
Age group							
Children (age 0-14 y)	87	Ref			Ref		
AYAs (age 15-39 y)	185	1.5	(0.9-2.6)	.09	1.2	(0.7-2.1)	.55
Treatment hospital							
Designated cancer care hospitals	180	Ref			Ref		
Nondesignated hospitals	92	**2.0**	**(1.3-3.1)**	**<.001**	**1.9**	**(1.2-3.0)**	**.01**
Sex							
Male	143	Ref			Ref		
Female	129	0.9	(0.6-1.4)	.6	0.9	(0.6-1.4)	.67

Abbreviations: AYAs, adolescents and young adults; CI, confidence interval; HR, hazard ratio.
Bold signifies statistical significance.

4.2 | Acute myeloid leukemia

In our study, 5y-OS of AML has improved from under 10% to over 60% in both children and AYAs, and there has been no survival difference between children and AYAs recently (Tables 2 and 3, Figures 2 and 3). In contrast to the reports comparing outcomes for children and AYAs with ALL, only a few reports and no prospective studies compared outcomes for children and AYAs with AML.[16,32-34] Canner et al reported that AYA patients were more likely to have high-risk disease of AML when risk was determined by both molecular and cytogenetic testing results.[32] Several reports demonstrated similarities in terms of event-free survival between children and AYAs but clearly showed higher rates of treatment-related mortality among AYA patients.[32,34,35] Treatments administered by pediatric and adult oncologists for AML are broadly similar; cytarabine and anthracyclines are the mainstay of treatment for AML although pediatric regimens are more intensive and routinely include intensive central nervous system–oriented therapies.[16] Moreover, the indications for HSCT overlap, although the variety of indications in adults is relatively broader.[16] Tomizawa et al have reported recent improvements in HSCT outcomes in Japan among both children and AYAs,[16] which may be partly responsible for the recent improvements in survival in both children and AYAs seen in our data. Focusing on recent cases, patients treated in the designated cancer care hospitals had a lower risk of death than those treated in nondesignated hospitals with a non-negligibly high HR in the multivariate analysis (Table 3). An association of transplant center size or physician factors with survival in adult patients after HSCT has been reported in the United States,[36,37] while another report has shown survival for AYAs with AML did not differ between NCI-designated and non–NCI-designated hospitals.[9] A fair assessment of a patient's mortality risk must take account of information such as patient's physical condition at diagnosis, participation in clinical trials, distance between patient's home and treatment hospital, patient's socioeconomic status,[9] and hospital's ability to perform HSCT, as confounding factors. Although our data do not include this information, as more complex treatments such as HSCT are required for AML than for ALL,[16] patient centralization to the designated cancer care hospitals might be one option to improve the survival of young patients with AML.

4.3 | Chronic myeloid leukemia

Survival of CML improved dramatically in both children and AYAs during the last three decades (Table 2, Figures 2, and 3). During the 1990s, HSCT became an important treatment modality for the complete cure of CML.[38] After the introduction of TKI, imatinib mesylate, as approved by the US FDA, in Japan in 2001, survival reached over 90% in both children and AYAs. TKIs are considered the most successful targeted anticancer agents with a high cumulative incidence of complete cytogenetic responses in patients with CML.[39] The improvement in survival seen in our data is a striking example of how effective treatments have dramatically changed patient survival.

4.4 | Cancer strategy for children and AYAs with cancer in Japan

In our data, children with leukemia had been already centralized to the designated cancer care hospitals in 2006-2011, while AYAs were not centralized in this way in Osaka (Figure 1). Compared with children with cancer, there are relatively large numbers of AYA patients with more diverse life stages, more variety of needs, and differing psychosocial difficulties,[40] making it harder to determine the ideal cancer care system for them. However, superior survival in AYAs with AML treated in the designated cancer care hospitals in this study indicates that patient centralization to specialized cancer care hospitals might be an option to improve patient survival. On the other hand, since 1974, the Japanese government has subsidized medical expenses for children and adolescents (under 18 years of age) with cancer,[5] and a public long-term care insurance system is available for Japanese residents aged over 40 years from 2000. Financial issues for AYAs have been reported to be a barrier to care at specialized hospitals and consequently contribute to poor outcomes.[9,41] Although the data in our study do not include financial details, considering that financial support for patients aged 19 to 39 years is inadequate compared with other age groups, governmental financial support might be important not only for children but also AYAs.

4.5 | Strengths and limitations

The foremost strength of our study is the long-term nature of the data allowing detection of trends in survival patterns by each leukemia type. In Japan, the national cancer registry started in 2016, founded by the Cancer Registration Promotion Act.[42] The OCR is one of the oldest prefectural cancer registries from which survival analysis is possible.[43-45] Cancer incidence in Osaka has been reported in "Cancer Incidence in Five Continents" volumes III to XI, and cancer survival data in Osaka has been reported in the "CONCORD study".[46-48] The quality of this data, therefore, can be assumed to have met the standards set in international studies during the last three decades.

On the other hand, a limitation of our study is the relatively small number of cases due to the rarity of this disease in this age group,

despite the fact that Osaka is a large prefecture with a population of 8.8 million. Another limitation of this study is the limited variables in the data. To investigate the reasons for the survival gap, clinical details such as patient's physical condition at diagnosis, gene abnormality, chemotherapy regimen, participation in clinical trials, information on the use of HSCT, patient's socioeconomic status, distance between patient's home and treatment hospital, and information on relapse are essential; however, our data do not include these details. A nationwide, population-based study that allowed links to clinical information would help to identify factors that account for the survival gap.

Our results confirmed a large improvement in survival of each type of leukemia among children and AYAs in Osaka, Japan over a 37-year period. The survival gap between children and AYAs is narrowing but persists among patients with ALL. Five-year OS of CML was over 90% among both children and AYAs after the introduction of the molecularly targeted therapy. Risk of death was significantly higher among patients treated outside of the designated cancer care hospitals for patients with AML. Patient centralization might be an option to improve survival.

DISCLOSURE

The authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

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