Association of clinical and genetic features with *IKZF1* deletion and *CRLF2* overexpression

The comparison of patient characteristics depending on *IKZF1* deletion and *CRLF2* overexpression is summarized in Table 2. Gender, initial WBC count, and NCI risk did not differ between patients with these genetic variations. *IKZF1* deletion was more frequently observed in older patients (1–9 years vs. 10–18 years, $P = 0.008$). In terms of concurrent chromosomal/genetic abnormalities, *IKZF1* deletion was observed in 1/68 of *ETV6-RUNX1*–positive + hyperdiploid/trisomy 4, 10, and 17 (triple trisomy [30]) patients compared to 18/134 of patients without those abnormalities ($P = 0.0059$). These findings suggest that *IKZF1* deletion and chromosomal abnormalities with good prognosis are mutually exclusive. Similarly, the status of *CRLF2* overexpression did not significantly correlate with gender, age at diagnosis, initial WBC count, or NCI risk. However, *CRLF2* overexpression was significantly associated with chromosomal abnormalities with an incidence of normal karyotype + hyperdiploid/triple trisomy of 12/36 compared to 4/71 for other karyotypes ($P = 0.014$). However, in our cohort, only one *P2RY8-CRLF2* fusion and no *CRLF2* F232C mutations were detected. In addition, this *P2RY8-CRLF2*–positive case did not have *IKZF1* deletion. *JAK2* mutations in exons 16, 20, or 21 were not detected in the 19 patients with *IKZF1* deletion. These findings suggest that genetic events in association with *IKZF1* deletion in our cohort might be different from those previously reported [21, 24, 25].

IKZF1 deletion, not CRLF2 overexpression, was strongly associated with a poor outcome

As seen in Figure 1, the 5-year EFS and OS for the patients with *IKZF1* deletion were inferior to those without *IKZF1* deletion. To compare our data internationally, we assigned patients in our cohort into NCI high risk (NCI-HR) and NCI standard risk (NCI-SR). In NCI-HR group ($n = 94$), the 5-year EFS and OS for patients with *IKZF1* deletion

Table 2. Association of clinical and genetic features with *IKZF1* deletion and *CRLF2* overexpression.

	IKZF1 deletion			*CRLF2* OE		
	Yes	No	*P*-value	Yes	No	*P*-value
Total	19	183		16	91	
Gender			0.51			0.38
Male	8	98		11	47	
Female	11	85		5	44	
Age (yrs) at diagnosis						
Median	10	5	0.08	4.0	5.0	0.41
1–9	9	143	0.009	14	63	0.16
10–18	10	40		2	28	
WBC count ($\times 10^3$cells/μL)						
Median	23,430	20,810	0.68	22,000	24,240	0.87
<100	17	165	0.92	14	78	0.31
≥ 100	2	18		2	13	
NCI risk group			0.15			0.14
SR	7	101		10	41	
HR	12	82		6	50	
Karyotype			0.003			0.014
No fusion genes	16	101		16	50	
(normal karyotype)	(7)	(32)		(5)	(18)	
(hyperdiploid/triple trisomy)*	(0)	(28)		(7)	(6)	
(others)**	(8)	(39)		(1)	(25)	
(undetermined)	(1)	(2)		(3)	(1)	
Fusion genes	3	82		0	41	
(*ETV6-RUNX1*)	(1)	(40)		(0)	(20)	
(*TCF3(E2A)-PBX1*)	(2)	(37)		(0)	(18)	
(11q23)	(0)	(5)		(0)	(3)	

*Triple trisomy indicates trisomy 4, 10, and 17.

**Karyotype other than normal karyotype, hyperdiploid, triple trisomy, and 11q23 abnormality, showing a negative result in screening for chimeric fusions, as described in the Materials and Methods.

OE, overexpression; NCI, National Cancer Institute; SR, standard risk; HR, high risk.

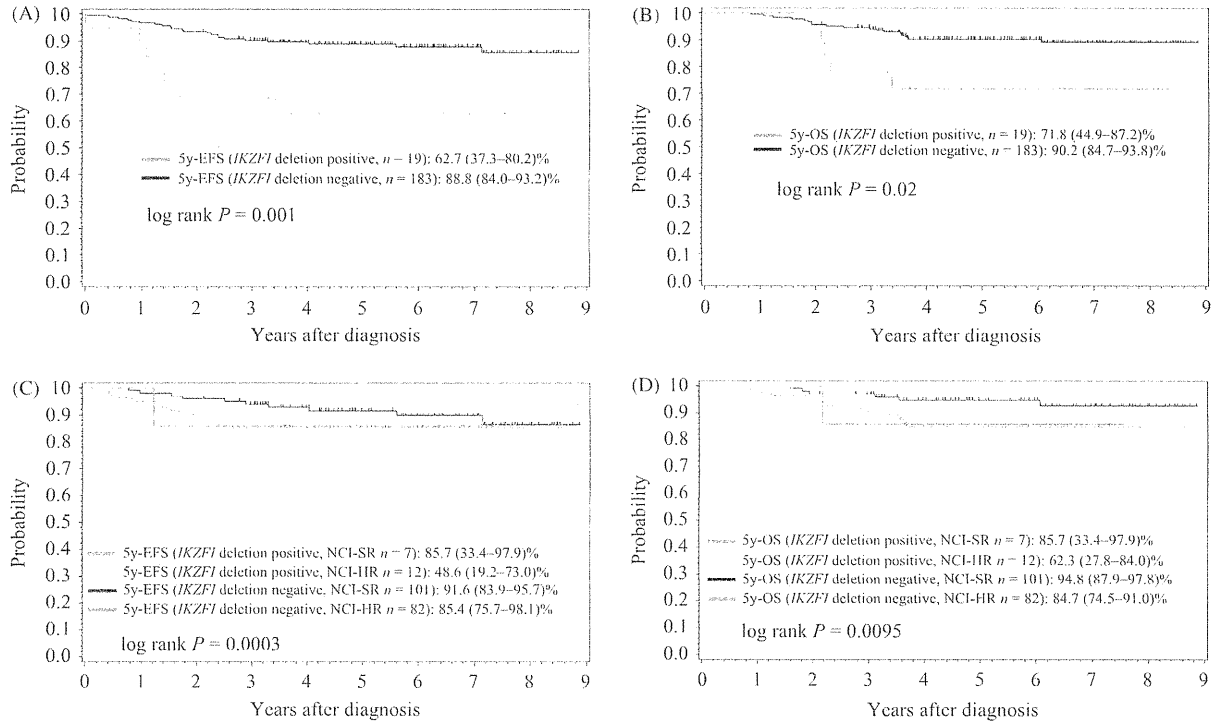

Figure 1. Kaplan–Meier estimates of event-free survival (EFS) and overall survival (OS) in BCP-ALL patients enrolled in the JACLS ALL02 HR cohort (n = 202). (A) EFS and (B) OS for patients with or without *IKZF1* deletion in this cohort. (C) EFS and (D) OS for patients with or without *IKZF1* deletion according to NCI risk group.

Table 3. Univariate cox model of event-free and overall survival of analyzed patients.

Variable	Hazard ratio	*P*	95% CI
Event-free survival			
Age (yrs) at diagnosis (1–9 vs. 10–18)	2.923	<0.01	1.404–6.089
Gender (male vs. female)	1.279	0.51	0.611–2.679
WBC count (×1000 cells/μL) (≥100 vs. <100)	2.682	0.03	1.090–6.600
NCI risk (HR vs. SR)	2.067	0.06	0.975–4.381
IKZF1 deletion (Yes vs. No)	3.701	<0.01	1.579–8.675
Overall survival			
Age (yrs) at diagnosis (1–9 vs. 10–18)	3.188	<0.01	1.406–6.089
Gender (male vs. female)	0.819	0.63	0.361–1.857
WBC count (×1000 cells/μL) (≥100 vs. <100)	2.678	0.05	0.994–7.216
NCI risk (HR vs. SR)	2.787	0.02	1.146–6.776
IKZF1 deletion (Yes vs. No)	3.069	0.03	1.139–8.269

NCI, National Cancer Institute; SR, standard risk; HR, high risk.

(n = 12) was inferior to those without *IKZF1* deletion. However, in NCI-SR patients (n = 108), the 5-year EFS and OS for the patients with *IKZF1* deletion (n = 7) was comparable to those without *IKZF1* deletion (Fig. 1). As summarized in Table 3, univariate analysis revealed that *IKZF1* deletion was associated with a significantly inferior EFS (P < 0.01). *IKZF1* deletion was also associated with a significantly inferior EFS by multivariate analysis

Table 4. Multivariate cox model of event-free and overall survival of analyzed patients.

Variable	Hazard ratio	*P*	95% CI
Event-free survival			
Age (yrs) at diagnosis (1–9 vs. 10–18)	2.586	0.02	1.192–5.610
WBC count (×1000 cells/μL) (≥100 vs. <100)	2.882	0.02	1.163–7.138
IKZF1 deletion (Yes vs. No)	2.668	0.03	1.086–6.553
Overall survival			
Age (yrs) at diagnosis (1–9 vs. 10–18)	3.016	0.01	1.281–7.102
WBC count (×1000 cells/μL) (≥100 vs. <100)	2.866	0.04	1.049–7.829
IKZF1 deletion (Yes vs. No)	2.049	0.18	0.723–5.807

($P = 0.03$, Table 4). However, NCI risk alone did not affect the EFS by univariate ($P = 0.06$) in our cohort. These findings suggest that *IKZF1* deletion is an independent prognostic factor in pediatric patients with BCP-ALL in JACLS-HR and NCI-HR groups in this cohort.

On the contrary, 5-year EFS achieved in the patients with *CRLF2* overexpression was 100%, suggesting *CRLF2* overexpression was not adverse prognostic factor in our current cohort.

Other microdeletions were not associated with a poor outcome

In our cohort, the frequencies of deletions of other genes tested were 81/202 (40%) for *CDKN2A*, 69/202 (34%) for *CDKN2B*, 59/202 (29%) for *PAX5*, 47/202 (23%) for *ETV6*, 12/202 (5.9%) for *RB1*, 15/202 (7.4%) for *BTG1*, and 22/202 (11%) for *EBF1*. None of these genetic alterations were associated with altered probability of relapse regardless of the presence/absence of *IKZF1* deletion (Table S3).

Discussion

To the best of our knowledge, this is the first report of *IKZF1*, *CRLF2*, and *JAK2* alterations in pediatric BCP-ALL in Japan. The frequency of *IKZF1* deletion in JACLS ALL02 HR patients was 19/202 (9.4%), which is consistent with previous reports [7, 11, 17]. In this study, univariate and multivariate analyses revealed that the *IKZF1* deletion was an independent factor for inferior EFS in pediatric BCP-ALL patients. More specifically, *IKZF1* deletion was strongly associated with a poor outcome in the NCI-HR patient group. As NCI-HR is defined by age and initial WBC alone, it consisted of patients who showed a good response to initial prednisolone administration, which corresponds to JACLS-HR, and those who did not, which corresponds to JACLS-ER. Nevertheless, the fact that *IKZF1* deletion affects outcomes in the NCI-HR group in our cohort indicates that this mutation is an independent prognostic factor irrespective of the initial prednisolone response. Thus, we believe that early risk stratification in pediatric BCP-ALL patients should be based on a new risk stratification system including *IKZF1* status [16].

In terms of prognostic value of *CRLF2* alteration, our study demonstrated that *CRLF2* overexpression was not necessarily associated with a poor prognosis as well as did the previous study [25]. The contradictory results reported by Cario et al. [24], in which *CRLF2* overexpression was associated with poor EFS in the ALL-BFM 2000 protocol (6-year EFS 28% vs. 71%, $P = 0.001$), were thought to be mainly due to the effect of the *P2RY8-CRLF2* fusion, and not simply *CRLF2* overexpression. The frequency of *CRLF2* overexpression was 16/107 (15.0%) in this cohort, which is comparable to previous reports. However, we could not confirm that the activating mutation of *JAK2* and *CRLF2* overexpression caused by *P2RY8-CRLF2* rearrangement was associated with *IKZF1* alteration. These findings might explain that *CRLF2* overexpression was not associated with a poor prognosis in the current cohort.

In previous reports, excluding patients with Down syndrome, the incidences of point mutations of *JAK2* exons 16, 20, and 21 causing gain of function have been associated with *IKZF1* deletion and *P2RY8-CRLF2* fusion: 87.5% of patients with *JAK2* mutations had *IKZF1* alterations ($P = 0.001$) [18] and 30–100% of patients with *JAK2* mutations had *P2RY8-CRLF2* fusion [21–25]. On the other hand, we detected only one patient with *P2RY8-CRLF2* fusion of 202, and this patient did not have point mutations of *JAK2* exon 16, 20, or 21 in this analysis. Although the reason for the discrepancy between our data and that of others is not clear, there might be several ones to be in consideration. First, the frequency of genetic alterations might depend on the ethnicity. It is interesting that genetic alterations of *JAK* and *CRLF2* are relatively frequent in Hispanic patients [23]. Although there is no report of the analysis of *JAK2* and *P2RY8-CRLF2* fusion in pediatric BCP-ALL from other Asian countries, it might be possible that the frequency of *JAK2* and *P2RY8-CRLF2* fusions are relatively low among Asian patients. Second, our genetic analysis carried out in this study was not comprehensive. For example, we were not able to analyze the *IgH@-CRLF2* fusion due to lack of the materials for FISH analysis and the type of *CRLF2* genomic aberrations might be varied in studied cohorts [23–25, 31, 32]. We did not analyze *JAK1* or *JAK3* which may also play roles in leukemogenesis, although the frequency of the alterations in these genes is thought to be considerably lower than those in *JAK2* [18]. Third, it is also possible that JACLS ALL02 HR cohort might not include

BCP-ALL cases with *BCR-ABL* like gene expression signature, in which *JAK2* activating mutation and *CRLF2* genomic aberration are concurrently present with *IKZF1* deletion. Thus, we are planning to carry out the genetic analysis of the BCP-ALL cases treated according to JACLS ALL02 ER group which might include more BCP-ALL cases with *BCR-ABL* like gene expression signature.

In conclusion, *IKZF1* deletion should be a valuable prognostic marker to include in future algorithms for early risk stratification in the treatment of pediatric BCP-ALL. Further studies are required to clarify the genetic alterations instead of *P2RY8-CRLF2* fusion and/or *JAK2* mutations, which may cooperate with *IKZF1* deletion in these leukemic patients in Japan.

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Conflict of Interest

The authors reported no potential conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Risk stratification in JACLS ALL02 trial.
Table S2. Primer list used in this study.
Table S3. Impact of other genetic alterations on outcome depending on *IKZF1* deletion.

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ORIGINAL ARTICLE

Incidence and survival rates of hematological malignancies in Japanese children and adolescents (2006–2010): based on registry data from the Japanese Society of Pediatric Hematology

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Abstract Neither accurate incidence nor survival data for pediatric patients with hematological malignancies (HM) have been available in Japan to date. Incidence of patients under 20 years of age, who were diagnosed with HM from 2006 to 2010, and their two-year survival rate (2y-OS) were obtained from disease registry data maintained by the Japan Society of Pediatric Hematology (JSPH). A total of 5,287 cases of HM were identified during this period. Acute lymphoblastic leukemia (ALL, 46.6 %) showed the highest incidence, followed by acute myeloid leukemia (AML, 16.7 %), non-Hodgkin lymphoma (NHL, 11.9 %), and histiocytosis (11.8 %). ALL, AML and histiocytosis were common in younger patients aged 1–4, while NHL tended to occur more frequently in older patients aged 5–14. The 2y-OS of HM was 91.6 %, with that for the most common B-precursor ALL rising to 96.2 %. The 2y-OS for M3 AML, lymphoblastic-B-precursor or diffuse large B cell NHL, Hodgkin lymphoma, myeloproliferative disorders, and Langerhans cell histiocytosis was >95 %. There were no gender differences in prognosis, while infants (88.0 %) and adolescents aged 15–19 (90.6 %) tended toward a poorer prognosis. This is the first report to describe incidence and survival times from the nationwide JSPH disease registry. More precise data with longer follow-up is needed.

Keywords Hematological malignancies · Children · Registry data · Survival

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Introduction

Until now, knowledge of the incidence of pediatric hematological malignancies in Japan has relied on registration at the Research Program for the Treatment of Chronic Pediatric Diseases of Specified Categories [1, 2] which is the epidemiological research done by the research and investigation section of the Ministry of Health, Labour and Welfare, and population-based cancer registries [3–6]. Because of the quality problems, all these available data is far from a comprehensive, systematic investigation of pediatric hematological diseases across the country, and the precision of the data gained thereby is limited. Furthermore, while the progress in treatment and supportive care for the last several decades have led to improve treatment outcome [7–14], the absence of nationwide data not only for the incidence but also for survival prognoses of

pediatric hematological malignancies has made it difficult to judge whether these advances in medical science have contributed to the welfare of children across the country.

In order to resolve these issues, the Japanese Society of Pediatric Hematology (JSPH), which unified with the Japan Society of Pediatric Oncology to the Japanese Society of Pediatric Hematology/Oncology since January, 2012, began a registry of newly diagnosed hematological diseases including non-malignant diseases partly in conjunction with the Japanese Society of Hematology in 2006, and planned complementary research into the prognoses (outcomes regarding dead or alive) as part of a research project intended to grasp the total number of pediatric patients with hematological diseases. This is the first report to describe survival times for the nationwide patients with pediatric hematological malignancies as well as the incidence of them from the JSPH disease registry [15, 16].

Materials and methods

The disease registry survey was conducted on the treatment facilities, where JSPH members are working and also pre-registered to JSPH Disease Registry Project. Using electronic or paper-based survey forms, the participating facilities voluntarily and continuously registered the cases of patients below the age of 20, who were diagnosed as hematological malignancies or benign hematological disorders after 2006. As for the electronic registration, E-DMS online by the e-Trial Co., Ltd. was used until December 2011 when it was replaced by Patient Data Organizing System (Ptosh) developed by the National Hospital Organization Nagoya Medical Center Clinical Research Center in collaboration with a non-profit organization, Organization for Supporting Clinical Research (NPO-OSCR). For fax registrations, the disease registry data were sent to the Data Management Department of NPO-OSCR. The database prepared for the registry was coordinated with the registry for epidemiological researches/clinical trials organized by Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG) in an attempt to "unify the registration" so as to provide more convenience to the participating facilities and to prevent non-registration.

In order to maintain the uniformity of the diagnoses concerning diseases to be registered, JSPH Disease Registry Committee prepared a guideline for diagnosis, to which the participants were requested to conform [17]. Acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), rare leukemia, myelodysplastic syndromes and/or myeloproliferative neoplasms (MDS and/or MPN), or transient abnormal myelopoiesis associated with Down syndrome (Down-TAM), non-Hodgkin (NHL) and Hodgkin lymphomas (HL), histiocytosis including Langerhans cell histiocytosis (LCH) and hemophagocytic lymphohistiocytosis (HLH), other lymphoproliferative disorders (LPD) and other hematological malignancies were defined as the hematological malignancies to be registered. Underlying diseases, pathological/immunological/cytogenetic characteristics, pathogenetic forms (primary/secondary), and other natures of diseases were also recorded.

When a patient is affected by multiple diseases, each disease was registered as one entry. Patients' genders, places of residence at the initial diagnosis, dates of birth, dates of diagnosis, etc., were registered as the basic patient information. The outcomes of the respective diseases (alive or death), along with the diagnosed disease information, were recorded up to the end of May and were registered for every calendar year.

The registered data were compiled according to diagnoses, diagnosed years, genders, age categories (0, 1–4, 5–9, 10–14, and 15–19) and residential areas at diagnosis (Hokkaido, Tohoku, Kanto-Koshinetsu, Tokai-Hokuriku, Kinki, Chugoku-Shikoku, and Kyushu-Okinawa) to indicate the numbers of cases, respectively. A crude incidence rate is the number of new cases by diagnoses in a gender/age-specified populations under age 20 as of each diagnosed year, expressed as the number of hematological malignancies per 100,000 population at risk. Overall survival (OS) was defined as the length of time from the diagnosis of hematological malignancies to death from any cause. Patients were censored at the time of loss of follow-up or June 15, 2011. OS was estimated using the Kaplan–Meier method, and 2-year survival rate (2y-OS) was measured with a 95 % confidence interval (95 % CI) using Greenwood's formula. All statistical analyses were carried out using the SAS software Release 9.1 (SAS Institute Inc., Cary, NC, USA).

This registry project is operated upon obtaining the approval of JSPH Clinical Research Review Committee, followed by consents from the head of each participating institute.

Results

Numbers of registered institutions and cases

The number of institutions registered had increased by 16 from 223 institutions of the 2007 survey to 239 by the time of the 2011 survey (including the 4 institutions which had withdrawn during this period), with participation from 47 prefectures throughout Japan. Registration of cases with hematological malignancies was conducted by 187 (78.2 %) among the 239 institutions. Since retrospective registration was allowed for cases diagnosed since 2006, increases in the number of registered cases were found up

to 3 years in plateau after the diagnoses. A total of 5,287 cases were registered as hematological malignancies from 2006 to 2010, and the numbers by year were 2006: 967 cases, 2007: 1,053 cases, 2008: 1,116 cases, 2009: 1,081 cases and 2010: 1,070 cases.

Incidences

The results of broadly classifying hematological malignancies into the disease groups of ALL, AML, MDS and/or MPN, NHL, HL, histiocytosis, LPD, other hematological malignancies and Down-TAM, and tabulating by the year of diagnosis are shown in Table 1. A total of 5,287 cases were registered in 5 years, which was an annual incidence of hematologic malignancies of 4.5 cases per 100,000 people. The greatest number of cases was ALL with 2,464 cases (46.6 %), followed by AML with 891 cases (16.9 %), NHL with 628 cases (11.9 %) and histiocytosis with 624 cases (11.8 %), and this trend remained nearly constant without any dependence on the year of diagnosis. On the other hand, the number of cases reported as Down-TAM in 2010 had increased by about 1.7 times from the average number of cases reported in previous years. In addition, there were a large number of cases reported as other LPD in 2007, about two times more than in other years. The number of registered cases including rare leukemia (36 cases), other LPD (51 cases) and other hematological malignancies (6 cases) were small.

Table 2 shows the number of registrations by gender, age category, and residential areas at diagnosis for each disease group classification.

In the tabulation of ALL by the immunophenotypic classification, the most part was accounted for by B-precursor ALL with 2,110 cases (85.6 %), followed by T-ALL with 1,269 cases (10.9 %) and mature B-ALL with 60 cases (2.4 %). The peak incidence of ALL occurs between 1 and 4 years of age. In addition, the incidence of ALL is slightly higher among male children than female children, and this difference is consistent regardless of the classification by immunophenotype. Genetic abnormalities in 2,464 cases with ALL included 281 cases (11.4 %) with hyperdiploid karyotype over 50 chromosomes, 247 cases (10.0 %) with ETV6-RUNX1, 135 cases (5.5 %) with MLL rearrangement, 113 cases (4.6 %) with E2A-PBX1, 106 cases (4.3 %) with BCR-ABL1 gene rearrangement, 29 cases (1.2 %) with t(v;8q24) and 583 cases (23.7 %) with other abnormalities.

In the tabulation of AML by FAB classification, overall the greatest number was M2 with 218 cases (24.5 %), followed by M7 with 212 cases (21.5 %), M5 with 124 cases (13.9 %) and M4 with 112 cases (12.6 %). The distribution by age category showed the greatest numbers of M2 for ages 5–9 and 10–14 years (the peak of incidence during age 10–14 years), but for ages 0 and 1–4 years the incidence of M7 was extremely high (the peak of incidence during age 1–4 years), making up almost half of the incidences. Half of patients diagnosed with M7 AML were associated with Down syndrome ($n = 114$), corresponding to 94.2 % of 121 AML patients with Down syndrome. No clear difference in the number of cases of disease was found between the genders.

Table 1 Numbers of cases and incidence rates of hematological malignancies in Japanese children and adolescents, diagnosed between 2006 and 2010

Disease	Total (%)	Crude incidence rate[a]	Year of diagnosis				
			2006	2007	2008	2009	2010
Acute lymphoblastic leukemia	2,464 (46.6)	2.1	444	506	532	504	478
Acute myeloid leukemia	891 (16.9)	0.8	167	165	184	193	182
Rare leukemia	36 (0.7)	0.0	9	7	4	10	6
Myelodysplastic syndrome and/or myeloproliferative neoplasms	296 (5.6)	0.3	61	60	46	54	75
Non-Hodgkin lymphoma	628 (11.9)	0.5	118	129	138	137	106
Hodgkin lymphoma	107 (2.0)	0.1	19	21	24	14	29
Histiocytosis	624 (11.8)	0.5	114	108	138	128	136
Transient abnormal myelopoiesis associated with Down syndrome	184 (3.5)	0.2	26	37	37	31	53
Other hematological malignancies	6 (0.1)	0.0	0	0	5	1	0
Other lymphoproliferative disorders	51 (1.0)	0.0	9	20	8	9	5
Hematological malignancies, Total	5,287 (100.0)	4.5	967	1,053	1,116	1,081	1,070

[a] Crude incidence rate is the number of new cases by diagnoses in a gender/age-specified populations under age 20 as of each diagnosed year, expressed as the number of hematological malignancies per 100,000 population at risk

Table 2 Numbers of incidences of hematological malignancies according to gender, age category, and residential areas at diagnosis in Japanese children and adolescents, diagnosed between 2006 and 2010

Disease	Subtype	*n* (%)	*n* (%)	Gender, *n* (%)		Age, *n* (%)					Residential areas at diagnosis, *n* (%)						
				Male	Female	0	1–4	5–9	10–14	15–19	Hokkaido	Tohoku	Kanto-Koshinetsu	Tokai-Hokuriku	Kinki	Chugoku-Shikoku	Kyushu-Okinawa
Acute lymphoblastic leukemia		2,464 (46.6)		1,411 (57.3)	1,053 (42.7)	108 (4.4)	1044 (42.4)	711 (28.9)	499 (20.3)	102 (4.1)	105 (4.3)	192 (7.8)	971 (39.4)	347 (14.1)	415 (16.8)	190 (7.7)	244 (9.9)
	B-precursor		2,110 (85.6)	1,151	959	102	979	580	372	77	83	168	829	306	350	164	210
	Mature B		60 (2.4)	38	22	5	9	24	20	2	4	2	22	6	11	7	8
	T cell		269 (10.9)	206	63	1	46	101	99	22	15	19	112	34	46	18	25
	Unknown		25 (1.0)	16	9	0	10	6	8	1	3	3	8	1	8	1	1
Acute myeloid leukemia		891 (16.9)		451 (50.6)	440 (49.4)	109 (12.2)	306 (34.3)	168 (18.9)	240 (26.9)	68 (7.6)	32 (3.6)	69 (7.7)	348 (39.1)	121 (13.6)	134 (15.0)	78 (8.8)	109 (12.2)
	M0		33 (3.7)	15	18	4	7	10	7	5	1	4	15	4	4	0	5
	M1		73 (8.2)	35	38	2	17	19	28	7	4	4	30	12	10	6	7
	M2		218 (24.5)	109	109	3	37	73	88	17	11	17	78	28	35	20	29
	M3, M3v		70 (7.9)	37	33	2	12	17	29	10	1	2	22	11	17	7	10
	M4, M4Eo		112 (12.6)	57	55	12	29	20	38	13	3	12	37	19	21	8	12
	M5a, M5b		124 (13.9)	63	61	28	33	16	39	8	6	9	47	15	20	13	14
	M6a, M6b		14 (1.6)	8	6	0	7	3	3	1	0	1	6	1	2	2	2
	M7		212 (23.8)	104	108	55	150	2	3	2	6	17	99	28	19	16	27
	Unknown		35 (3.9)	23	12	3	14	8	5	5	0	3	14	3	6	6	3
Rare leukemia		36 (0.7)		24 (66.7)	12 (33.3)	5 (13.9)	8 (22.2)	6 (16.7)	14 (38.9)	3 (8.3)	2 (5.6)	2 (5.6)	14 (38.9)	4 (11.1)	4 (11.1)	5 (13.9)	5 (13.9)
Myelodysplastic syndrome (MDS) and/or Myeloproliferative neoplasms (MPN)		296 (5.6)		171 (57.8)	125 (42.2)	42 (14.2)	73 (24.7)	66 (22.3)	92 (31.1)	23 (7.8)	13 (4.4)	10 (3.4)	127 (42.9)	40 (13.5)	43 (14.5)	34 (11.5)	29 (9.8)
	MPN		111 (37.5)	62	49	2	13	33	57	6	4	3	46	17	19	13	9
	MDS/MPN		49 (16.6)	32	17	27	18	1	1	2	2	2	23	7	5	3	7
	MDS		136 (45.9)	77	59	13	42	32	34	15	7	5	58	16	19	18	13
Non-Hodgkin lymphoma		628 (11.9)		446 (71.0)	182 (29.0)	7 (1.1)	96 (15.3)	237 (37.7)	240 (38.2)	48 (7.6)	26 (4.1)	45 (7.2)	218 (34.7)	107 (17.0)	107 (17.0)	56 (8.9)	69 (11.0)
	Lymphoblastic-T-precursor		136 (21.7)	100	36	0	14	48	63	11	8	14	51	21	24	8	10
	Lymphoblastic-B-precursor		71 (11.3)	42	29	5	20	31	12	3	5	4	25	14	7	9	7
	Burkitt		154 (24.5)	128	26	0	30	75	43	6	3	9	52	28	30	14	18
	Diffuse large B cell		121 (19.3)	80	41	0	12	42	50	17	4	9	35	17	22	17	17
	Anaplastic large cell		100 (15.9)	71	29	0	13	31	49	7	4	5	35	21	17	7	11

Table 2 continued

Disease	Subtype	*n* (%)	*n* (%)	Gender, *n* (%)		Age, *n* (%)					Residential areas at diagnosis, *n* (%)						
				Male	Female	0	1–4	5–9	10–14	15–19	Hokkaido	Tohoku	Kanto-Koshinetsu	Tokai-Hokuriku	Kinki	Chugoku-Shikoku	Kyushu-Okinawa
	Other		46 (7.3)	25	21	2	7	10	23	4	2	4	20	6	7	1	6
Hodgkin lymphoma		107 (2.0)		61 (57.0)	46 (43.0)	0 (0.0)	6 (5.6)	28 (26.2)	55 (51.4)	18 (16.8)	4 (3.7)	9 (8.4)	37 (34.6)	19 (17.8)	15 (14.0)	7 (6.5)	16 (15.0)
Histiocytosis		624 (11.8)		329 (52.7)	295 (47.3)	113 (18.1)	259 (41.5)	139 (22.3)	95 (15.2)	18 (2.9)	27 (4.3)	36 (5.8)	213 (34.1)	96 (15.4)	125 (20.0)	55 (8.8)	72 (11.5)
	Langerhans cell histiocytosis		345 (55.3)	199	146	66	143	81	50	5	20	20	110	50	66	39	40
	Hemophagocytic lymphohistiocytosis		265 (42.5)	123	142	44	108	56	44	13	6	15	97	44	55	16	32
	Other		14 (2.2)	7	7	3	8	2	1	0	1	1	6	2	4	0	0
Transient abnormal myelopoiesis associated with Down syndrome		184 (3.5)		100 (54.4)	84 (45.7)	182 (98.9)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.2)	3 (1.6)	86 (46.7)	23 (12.5)	28 (15.2)	13 (7.1)	27 (14.7)
Other	lymphoproliferative disorders		51 (1.0)		24 (47.1)	27 (52.9)	1 (2.0)	9 (17.7)	19 (37.3)	18 (35.3)	4 (7.8)	0 (0.0)	4 (7.8)	13 (25.5)	8 (15.7)	9 (17.7)	11 (21.6)
6 (11.8)																	
Other hematologic malignancies		6 (0.1)		2 (33.3)	4 (66.7)	5 (83.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
Hematological malignancies	Total	5,287 (100.0)		3,019 (57.1)	2,268 (42.9)	572 (10.8)	1,803 (34.1)	1,375 (26.0)	1,253 (23.7)	284 (5.4)	215 (4.1)	370 (7.0)	2,029 (38.4)	766 (14.5)	880 (16.6)	449 (8.5)	578 (10.9)

Among NHL patients, those with Burkitt lymphoma (BL, 24.5 %), precursor T-lymphoblastic lymphoma (21.7 %), or diffuse large B cell lymphoma (DLBCL, 19.3 %), respectively, accounted for more than 20 %. When combined with those with anaplastic large cell lymphoma (ALCL, 15.9 %) and those with precursor B-lymphoblastic lymphoma (11.3 %), patients with these types of lymphoma accounted for 92.7 % of all NHL patients. Three subtypes, i.e., nodular sclerosis (37 cases), nodular lymphocyte predominance (29 cases), and mixed cellularity (31 cases), accounted for 90.7 % of all HL patients. While NHL patients were predominantly male, accounting for 2.5 times the number of female patients, no significant gender difference was observed for HL, with only 1.3 times male predominance. Peak incidences of both NHL and HL occurred at 5 years of age or older. While the incidence of BL peaked between ages 5 and 9, the incidence of precursor T-lymphoblastic lymphoma, DLBCL, and ALCL increased with age and peaked between ages 10 and 14.

The majority of histiocytosis included LCH, at 345 cases (55.3 %), followed by HLH at 265 cases (42.5 %). Incidences of both HLH and LCH mainly occurred in children aged four and under.

Among patients with MDS and/or MPN, those with MDS made up the majority (136 cases, 45.9 %), followed by MPN (111 cases, 37.5 %), including chronic myeloid leukemia (CML), and MDS/MPN (49 cases, 16.6 %), including juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML). The breakdown of registered cases of MDS by the JSPH guideline for diagnosis showed that refractory anemia (33 cases) account for 22 %, refractory cytopenia with multi-lineage dysplasia (25 cases) for 18 %, refractory anemia with excess blasts (RAEB)-1 (22 cases) for 16 %, and RAEB2 (19 cases) for 14 %, respectively.

Down-TAM accounted for 3.5 % of all cases, with the incidence rate being slightly higher in males (1.2 times higher than females).

No significant regional difference was observed when looking at age-specific incidences (data not shown).

Survival

Table 3 and Figs. 1, 2, 3, 4, 5 and 6 show disease-specific prognostic information for 5,287 cases of patients who were diagnosed with pediatric hematological malignancies between 2006 and 2010. The median observation period (range) was 1.7 (0.0–5.3) years. The point estimate (95 %CI) of 2y-OS for all pediatric patients with hematological malignancies was 91.6 (90.7–92.5) %. No difference was observed in survival rates in terms of gender (2y-OS 91.5 % for male, 91.9 % for female; log-rank test p value = 0.76) or residential areas at diagnosis (2y-OS 88.0 % for Hokkaido, 93.3 % for Tohoku, 91.5 % for Kanto-Koshinetsu, 91.7 % for Tokai-Hokuriku, 94.2 % for Kinki, 92.2 % for Chugoku-Shikoku, and 88.1 % for Kyushu-Okinawa; p value = 0.11). Survival rates in different age categories showed that children aged 5–9 years had the best prognosis (94.4 %). This was followed by children aged 1–4 years (93.8 %) and those aged 10–14 years (90.8 %), indicating a 2y-OS of more than 90 %. On the other hand, the 2y-OS for patients aged 15–19 years was about 10 % points lower at 80.5 %. The 2y-OS for infants less than 1 year old did not reach 90 % either at 85.6 % (log-rank test p value < 0.0001).

The comparison of 2y-OS among different diseases indicates that patients with HL (95.2 %) had the best prognosis.

Table 3 Survival for Japanese children and adolescents diagnosed with hematological malignancies

Disease	n	1 year		2 year		3 year		4 year		5 year	
		1-yr OS	95 % CI	2-yr OS	95 % CI	3-yr OS	95 % CI	4-yr OS	95 % CI	5-yr OS	95 % CI
Acute lymphoblastic leukemia	2,464	97.3	96.5–97.9	94.2	93.0–95.2	91.1	89.4–92.5	89.1	87.0–90.9	88.7	86.4–90.6
B-precursor	2,110	98.0	97.3–98.6	96.2	95.1–97.0	93.6	92.0–94.9	91.8	89.7–93.5	91.3	88.9–93.2
Mature B	60	95.6	83.4–98.9	84.7	68.8–92.9						
T cell	269	92.4	87.9–95.2	81.3	74.3–86.5	71.0	61.8–78.3	66.9	56.3–75.4		
Unknown	25	90.5	67.0–97.5	75.4	33.3–93.0						
Acute myeloid leukemia	891	91.2	88.9–93.0	83.3	80.1–86.1	77.4	73.3–80.9	76.3	71.9–80.1	75.2	70.3–79.4
M0	33	81.2	60.5–91.8	71.8	49.3–85.7	59.9	30.0–80.3				
M1	73	87.7	75.8–94.0	80.5	66.3–89.2	76.8	61.0–86.9				
M2	218	93.5	88.8–96.3	85.9	79.2–90.6	78.9	70.2–85.3	76.4	66.4–83.8	72.2	58.8–81.9
M3, M3v	70	95.6	87.0–98.6	95.6	87.0–98.6						
M4, M4Eo	112	91.7	84.0–95.8	79.0	68.1–86.6	72.4	59.5–81.7				

Table 3 continued

Disease	*n*	1 year		2 year		3 year		4 year		5 year	
		1-yr OS	95 % CI	2-yr OS	95 % CI	3-yr OS	95 % CI	4-yr OS	95 % CI	5-yr OS	95 % CI
M5a, M5b	124	83.7	74.9–89.6	76.7	66.4–84.2	70.5	58.3–79.7	67.4	54.1–77.6		
M6a, M6b	14	90.9	50.8–98.7	90.9	50.8–98.7						
M7	212	94.0	89.1–96.8	84.8	77.0–90.1	80.2	70.8–86.9				
Unknown	35	90.7	73.9–96.9	82.9	63.2–92.6	56.8	21.9–81.0				
Rare leukemia	36	90.6	73.5–96.9	75.2	51.5–88.5	68.9	43.9–84.5				
Myelodysplastic syndrome (MDS) and/or myeloproliferative neoplasms (MPN)	296	96.2	93.1–98.0	92.8	88.4–95.6	87.9	81.8–92.1	85.3	76.6–91.0		
MPN	111	100.0	–	98.6	90.2–99.8	96.7	87.4–99.2				
MDS/MPN	49	90.6	76.5–96.4	86.6	69.9–94.4	80.0	57.2–91.4				
MDS	136	95.0	89.2–97.7	90.0	81.9–94.6	82.6	71.3–89.7	76.2	57.8–87.4		
Non-Hodgkin lymphoma	628	94.6	92.3–96.2	92.1	89.3–94.2	90.5	87.0–93.1				
Lymphoblastic-T-precursor	136	96.4	90.6–98.6	90.4	82.2–95.0	86.9	77.0–92.7	83.1	69.8–90.9		
Lymphoblastic-B-precursor	71	98.4	89.3–99.8	96.2	85.3–99.1						
Burkitt	154	93.3	87.4–96.4	91.1	84.4–95.0						
Diffuse large B cell	121	97.1	91.3–99.1	97.1	91.3–99.1						
Anaplastic large cell	100	91.0	82.7–95.4	91.0	82.7–95.4						
Other	46	90.7	76.9–96.4	83.8	66.7–92.6						
Hodgkin lymphoma	107	98.7	91.2–99.8	95.2	85.5–98.4						
Histiocytosis	624	94.9	92.8–96.5	93.9	91.4–95.6						
Langerhans cell histiocytosis	345	99.3	97.3–99.8	98.7	95.8–99.6						
Hemophagocytic lymphohistiocytosis	265	88.9	84.3–92.3	87.7	82.8–91.4						
Other	14	100.0	–	90.0	47.3–98.5						
Transient abnormal myelopoiesis associated with Down syndrome	184	89.8	84.3–93.4	89.8	84.3–93.4						
Other lymphoproliferative disorders	51	89.5	76.6–95.5	86.3	71.6–93.7						
Other hematologic malignancies	6	83.3	27.3–97.5	83.3	27.3–97.5						
Hematological malignancies, Total	5,281	95.2	94.6–95.8	91.6	90.7–92.5	88.8	87.6–89.8	87.5	86.2–88.8	87.0	85.4–88.3
Gender											
Female	2,268	95.3	94.2–96.1	91.9	90.5–93.1	89.3	87.4–90.8	87.6	85.5–89.5	86.8	84.3–88.9
Male	3,019	95.2	94.3–96.0	91.5	90.2–92.6	88.4	86.8–89.8	87.5	85.7–89.0	87.2	85.3–88.8
Age											
0	572	88.0	84.8–90.5	85.6	82.0–88.5	83.7	79.7–87.0				
1–4	1,803	96.7	95.7–97.5	93.8	92.4–95.0	91.4	89.5–93.0	90.9	88.8–92.6		
5–9	1,375	97.1	96.0–97.9	94.4	92.7–95.7	91.0	88.7–92.9	89.5	86.7–91.7		
10–14	1,253	95.4	93.9–96.5	90.8	88.6–92.5	88.1	85.5–90.3	85.9	82.7–88.6	84.0	79.6–87.5
15–19	284	90.6	86.2–93.7	80.5	74.2–85.5	73.7	65.8–80.1			69.1	56.6–78.6
Residential areas											
Hokkaido	215	92.8	87.9–95.8	88.0	81.7–92.3	85.9	78.8–90.8			82.6	72.1–89.4
Tohoku	370	96.6	93.9–98.1	93.3	89.4–95.8	89.1	83.7–92.7	86.9	80.5–91.3		
Kanto-Koshinetsu	2,029	95.0	93.9–96.0	91.5	89.9–92.8	87.8	85.6–89.6	86.5	84.0–88.6		
Tokai-Hokuriku	766	95.5	93.6–96.8	91.7	89.1–93.7	90.8	88.0–93.0	90.3	87.3–92.7	89.0	84.7–92.2
Kinki	880	97.1	95.6–98.0	94.2	92.1–95.7	90.7	87.7–93.0	89.0	85.3–91.8	88.0	83.7–91.2
Chugoku-Shikoku	449	94.0	91.1–96.0	92.2	88.8–94.6	88.1	83.4–91.6				
Kyushu-Okinawa	578	93.6	91.1–95.4	88.1	84.6–90.9	87.3	83.7–90.9	87.3	83.7–90.2	85.1	80.5–88.7

yr year, *OS* overall survival

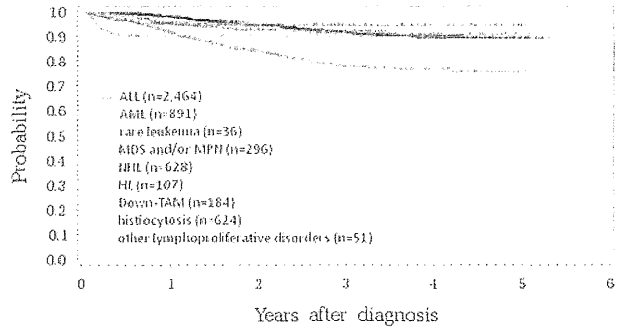

Fig. 1 Overall survival for patients diagnosed with hematological malignancies ($n = 5{,}287$). *ALL* acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *MDS and/or MPN* myelodysplastic syndrome and/or myeloproliferative neoplasms, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *Down-TAM* transient abnormal myelopoiesis associated with Down syndrome

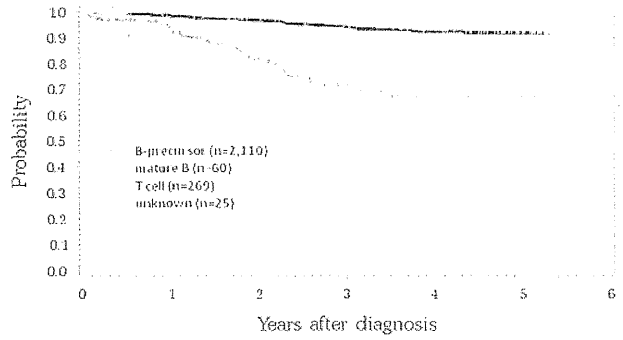

Fig. 2 Overall survival for patients diagnosed with acute lymphoblastic leukemia

Fig. 3 Overall survival for patients diagnosed with acute myeloid leukemia

This was followed by patients with ALL (94.2 %), histiocytosis (93.9 %), MDS/MPN (92.4 %), and NHL (92.1 %). All patients had a survival rate of 90 % or more within 2 years after their disease was diagnosed. The 2y-OS for patients with Down-TAM (89.8 %) and those with other LPD (86.3 %) was estimated more than 85 %, while that for AML (83.3 %) and rare leukemia (75.2 %) was inferior to it.

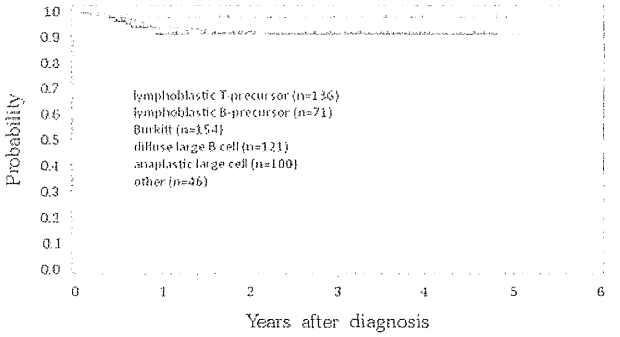

Fig. 4 Overall survival for patients diagnosed with non-Hodgkin lymphoma

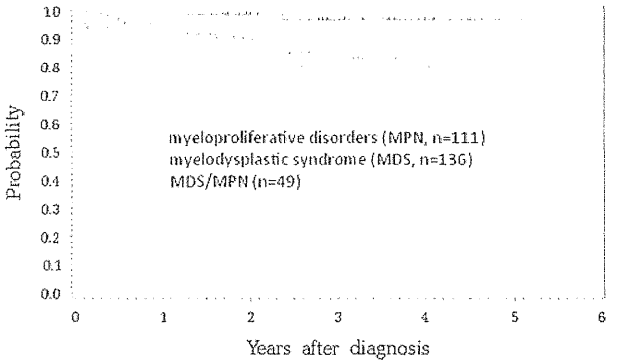

Fig. 5 Overall survival for patients diagnosed with myelodysplastic syndrome and/or myeloproliferative. *MDS* myelodysplastic syndrome, *MPN* myeloproliferative neoplasms

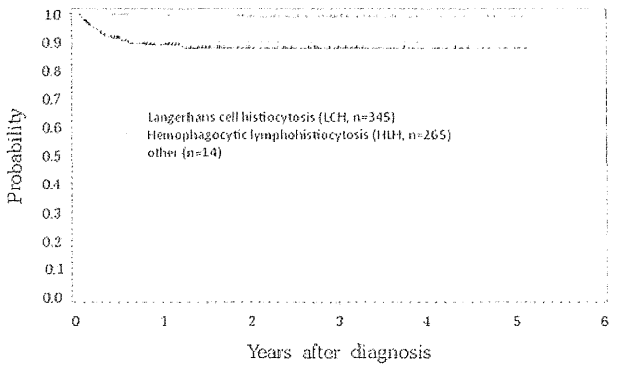

Fig. 6 Overall survival for patients diagnosed with histiocytosis

Examination based on the immunophenotypic classification of ALL shows that patients with B-precursor ALL had the highest 2y-OS at 96.2 %, surpassing the 2y-OS for patients with mature B cell ALL (84.7 %) or T cell ALL (81.3 %).

Examination based on the FAB classification of AML indicates that M3 had the best prognosis (2y-OS 95.6 %),

followed by M6 (90.6 %). The 2y-OS accounted for more than 80 % with the exception of M0 (71.8 %), M5 (76.7 %), and M4 (79.0 %) whose survival rates did not reach 80 %.

Any type of NHL, without being based on the immunological classification, indicated a survival rate of more than 90 % within 2 years after diagnosis; especially, DLBCL (97.1 %) and precursor B-lymphoblastic lymphoma (96.2 %) had excellent prognoses.

Among histiocytosis, LCH indicated an extremely excellent 2y-OS of 98.7 % while that of HLH was 87.7 %. As for MDS and/or MPN, the 2y-OS of MPN was 98.6 % and the best, followed by MDS (90.0 %) and MDS/MPN (86.6 %).

Discussion

This study, which includes the largest childhood cohorts of hematological malignancies ever reported in Japan, documented progressive improvements in survival for children enrolled onto the disease registry project of the JSPH between 2007 and 2011. Considering the number of participating institutions, we estimated that our patient sample collected through the system represented about 80 % of all the cases of hematological malignancies in Japan. As cases newly diagnosed during the 5 years from January 1, 2006 to December 31, 2010, it has reported 5,287 cases of hematological malignancies from 187 institutions (diagnosis and treatment departments) across 47 prefectures nationwide; this result is equivalent to the prevalence of 4.5 cases per 100,000 people per year. The number of registered cases for age 15–19 years is much lower than those at age 14 or younger, which may be reflecting the fact that patients over the age of 16 usually visit internists rather than pediatrician. In order to figure out the exact trends in disease incidence for this age category in Japan, it is necessary to establish a registration system that can be accessed both by internists and pediatricians.

Regarding the incidence by disease group, ALL accounted for approximately half of hematological malignancies and more than 80 % when combined with AML, NHL and histiocytosis, which accounted for 10–15 %, respectively. The incidence by disease was nearly constant regardless of the diagnosis year. The reason why reports of Down-TAM almost doubled in 2010 is inferred that such increase accompanied wider recognition and utilization of the TAM central diagnosis system realized through a nationwide clinical observational study, JPLSG TAM-10, started in the same year (UMIN # 000005418).

According to the immunophenotypic classification counting of ALL, although the percentage of B-precursor ALL in Japan is higher than that in the US (85.6 vs. 63 %), T-ALL and mature B-ALL showed almost the same ratios [18]. It was also consistent with the findings in the US that the age of peak incidence was under 4 years old and that the incidence of ALL is slightly higher among male children than female children [19]. It is reported that introduction of risk-stratified treatment and improvement in supportive care have helped to achieve better treatment results of ALL with its 5y-OS higher than 85 % [14]. Our data showed that the 2y-OS of ALL was 94.2 % while its 5y-OS also exceeded 80 %. This indicates an improvement compared to the results of the European disease registry data during the second half of the twentieth century (1978–1997) [20], suggesting that prognoses as good as those in the results of recent foreign clinical studies have been achieved nationwide [14].

A dramatic improvement in the success rate of the treatment of AML has been seen [21], from about 20 % during the 1970s to 55 % in the decade following 2000. Although there are differences in thinking among different groups studying the treatment, such as those with regard to chemotherapy as well as hematopoietic stem cell transplantation depending on the disease risk, the overall survival in clinical trial has also been improved to have reached 42 ~ 62 % [22–24]. In the AML99 clinical trials (2000–2002) [25–28] conducted in Japan, good results of a 5y-OS of over 76 % were obtained. In the present study also, it was found that by and large a good 2y-OS of higher than 80 % has been obtained even when M3 (2y-OS: 95.6 %), with the best prognosis, is excluded.

The incidence of HL in our data was very low compared to that from other countries. There are reports, both domestic and from overseas, that the incidences of both NHL and HL are relatively high in adolescents, and that the ratio of male to female children is high [29–33]. In our data, NHL is uncommon in infant, and the incidence of NHL increases throughout life. Although NHL is more common than HL in children younger than 15 years, the relative incidence of HL increases in children older than 10 years, making the incidence of HL in children aged between 15 and 19, almost twice that of NHL. In addition, higher incidence of NHL in male children was observed, while there was a slight male predominance in the incidence of HL, with an incidence ratio of 1.3 in male and female children. For NHL, favorable outcomes of treatment were obtained in more than 90 % of the cases within 2 years after diagnosis regardless of the immunological classification, which were similar to reports of clinical trials from inside and outside of the country [34–37].

Similarly, there was a high incidence of LCH, which accounts for the majority of cases of histiocytosis, in the age group of 1–4 years as in the overseas reports [38], and the prognosis was also good [39]. About half of the patients (42.5 %) with histiocytosis were diagnosed as having

HLH. In accordance with the previous literature in Japan, our data showed that the incidence of HLH cases per year was about 50 (mean 53, range 43–64) [40]. And clinical outcomes of HLH were considerably improved compared to the results of HLH-94 study [41].

With regard to MDS and/or MPN, hematopoietic stem cell transplantation, rather than conventional chemotherapy, has come to be a good indication [42] in cases in which there is an HLA-matched sibling donor. Children with low-risk MDS, including refractory anemia and refractory anemia with ring sideroblasts, were not candidates for hematopoietic stem cell transplantation [43]. Although the 5y-OS of children under the age of 16 was, respectively, 50–67 % for MDS and 51–75 % for MPN, depending on the type of transplant, in the national survey results (2011 report) from 1991 to 2010 by the Japan Society for Hematopoietic Cell Transplantation (JSHCT), our data showed that there was an improvement to 86.6 % for MDS/MPN including JMML, for which the prognoses are the worst [44], although the follow-up period was not sufficient.

In treatments for hematological malignancies during childhood and adolescents, long-term toxicity, including treatment-related deaths and secondary neoplasms, still remain as important issues. Therefore, we will continuously evaluate the trends in the national levels of diagnosis and treatment through the JSPH disease registry project and will show data concerning trends in disease incidence and deaths accompanied by prognostic information. Continuous activity to monitor the level of medical care is considered quite important in aiming at the development of more effective treatments which maintain long-term safety.

Acknowledgments The survey on hematological malignancies incidence in Japan was conducted with contributions from the 187 institutions, described in Appendix 1. The authors thank deeply the members, especially Kaori Nagai, Kazumi Takeuchi, Maki Nishimura, and Midori Otomo of the Data Management Department of the NPO-OSCR, for their support in the management of the electronic or paper-based survey system and in the cleaning and tabulation of the registered data.

Conflict of interest The authors have no financial relationship to declare.

Appendix

See appendix Table 4.

Table 4 Institutions with registered cases of hematological malignancies

S. no.	District	Institutions
1	Hokkaido	Oji General Hospital
2	Hokkaido	Sapporo Medical University Hospital
3	Hokkaido	Hokkaido Medical Center for Child Health and Rehabilitation
4	Hokkaido	Sapporo Hokuyu Hospital
5	Hokkaido	Hokkaido University Hospital
6	Hokkaido	KKR Sapporo Medical Center
7	Hokkaido	Asahikawa Medical University Hospital
8	Hokkaido	Hospital Hakodate Hokkaido
9	Hokkaido	Kushiro city General Hospital
10	Hokkaido	National Hospital Organization Hokkaido Cancer Center
11	Tohoku	Hirosaki University school of Medicine and Hospital
12	Tohoku	Nakadori General Hospital
13	Tohoku	Akita University Hospital
14	Tohoku	Iwate Medical University Hospital
15	Tohoku	Iwate Prefectural Chubu Hospital
16	Tohoku	Iwaki Kyoritsu Hospital
17	Tohoku	Fukushima Medical University Hospital
18	Tohoku	Tohoku University Hospital
19	Tohoku	Miyagi Children's Hospital
20	Tohoku	Yamagata University Hospital
21	Tohoku	Sendai City Hospital
22	Kanto and Koshinetsu	Ibaraki Children's Hospital
23	Kanto and Koshinetsu	Tsukuba University Hospital

Table 4 continued

S. no.	District	Institutions
24	Kanto and Koshinetsu	Yokohama City University Hospital
25	Kanto and Koshinetsu	Saiseikai Yokohama City Nanbu Hospital
26	Kanto and Koshinetsu	Kitasato University Hospital
27	Kanto and Koshinetsu	Tokai University Hospital
28	Kanto and Koshinetsu	Showa University Fujigaoka Hospital
29	Kanto and Koshinetsu	Kanagawa Children's Medical Center
30	Kanto and Koshinetsu	St. Marianna University School of Medicine Hospital
31	Kanto and Koshinetsu	Gunma Children's Medical Center
32	Kanto and Koshinetsu	Gunma University Hospital
33	Kanto and Koshinetsu	Saitama Medical Center
34	Kanto and Koshinetsu	Saitama Children's Medical Center
35	Kanto and Koshinetsu	National Defense Medical College Hospital
36	Kanto and Koshinetsu	Teikyo University Chiba Medical Center
37	Kanto and Koshinetsu	Kameda Medical Center
38	Kanto and Koshinetsu	Nippon Medical School Chiba Hokusoh Hospital
39	Kanto and Koshinetsu	Kokuho Asahi General Hospital
40	Kanto and Koshinetsu	Japanese Red Cross Narita Hospital
41	Kanto and Koshinetsu	Chiba University Hospital
42	Kanto and Koshinetsu	Chiba Children's Hospital
43	Kanto and Koshinetsu	Matsudo City Hospital
44	Kanto and Koshinetsu	National Center for Global Health and Medicine
45	Kanto and Koshinetsu	Nihon University Itabashi Hospital
46	Kanto and Koshinetsu	Japanese Red Cross Musashino Hospital
47	Kanto and Koshinetsu	Teikyo University Hospital
48	Kanto and Koshinetsu	Tokyo Medical And Dental University Hospital Faculty of Medicine
49	Kanto and Koshinetsu	The Jikei University Daisan Hospital
50	Kanto and Koshinetsu	Tokyo Metropolitan Children's Medical Center
51	Kanto and Koshinetsu	The Jikei University Hospital
52	Kanto and Koshinetsu	Nippon medical School Hospital
53	Kanto and Koshinetsu	Tokyo Women's Medical University Medical Center East
54	Kanto and Koshinetsu	The University of Tokyo Hospital
55	Kanto and Koshinetsu	Keio University Hospital
56	Kanto and Koshinetsu	Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital
57	Kanto and Koshinetsu	Toho University Omori Medical Center
58	Kanto and Koshinetsu	Showa University Hospital
59	Kanto and Koshinetsu	Juntendo University Hospital
60	Kanto and Koshinetsu	National Center for Child Health and Development
61	Kanto and Koshinetsu	St. Luke's International Hospital
62	Kanto and Koshinetsu	Kyorin University Hospital
63	Kanto and Koshinetsu	Tokyo Dental College Ichikawa General Hospital
64	Kanto and Koshinetsu	Dokkyo Medical University Hospital
65	Kanto and Koshinetsu	Jichi Medical University Hospital
66	Kanto and Koshinetsu	Shinshu University Hospital
67	Kanto and Koshinetsu	Nagano Children's Hospital
68	Kanto and Koshinetsu	Niigata University Medical and Dental Hospital
69	Kanto and Koshinetsu	Niigata Cancer Center Hospital
70	Kanto and Koshinetsu	University of Yamanashi Hospital
71	Kanto and Koshinetsu	Japanese Red Cross Maebashi Hospital

Table 4 continued

S. no.	District	Institutions
72	Kanto and Koshinetsu	Saitama Medical University International Medical Center
73	Kanto and Koshinetsu	Yokosuka Kyosai Hospital
74	Kanto and Koshinetsu	Kofu Municipal Hospital
75	Kanto and Koshinetsu	Teikyo University School of medicine University Hospital, Mizonokuchi
76	Tokai and Hokuriku	Fujita Health University
77	Tokai and Hokuriku	Aichi Medical University Hospital
78	Tokai and Hokuriku	Komaki City Hospital
79	Tokai and Hokuriku	National Hospital Organization Nagoya Medical Center
80	Tokai and Hokuriku	Nagoya Daini Red Cross Hospital
81	Tokai and Hokuriku	Anjo Kosei Hospital
82	Tokai and Hokuriku	Japanese Red Cross Nagoya Daiichi Hospital
83	Tokai and Hokuriku	Nagoya University Hospital
84	Tokai and Hokuriku	Kasugai Municipal Hospital
85	Tokai and Hokuriku	Nagoya City University Hospital
86	Tokai and Hokuriku	Toyohashi Municipal Hospital
87	Tokai and Hokuriku	Ichinomiya Municipal Hospital
88	Tokai and Hokuriku	Okazaki City Hospital
89	Tokai and Hokuriku	Kanazawa University Hospital
90	Tokai and Hokuriku	Ishikawa Prefectural Central Hospital
91	Tokai and Hokuriku	Kanazawa Medical University Hospital
92	Tokai and Hokuriku	Gifu Municipal Hospital
93	Tokai and Hokuriku	Toki Municipal General Hospital
94	Tokai and Hokuriku	Gifu University Hospital
95	Tokai and Hokuriku	Hamamatsu Medical Center
96	Tokai and Hokuriku	Hamamatsu University School of Medicine, University Hospital
97	Tokai and Hokuriku	Shizuoka Children's Hospital
98	Tokai and Hokuriku	Iwata City Hospital
99	Tokai and Hokuriku	Seirei Hamamatsu General Hospital
100	Tokai and Hokuriku	Toyama University Hospital
101	Tokai and Hokuriku	Fukui Red Cross Hospital
102	Tokai and Hokuriku	University of Fukui Hospital
103	Tokai and Hokuriku	Mie University Hospital
104	Tokai and Hokuriku	National Mie Hospital
105	Tokai and Hokuriku	Nagoya City East Medical Center
106	Kinki	National Hospital Organization Osaka National Hospital
107	Kinki	Osaka City University Hospital
108	Kinki	Kinki University Hospital
109	Kinki	Yao Municipal Hospital
110	Kinki	Matsushita Memorial Hospital
111	Kinki	Osaka Medical Center and Research Institute for Maternal and Child Health
112	Kinki	Toyonaka Municipal Hospital
113	Kinki	Osaka University Hospital
114	Kinki	Sakai Hospital Kinki University Faculty of Medicine
115	Kinki	Osaka Medical College Hospital
116	Kinki	Kansai Medical University Hirakata Hospital
117	Kinki	Kitano Hospital, The Tazuke Kofukai Medical Research Institute
118	Kinki	Osaka City General Hospital
119	Kinki	Osaka Red Cross Hospital

Table 4 continued

S. no.	District	Institutions
120	Kinki	Osaka General Medical Center
121	Kinki	Nakano Children's Hospital
122	Kinki	Kishiwada City Hospital
123	Kinki	Japanese Red Cross Kyoto Daiichi Hospital
124	Kinki	Kyoto-Katsura Hospital
125	Kinki	Kyoto University Hospital
126	Kinki	Kyoto City Hospital
127	Kinki	National Hospital Organization Maizuru Medical Center
128	Kinki	University Hospital, Kyoto Prefectural University of Medicine
129	Kinki	Takashima General Hospital
130	Kinki	Shiga University of Medical Science Hospital
131	Kinki	Shiga Medical Center for Children
132	Kinki	Otsu Red Cross Hospital
133	Kinki	Tenri Hospital
134	Kinki	Nara Medical University Hospital
135	Kinki	Kobe University Hospital
136	Kinki	Kobe City Medical Center General Hospital
137	Kinki	Japanese Red Cross Society Himeji Hospital
138	Kinki	Akashi Municipal Hospital
139	Kinki	Hyogo Prefectural Kobe Children's Hospital
140	Kinki	Hyogo College of Medicine Hospital
141	Kinki	Nishi-Kobe Medical Center
142	Kinki	Japanese Red Cross Society Wakayama Medical Center
143	Kinki	Wakayama Medical University Hospital
144	Chugoku and Shikoku	Ehime Prefectural Central Hospital
145	Chugoku and Shikoku	Ehime University Hospital
146	Chugoku and Shikoku	National Hospital Organization Okayama Medical Center
147	Chugoku and Shikoku	Okayama University Hospital
148	Chugoku and Shikoku	Okayama Saiseikai General Hospital
149	Chugoku and Shikoku	Kawasaki Medical School Hospital
150	Chugoku and Shikoku	Kurashiki Central Hospital
151	Chugoku and Shikoku	National Hospital Organization Kagawa Children's Hospital
152	Chugoku and Shikoku	Kagawa University Hospital
153	Chugoku and Shikoku	National Hospital Organization Kochi Medical Center
154	Chugoku and Shikoku	Japanese Red Cross Kochi Hospital
155	Chugoku and Shikoku	Kochi Medical School Hospital
156	Chugoku and Shikoku	Shimane University Hospital
157	Chugoku and Shikoku	Shimane Prefectural Central Hospital
158	Chugoku and Shikoku	Tokushima University Hospital
159	Chugoku and Shikoku	Tottori University Hospital
160	Chugoku and Shikoku	Tottori Prefectural Chuou Hospital
161	Chugoku and Shikoku	Hiroshima University Hospital
162	Chugoku and Shikoku	Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital
163	Chugoku and Shikoku	Yamaguchi University Hospital
164	Chugoku and Shikoku	Tokushima Red Cross Hospital
165	Chugoku and Shikoku	Matsue Red Cross Hospital
166	Kyushu and Okinawa	National Hospital Organization Beppu Medical Center
167	Kyushu and Okinawa	Oita Prefectural Hospital

Table 4 continued

S. no.	District	Institutions
168	Kyushu and Okinawa	Oita University Hospital
169	Kyushu and Okinawa	Hospital, University of the Ryukyus
170	Kyushu and Okinawa	Okinawa Prefectural Nanbu Medical Center and Children's Medical Center
171	Kyushu and Okinawa	Kagoshima City Hospital
172	Kyushu and Okinawa	Kagoshima University Medical And Dental Hospital
173	Kyushu and Okinawa	National Hospital Organization Kumamoto Medical Center
174	Kyushu and Okinawa	Kumamoto university hospital
175	Kyushu and Okinawa	Japanese Red Cross Kumamoto Hospital
176	Kyushu and Okinawa	Saga University Hospital
177	Kyushu and Okinawa	Nagasaki University Hospital
178	Kyushu and Okinawa	Kitakyushu Municipal Medical Center
179	Kyushu and Okinawa	Center for Pediatric Emergency Medicine Kitakyushu Municipal Yahata Hospital
180	Kyushu and Okinawa	Kurume University Hospital
181	Kyushu and Okinawa	University Hospital of Occupational and Environmental Health
182	Kyushu and Okinawa	Kyushu University Hospital
183	Kyushu and Okinawa	National Hospital Organization Kyushu Cancer Center
184	Kyushu and Okinawa	Fukuoka University Hospital
185	Kyushu and Okinawa	University of Miyazaki Hospital
186	Kyushu and Okinawa	Sasebo Municipal General Hospital
187	Kyushu and Okinawa	General Hospital Hamanomachi

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