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Original Research

Survival of European children, adolescents and young adults diagnosed with haematological malignancies in the period 2000–2013: Results from EUROCARE-6, a population-based study

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ABSTRACT

Background: While cancer survival has steadily improved over time for adolescents and young adults (AYAs), previous studies have shown poorer survival in AYAs compared to children with leukaemia and lymphomas. In this study, we provided updated European 5-year relative survival (RS) estimates for AYAs with haematologic malignancies compared to children and assessed improvements in survival over time.

Methods: We used the EUROCARE-6 database, with population-based cancer registries data from 29 European countries. Using the period approach, we calculated 5-year RS for European children (0-14 years) and AYAs

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(15-39 years) in the follow-up period 2010- 2014 separately for leukaemia, lymphomas, relevant morphological subgroups, age- subgroups, and sex. We estimated 5-year RS time trends between 2000 and 2013.
Results: Compared to children, AYAs had a worse RS for all acute lymphoblastic leukaemias (ALL) and acute myeloid leukaemia (AML), but a better survival for chronic myeloid leukaemia (CML). No differences in RS were observed between children and AYAs with acute promyelocytic leukaemia (APL). Compared to children, AYAs had a worse RS for HL and NHL in general, and specifically for lymphoblastic, Burkitt, follicular and NK/T cell lymphomas. In AYAs, RS increased between 2000-2013 for leukaemia overall (by 9% points), ALL (by 11% points), AML (by 8% points) and CML (by 11% points).
Conclusion: Despite increasing European survival for AYAs with haematological malignancies, we showed poorer survival in AYAs than in children for most types of leukaemia and lymphomas. These results reflect that further efforts are needed to improve the survival for this distinctive patient group.

1. Introduction

1.1. Background and rationale

Cancer is the leading cause of natural death in the adolescent and young adult (15–39 years at cancer diagnosis [AYAs]) population with approximately 30 % coming from haematological malignancies. Across Europe, there is marked variability between the definitions of AYAs, ranging from 15–24 to 18–39 years old. These varying age ranges may influence access to different healthcare services, and may be problematic for healthcare delivery across different jurisdictions [1].

Over the past two decades, AYAs have been recognised as a distinct population within the oncology community in terms of unique aspects of cancer biology, incidence, mortality, and unmet psychosocial and survivorship care needs [2]. AYA cancer survival has steadily improved from 2000 to 2013 with 5-year overall survival rates now approaching 85 % in high-income countries [3,4] . The haematological malignancies, especially acute leukaemia and non-Hodgkin's lymphomas (NHL) have seen marked impressive improvements over the same time period [5–7] . However, in AYAs, acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) survival is still around 60 % [4]. Furthermore, EUROCARE 5 (period of diagnosis 2000–2007) showed poorer survival in AYAs than in children for ALL, AML, Hodgkin's lymphoma (HL), and NHL. Apart from age, sex has also been shown to impact survival rates with males doing slightly worse than females in terms of 5-year relative survival (RS) [3].

To our knowledge this is the only study reporting European-wide survival for different haematological cancers at different ages after the previous publication of EUROCARE-5. National studies are available [8–12], however, the present work benefits from a large population database which has made it possible to study different groups within rare haematological tumour entities which are difficult to estimate at a national level.

1.2. Objectives

Using the most recent data available in the EUROCARE database, the widest and most representative population-based dataset on cancer survival in Europe, this study aims to provide: (i) 5-year RS and RS trends for AYAs with haematological malignancies and (ii) comparisons of the difference in RS between AYAs and children (aged 0–14 years) diagnosed with haematological tumours.

2. Methods

2.1. Study design and data collection

We used the EUROCARE-6 database which contains data on cases from 108 population-based cancer registries (CRs) from 29 European countries. Further details on the database, and its population coverage

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have been previously described [4]. We performed systematic data checks according to the International Association of Cancer Registries (IACR) and International Agency for Research on Cancer (IARC) rules, together with standard data quality indicators, including the proportion of cases identified from the death certificate only (DCO), the proportion of cases diagnosed incidentally at autopsy, the proportion of microscopically verified (MV) cases, and the proportion with not otherwise specified (NOS) morphology [13].

All primary haematological malignancies, coded according to the International Classification of Disease for Oncology, Third Edition (ICD-O-3), were included in the analyses. Haematological malignancies were grouped into two broad diagnostic categories: 1) Leukemia and related disorders; and 2) Lymphomas. Each category was then divided into relevant subgroups as reported in Supplementary materials Table S1. All primary neoplasms were included in the analyses, thus survival estimates refer to individuals who have been diagnosed for a cancer as their first or subsequent primary cancer.

The AYA-population was also defined into three age groups, namely 15–19 years old, 20–24 years old, and 25–39 years old, on the basis of biological and clinical considerations to unravel possible prognostic differences across AYA age groups.

2.2. Statistical analysis

2.2.1. Survival 2010-2014

To perform survival analyses, we excluded 13 CRs which specialised in specific groups of tumours other than haematological ones and selected data from 95 general CRs which cover around 57 % of the European population.

Using the period approach [14], we calculated 5-year RS for the follow-up period 2010–2014. These RS estimates were based on the survival experience of cases diagnosed in 2006–2013, who were followed up for vital status to December 31, 2014 (Supplementary materials Fig. S1). RS was defined as the ratio of observed patients' survival to the expected survival of the general population with the same age, calendar year, place of residence, and sex. RS allows to correct for deaths from causes other than the cancer under investigation when the actual cause of death is unavailable. We estimated the expected survival by the Ederer II method [15].

5-years RS was estimated by sex and by age at diagnosis. As stated above, children were defined as aged 0–14 whilst AYAs were either considered overall (age 15–39) or divided into three age groups (15–19, 20–24 and 25–39 years). We used the z-test to assess for significant survival differences between children and AYAs as well as between males and females.

2.2.2. Survival trends

We estimated 5-year RS between 2000 and 2013 using three follow-up periods: 2004–2006 (cohorts diagnosed 2000–2006), 2007–2009 (cohorts diagnosed 2003–2009) and 2010–2014 (cohorts diagnosed 2006–2013) (Supplementary materials Fig. S1). We estimated the 5-year RS trends for children, for AYAs, and for the three age groups of AYAs.

For survival trend analyses, 69 of the 95 CRs were included because they provided data covering at least the period of diagnosis 2001–2010.

3. Results

3.1. Data quality

Only 2 % (1544 out of 90,841) of haematological cases in AYAs and children were excluded: 755 because the records contained non-recoverable major errors (i.e., missing or invalid data items), 330 because the tumours were ascertained from death certificate or autopsy only, and 329 because they were censored immediately after diagnosis (i.e., lack of follow-up data) (Supplementary materials Table S2). The ICD-O-3 morphology was unspecified for 6 % of the cases included in the analysis. Croatia and Poland had the highest proportions of cancers with unspecified morphology, but half of the other countries had less than 3 % unspecified morphology (Supplementary materials Table S2). Only 1 % of cases were lost during follow-up. Quality indicators were similar for CRs used for the trend analyses.

3.2. 5-year relative survival

We analysed the survival of approximately 34,000 AYAs and 10,000 children who were diagnosed in Europe with haematologic tumours between 2006 and 2013.

In AYAs, all types of ALL and AML had a RS of approximately 60 %. The RS among patients diagnosed with acute promyelocytic leukaemia (APL) and chronic myeloid leukaemia (CML) was higher (85 % and 93 %, respectively) (Table 1). RS for ALL and B-cell ALL, varied between AYA age groups, being highest among adolescents (i.e., 15–19 years old) and decreased in the 20–24 and 25–39 age groups (Table 1, Fig. 1). RS did not differ between AYA age groups for T-cell ALL, AML, APL, and CML. Compared to children, AYAs had a worse RS for all ALL subtypes and AML, but a better survival for CML (Table 1). The same pattern of survival differences was observed between children and different AYA age groups, except for T-cell ALL, which had the same RS in children and adolescents. No differences in RS were observed between children and AYAs diagnosed with APL (Table 1).

AYA patients diagnosed with lymphomas had a RS of 89 % with a higher survival in HL than NHL (94 % vs 84 %) (Table 1). Among NHLs, RS was highest (>90 %) for MALT, follicular, and primary mediastinal large B cell lymphomas and was lowest (approximately 60 %) for NK/T cell and lymphoblastic lymphomas (Table 1). No differences in survival were found between AYA age groups for different lymphoma subtypes (Table 1, Fig. 1). Compared to children, AYAs had a worse RS for HL and NHL in general, and specifically for lymphoblastic, Burkitt, follicular and NK/T cell lymphomas (Table 1).

Regarding sex differences, in AYAs, females had better RS than males for leukaemia overall, AML, lymphomas overall, NHL and NK/T-cell lymphoma. In children, no significant differences in RS were found between sex except for ALL and Diffuse Large B cell lymphoma (DLBCL), for which girls had better survival than boys (Table 2).

3.3. Survival trends over time

In AYAs, RS increased between follow-up periods 2004–2006 and 2010–2014 for leukaemia overall (by 9 % points), ALL (by 11 % points), AML (by 8 % points) and CML (by 11 % points) (Table 3). Across AYA age groups, RS changes were similar to those observed for AYAs overall with a few exceptions: RS did not change for adolescent AML patients, while RS increased for APL patients aged 25–39 over the same period.

In children, the RS increased for leukaemia overall and related subtypes but not for T-cell ALL. Compared to AYAs, in children, the increase in RS was lower for the overall group of leukaemia (5 % vs 9 %), lower for ALL (4 % *vs* 11 %), higher for AML (11 % *vs* 8 %) and similar for CML (11 %) (Table 3, Fig. 2).

Regarding lymphomas, RS in AYAs increased between follow-up periods 2004–2006 and 2010–2014 by 4 % for lymphomas overall and specially by 6 % points in NHL and 2 % in HL (Table 3). Among NHL, RS increased for all subtypes except for lymphoblastic, Burkitt and anaplastic T- and null-cell lymphomas. Primary mediastinal large B-cell lymphoma had the largest increase (by 12 % points). Trends in RS varied by AYA age groups. In adolescents, the RS only increased for patients with HL (by 2 % points). In the 20–24 age group, RS increased for the overall group of NHL, NHL NOS and HL (Table 3). Lastly, trends in RS in those aged 25–39 years old were similar to that for the AYA group overall, except for NK/T-cell lymphoma which did not change significantly for this age group between 2004 and 2014. In children, RS only increased for Burkitt lymphoma (by 6 % points).

Table 1
Five-year Relative Survival (RS) of children and AYAs diagnosed with a haematological malignancy in by subtype and age at diagnosis, 2010–2014 period estimates.

	0-14 years				15-39 years						15-19 years						20-24 years						25-39 years					
	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Absolute difference 0-14 - 15-39 years		Mean N+	RS	RS lower	RS upper	Absolute difference 0-14 - 15-19 years		Mean N+	RS	RS lower	RS upper	Absolute difference 0-14 - 20-24 years		Mean N+	RS	RS lower	RS upper	Absolute difference 0-14 - 15-39 years	
									Diff.	pvalue					Diff.	pvalue					Diff.	pvalue					Diff.	pvalue
1. Leukemias and related disorders	7414	86.4%	85.5%	87.1%	9810	72.7%	71.8%	73.6%	13.7%	0.00	1652	71.6%	69.3%	73.8%	14.7%	0.00	1501	69.9%	67.5%	72.3%	16.4%	0.00	6658	73.6%	72.5%	74.7%	12.7%	0.00
1.1 Acute lymphoblastic leukemia (ALL)	5668	90.1%	89.3%	90.9%	2282	61.3%	59.2%	63.3%	28.8%	0.00	862	73.3%	70.1%	76.2%	16.8%	0.00	481	59.5%	54.8%	63.9%	30.6%	0.00	955	51.0%	47.7%	54.3%	39.1%	0.00
1.1.a ALL, B-cell	1594	91.4%	89.9%	92.7%	559	64.0%	59.8%	67.8%	27.4%	0.00	220	77.3%	71.0%	82.3%	14.1%	0.00	112	55.8%	46.3%	64.3%	35.6%	0.00	226	55.9%	49.1%	62.1%	35.5%	0.00
1.1.b ALL, T cell	307	78.2%	73.1%	82.4%	292	59.1%	52.9%	64.7%	19.1%	0.00	93	67.9%	56.9%	76.8%	10.2%	0.07	71	64.0%	51.7%	73.9%	14.2%	0.02	130	50.6%	41.2%	59.2%	27.6%	0.00
1.2 Acute myeloid leukemia (AML)	1120	70.5%	67.6%	73.2%	3271	58.1%	56.3%	59.9%	12.4%	0.00	461	59.9%	55.0%	64.4%	10.7%	0.00	544	61.1%	56.7%	65.2%	9.4%	0.00	2267	57.1%	54.9%	59.2%	13.5%	0.00
1.2.a Acute promyelocytic leukemia (APL)	87	90.3%	81.4%	95.1%	427	85.2%	81.3%	88.3%	5.1%	0.17	58	82.5%	69.8%	90.2%	7.9%	0.17	72	84.6%	73.8%	91.2%	5.7%	0.29	301	86.1%	81.5%	89.7%	4.2%	0.28
1.3 Chronic myeloid leukemia (CML)	181	82.4%	75.5%	87.5%	1428	92.8%	91.3%	94.1%	-10.4%	0.00	107	90.9%	83.5%	95.1%	-8.5%	0.04	183	97.3%	93.2%	98.9%	-14.8%	0.00	1142	92.3%	90.5%	93.8%	-9.9%	0.00
2. Lymphomas	2962	93.1%	92.1%	94.0%	24730	89.4%	89.0%	89.8%	3.8%	0.00	3297	92.0%	91.0%	92.9%	1.2%	0.09	4581	91.6%	90.8%	92.4%	1.5%	0.02	16873	88.3%	87.7%	88.8%	4.9%	0.00
2.1 Non-Hodgkin lymphomas	1511	90.1%	88.4%	91.6%	9851	83.8%	83.0%	84.5%	6.3%	0.00	860	83.5%	80.8%	86.0%	6.6%	0.00	1269	83.0%	80.8%	85.0%	7.1%	0.00	7739	84.0%	83.1%	84.8%	6.1%	0.00
2.1.1 Lymphoblastic	292	86.8%	82.2%	90.3%	340	63.1%	57.6%	68.1%	23.7%	0.00	91	70.6%	59.9%	78.9%	16.2%	0.00	75	59.2%	47.2%	69.3%	27.6%	0.00	172	60.7%	52.6%	67.8%	26.1%	0.00
2.1.2 Burkitt	612	92.5%	90.0%	94.4%	613	75.7%	72.0%	79.0%	16.8%	0.00	123	78.3%	69.3%	84.9%	14.3%	0.00	103	84.7%	76.5%	90.2%	7.8%	0.03	380	72.1%	67.1%	76.5%	20.4%	0.00
2.1.3 Diffuse large B-cell (DLBCL)	176	87.3%	81.0%	91.6%	3385	82.3%	80.9%	83.6%	5.0%	0.07	253	85.0%	79.7%	89.0%	2.3%	0.52	461	81.9%	77.9%	85.2%	5.4%	0.09	2681	82.1%	80.6%	83.6%	5.2%	0.06
2.1.4 Primary mediastinal large B-cell	7	83.4%	27.3%	97.5%	403	90.6%	87.3%	93.1%	-7.2%	0.64	45	91.2%	78.0%	96.6%	-7.8%	0.62	82	89.2%	80.7%	94.1%	-5.8%	0.71	274	90.8%	86.7%	93.7%	-7.5%	0.63
2.1.5 Anaplastic T- and null-cell excluding NK/T-cell	122	89.6%	82.4%	94.0%	366	82.8%	78.3%	86.5%	6.8%	0.06	67	85.7%	74.3%	92.3%	3.9%	0.46	78	87.4%	77.1%	93.3%	2.2%	0.66	223	80.2%	73.9%	85.1%	9.4%	0.02
2.1.6 Follicular	26	100%	.	.	1533	94.7%	93.4%	95.8%	5.3%	0.00	46	95.3%	81.9%	98.8%	4.7%	0.16	85	97.7%	90.7%	99.4%	2.3%	0.16	1409	94.5%	93.1%	95.6%	5.5%	0.00
2.1.7 NK/T-cell	79	78.3%	67.1%	86.1%	510	60.1%	55.6%	64.4%	18.2%	0.00	46	66.6%	49.8%	79.0%	11.7%	0.19	70	63.4%	50.5%	73.8%	14.9%	0.05	395	58.8%	53.6%	63.7%	19.5%	0.00
2.1.8 Mucosa-associated lymphoid tissue (MALT)	23	89.6%	64.2%	97.3%	646	95.0%	92.9%	96.5%	-5.4%	0.44	30	100%	.	.	-10.4%	0.14	58	96.5%	86.7%	99.1%	-6.9%	0.35	555	94.6%	92.2%	96.3%	-5.0%	0.48
2.1.9 Other non-Hodgkin lymphoma Not otherwise specified (NOS)	147	89.2%	82.1%	93.6%	1540	80.9%	78.7%	82.9%	8.3%	0.01	127	84.5%	76.4%	90.0%	4.8%	0.28	202	84.2%	78.0%	88.8%	5.0%	0.20	1218	79.9%	77.4%	82.2%	9.3%	0.00
2.2 Hodgkin lymphoma	1118	97.3%	96.1%	98.1%	13425	94.5%	94.1%	94.9%	2.8%	0.00	2339	95.3%	94.4%	96.1%	2.0%	0.00	3178	95.3%	94.5%	96.0%	2.0%	0.00	7920	93.9%	93.3%	94.4%	3.4%	0.00

* Based on EUROPEAN pool of 95 registries

+ Mean N is the average number of people alive at the start of the first interval in the cohorts of diagnosis included in the period survival analysis (Supplementary materials Fig. S1)

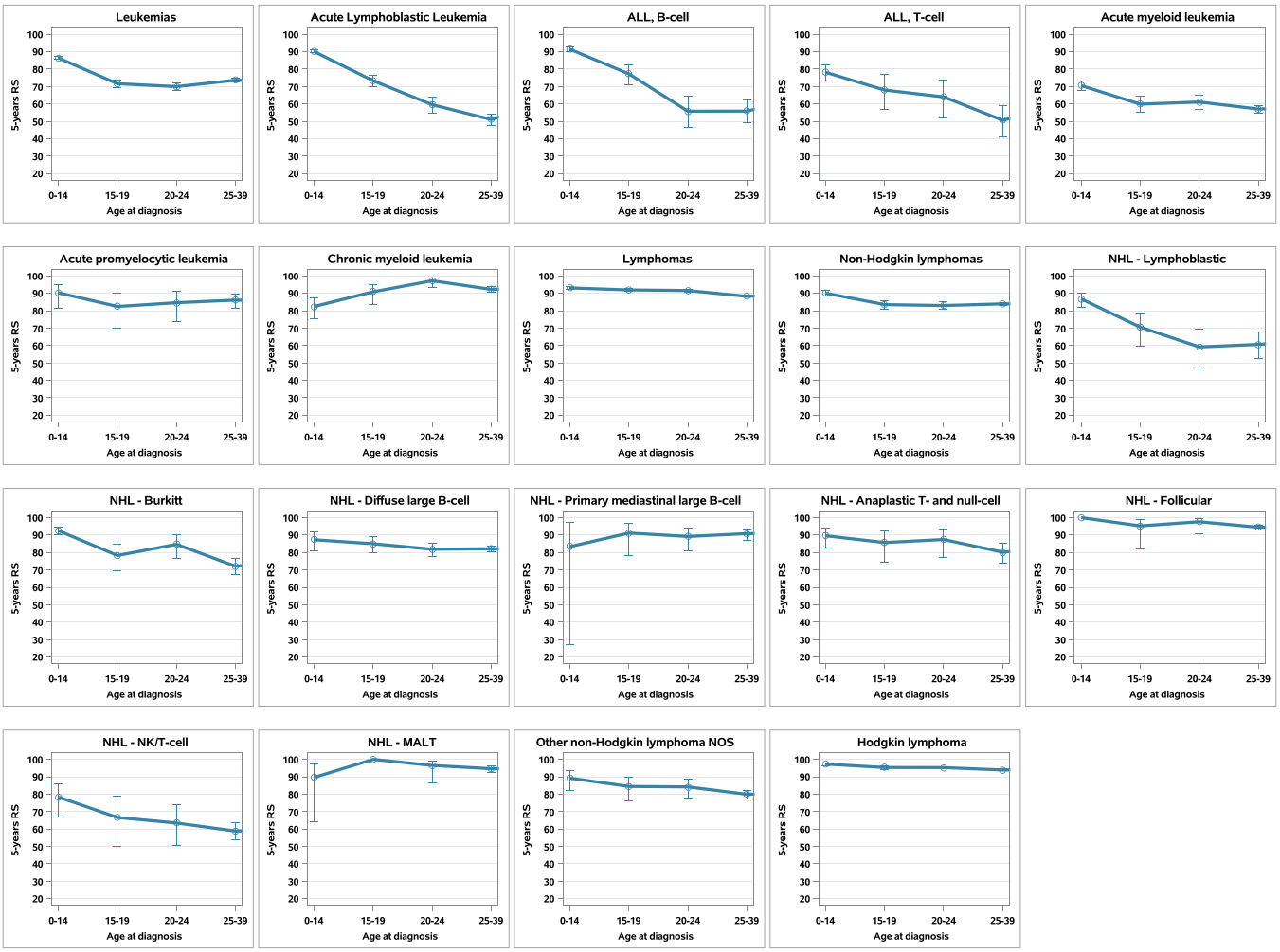

Fig. 1. Five-year Relative Survival (RS) of children and AYAs diagnosed with a haematological malignancy in Europe* by subtype and age at diagnosis, 2010–2014 period estimates.
* Based on EUROPEAN pool of 95 registries.

4. Discussion

In Europe, for most haematological cancers, the RS among children and AYAs increased in the follow-up period between 2004–2006 and 2010–2014. This increase in survival can be attributed to better prognostication and risk-adapted therapy informed by a better understanding of the genetic alterations associated with these malignancies [16], increased use of targeted therapies [17,18], and better supportive care and salvage therapy [19,20].

However, European AYAs continue to have worse 5-year RS than European children diagnosed in the same period. Similar results have been observed in other studies, which report higher survival in children than among AYAs diagnosed with AML [11], ALL [21], lymphoblastic lymphoma, Burkitt lymphoma [12], and HL [22]. In contrast to other haematological malignancies, we found lower survival among children with CML compared to AYAs. This is in line with previous studies which have considered whether CML present more aggressively in children compared to AYAs and older adults [23,24]. Due to the rarity of NK/T-cell lymphomas and follicular lymphomas, no prior analysis comparing survival differences between children and AYAs could be found in the literature.

Differences in tumour aggressiveness in children and AYAs due to biological factors [25] may not completely explain these survival disparities. Other factors which may explain the survival differences are variations in paediatric and adult protocols [26], higher treatment toxicity for AYAs [27], lower participation of AYAs in clinical trials compared to that of children [28], differences in psychosocial factors [29], and possible lower treatment adherence among AYAs [30].

For ALL, high survival differences persisted between children and AYAs. These significantly better outcomes among children may be partly explained by unique biologic characteristics [31], and a greater incidence of treatment related toxicity seen among AYAs [32]. Nevertheless, survival of AYAs has progressed significantly between 2004 and 2014 which can be partially attributed to the introduction of paediatric inspired regimens or use of paediatric focused regimens which use minimal residual disease (MRD) measurements to inform risk-stratification [26,33].

Lymphoblastic lymphoma, similar to ALL, also showed survival differences of more than 20 % between children and AYAs. This survival disparity is thought to be multifactorial, including more AYAs undergoing HSCT [12] and biological differences which are not yet well understood.

APL, not surprisingly, was the only subtype of AML which did not show a survival difference between children and AYAs. Despite children often having a more aggressive form of APL, RS has improved over time. RS also improved for AYAs since the introduction of all-trans retinoic acid in the 1980s and 1990s, the introduction of risk-stratified treatment protocols across these age groups, and the introduction of arsenic trioxide in the 2000s [34–36].

Although CML survival has significantly improved since the

Table 2
Five-year Relative Survival (RS) of children and AYAs diagnosed with a haematological malignancy in Europe* by subtype and sex, 2010–2014 period estimates.

	0-14 years										15-39 years									
	Males				Females				Absolute difference females-males		Males				Females				Absolute difference females-males	
	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Diff.	pvalue	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Diff.	pvalue
1. Leukemias and related disorders	4117	85.7%	84.6%	86.8%	3297	87.2%	85.9%	88.3%	1.5%	0.08	5486	71.1%	69.8%	72.3%	4332	74.7%	73.4%	76.1%	3.6%	0.00
1.1 Acute lymphoblastic leukemia (ALL)	3180	89.3%	88.1%	90.3%	2496	91.1%	89.9%	92.2%	1.8%	0.03	1467	61.2%	58.6%	63.7%	833	61.3%	57.8%	64.7%	0.1%	0.95
1.1.a ALL, B-cell	830	90.5%	88.2%	92.3%	764	92.4%	90.2%	94.1%	2.0%	0.17	315	64.2%	58.8%	69.1%	224	63.8%	57.1%	69.7%	-0.4%	0.92
1.1.b ALL, T cell	219	78.3%	72.2%	83.2%	87	77.6%	67.2%	85.1%	-0.6%	0.91	215	58.6%	51.5%	65.1%	73	60.4%	47.7%	71.0%	1.8%	0.80
1.2 Acute myeloid leukemia (AML)	591	69.3%	65.2%	72.9%	531	71.9%	67.7%	75.6%	2.7%	0.35	1665	55.3%	52.8%	57.7%	1606	61.1%	58.5%	63.5%	5.8%	0.00
1.2.a Acute promyelocytic leukemia (APL)	38	95.7%	72.9%	99.4%	52	86.5%	73.7%	93.3%	-9.2%	0.15	197	83.0%	76.8%	87.7%	232	87.1%	81.8%	91.0%	4.2%	0.24
1.3 Chronic myeloid leukemia (CML)	111	80.5%	71.0%	87.1%	70	85.3%	73.5%	92.1%	4.8%	0.43	871	92.2%	90.1%	93.9%	564	93.8%	91.3%	95.6%	1.5%	0.29
2. Lymphomas	1944	93.2%	91.9%	94.3%	1025	93.0%	91.2%	94.4%	-0.2%	0.81	13518	88.1%	87.5%	88.6%	11213	91.0%	90.4%	91.5%	2.9%	0.00
2.1 Non-Hodgkin lymphomas	1078	90.6%	88.6%	92.3%	433	88.8%	85.3%	91.5%	-1.8%	0.31	5825	82.3%	81.3%	83.3%	4026	85.9%	84.7%	86.9%	3.5%	0.00
2.1.1 Lymphoblastic	192	87.0%	81.0%	91.2%	100	86.7%	78.1%	92.1%	-0.3%	0.95	262	63.2%	56.8%	68.9%	85	62.4%	50.6%	72.1%	-0.8%	0.90
2.1.2 Burkitt	494	93.2%	90.4%	95.2%	119	89.8%	82.2%	94.2%	-3.4%	0.28	469	76.4%	72.1%	80.1%	146	73.7%	65.5%	80.3%	-2.6%	0.54
2.1.3 Diffuse large B-cell (DLBCL)	118	83.6%	74.9%	89.5%	59	94.3%	83.2%	98.1%	10.7%	0.03	1999	82.3%	80.4%	84.0%	1386	82.4%	80.2%	84.3%	0.1%	0.94
2.1.4 Primary mediastinal large B-cell	3	100%	.	.	4	75.0%	12.8%	96.1%	-25.0%	0.25	172	88.7%	82.8%	92.6%	231	92.0%	87.7%	94.8%	3.3%	0.27
2.1.5 Anaplastic T- and null-cell excluding NK/T-cell	71	90.8%	80.5%	95.8%	51	87.8%	74.8%	94.4%	-2.9%	0.62	213	82.7%	76.6%	87.4%	155	82.8%	75.3%	88.1%	0.1%	0.99
2.1.6 Follicular	22	100%	.	.	5	100%	.	.	0.0%	.	872	94.8%	93.0%	96.2%	663	94.6%	92.4%	96.1%	-0.3%	0.83
2.1.7 NK/T-cell	52	84.3%	70.9%	91.8%	26	65.2%	42.4%	80.8%	-19.1%	0.09	316	54.7%	48.9%	60.1%	194	69.5%	62.1%	75.7%	14.8%	0.00
2.1.8 Mucosa-associated lymphoid tissue (MALT)	12	90.1%	47.1%	98.6%	10	90.9%	50.8%	98.7%	0.9%	0.95	353	93.4%	90.0%	95.7%	278	96.6%	93.6%	98.2%	3.2%	0.08
2.1.9 Other non-Hodgkin lymphoma Not otherwise specified (NOS)	102	89.5%	80.8%	94.4%	45	88.6%	72.3%	95.6%	-1.0%	0.88	901	78.4%	75.3%	81.1%	639	84.4%	81.1%	87.1%	6.0%	0.00
2.2 Hodgkin lymphoma	668	97.4%	95.9%	98.4%	453	97.1%	94.9%	98.3%	-0.4%	0.71	6839	93.9%	93.3%	94.5%	6586	95.0%	94.5%	95.5%	1.1%	0.01

*Based on EUROPEAN pool of 95 registries
+ Mean N is the average number of people alive at the start of the first interval in the cohorts of diagnosis included in the period survival analysis (Supplementary materials Fig. S1)

Table 3
Trends over time in five-year Relative Survival (RS) of children and AYAs diagnosed with a haematological malignancy in Europe* by subtype and age at diagnosis, period estimates of 2004–2006, 2007–2009 and 2010–2014.

	0-14 years														15-39 years											
	2004-2006				2007-2009				2010-2014				Absolute difference 2010-2014 - 2004-2006		2004-2006				2007-2009				2010-2014				Absolute difference 2010-2014 - 2004-2006	
	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Diff.	pvalue	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Diff.	pvalue
1. Leukemias and related disorders	4792	81.4%	80.2%	82.4%	4999	83.7%	82.7%	84.7%	6299	86.3%	85.4%	87.2%	4.9%	0.00	5801	63.2%	61.9%	64.4%	6192	66.4%	65.2%	67.6%	7793	71.9%	70.9%	72.9%	8.7%	0.00
1.1 Acute lymphoblastic leukemia (ALL)	3679	86.3%	85.2%	87.4%	3829	88.2%	87.1%	89.2%	4837	90.0%	89.1%	90.8%	3.6%	0.00	1419	50.7%	48.0%	53.3%	1476	53.1%	50.5%	55.7%	1838	61.3%	59.0%	63.6%	10.6%	0.00
1.1.a ALL, B-cell	545	86.3%	83.3%	88.9%	809	90.3%	88.1%	92.2%	1203	90.7%	88.9%	92.3%	4.4%	0.01	167	56.2%	48.1%	63.6%	242	63.0%	56.6%	68.7%	391	63.6%	58.6%	68.1%	7.3%	0.12
1.1.b ALL, T cell	97	80.5%	71.0%	87.1%	141	79.7%	72.4%	85.2%	225	80.1%	74.3%	84.8%	-0.4%	0.94	84	59.2%	47.6%	69.0%	136	47.6%	39.6%	55.1%	206	56.5%	49.2%	63.2%	-2.6%	0.69
1.2 Acute myeloid leukemia (AML)	756	59.5%	55.9%	62.9%	763	64.8%	61.3%	68.1%	944	70.2%	67.1%	73.1%	10.7%	0.00	2052	49.4%	47.2%	51.5%	2135	52.0%	49.8%	54.1%	2639	57.2%	55.2%	59.1%	7.8%	0.00
1.2.a Acute promyelocytic leukemia (APL)	44	74.4%	59.8%	84.4%	55	91.9%	81.5%	96.6%	70	91.4%	81.6%	96.1%	17.0%	0.02	224	80.9%	75.3%	85.3%	249	83.0%	77.8%	87.1%	351	84.8%	80.5%	88.3%	3.9%	0.22
1.3 Chronic myeloid leukemia (CML)	117	70.5%	61.3%	77.9%	136	79.6%	71.6%	85.6%	153	81.4%	73.6%	87.0%	10.9%	0.05	981	81.5%	78.9%	83.9%	973	87.2%	84.8%	89.2%	1158	92.3%	90.5%	93.7%	10.8%	0.00
2. Lymphomas	1942	89.2%	87.7%	90.5%	1920	89.8%	88.4%	91.1%	2432	92.6%	91.4%	93.6%	3.4%	0.00	14837	85.0%	84.4%	85.5%	15707	87.2%	86.6%	87.7%	20084	88.9%	88.5%	89.4%	4.0%	0.00
2.1 Non-Hodgkin lymphomas	934	84.5%	82.0%	86.7%	972	86.7%	84.4%	88.7%	1250	89.7%	87.8%	91.3%	5.2%	0.00	5699	77.4%	76.3%	78.5%	6150	80.8%	79.8%	81.8%	7984	83.5%	82.7%	84.4%	6.1%	0.00
2.1.1 Lymphoblastic	175	83.9%	77.5%	88.6%	186	84.5%	78.5%	88.9%	240	85.5%	80.2%	89.5%	1.6%	0.66	189	63.5%	56.2%	69.9%	206	64.5%	57.4%	70.7%	271	64.6%	58.4%	70.0%	1.0%	0.82
2.1.2 Burkitt	343	85.7%	81.5%	89.0%	369	89.4%	85.9%	92.1%	505	91.9%	89.0%	94.1%	6.3%	0.01	297	69.7%	64.5%	74.4%	351	76.4%	71.5%	80.5%	497	74.3%	70.1%	78.0%	4.6%	0.16
2.1.3 Diffuse large B-cell (DLBCL)	99	82.6%	73.7%	88.7%	116	90.7%	83.8%	94.8%	137	88.5%	81.3%	93.0%	5.9%	0.22	1811	75.7%	73.7%	77.6%	2047	79.5%	77.7%	81.2%	2708	82.3%	80.7%	83.7%	6.6%	0.00
2.1.4 Primary mediastinal large B-cell	.	.	.	.	4	71.5%	25.8%	92.0%	6	83.4%	27.3%	97.5%	.	.	103	78.6%	69.9%	85.1%	147	89.1%	82.9%	93.2%	277	90.7%	86.7%	93.6%	12.1%	0.00
2.1.5 Anaplastic T- and null-cell excluding NK/T-cell	55	83.3%	71.2%	90.7%	62	90.8%	80.3%	95.8%	101	89.3%	81.0%	94.1%	6.0%	0.30	191	75.9%	69.2%	81.3%	218	73.2%	66.9%	78.5%	279	81.4%	76.1%	85.7%	5.5%	0.16
2.1.6 Follicular	16	100%	.	.	13	90.9%	50.8%	98.7%	22	100%	.	.	0.0%	.	888	91.1%	88.9%	92.8%	969	92.7%	90.8%	94.2%	1277	94.6%	93.1%	95.7%	3.5%	0.00
2.1.7 NK/T-cell	41	74.9%	59.3%	85.3%	47	79.7%	65.3%	88.6%	70	78.6%	66.6%	86.8%	3.7%	0.65	260	53.3%	47.3%	58.9%	303	53.4%	47.7%	58.9%	430	61.7%	56.7%	66.3%	8.4%	0.03
2.1.8 Mucosa-associated lymphoid tissue (MALT)	11	80.0%	50.0%	93.1%	15	87.5%	58.6%	96.7%	19	88.5%	61.0%	97.0%	8.5%	0.51	243	90.2%	85.8%	93.3%	335	91.6%	88.1%	94.1%	510	94.5%	91.9%	96.2%	4.3%	0.05
2.1.9 Other non-Hodgkin lymphoma Not otherwise specified (NOS)	172	83.7%	76.9%	88.6%	139	78.3%	69.9%	84.6%	130	88.8%	81.0%	93.5%	5.1%	0.23	1427	73.1%	70.6%	75.4%	1243	76.8%	74.3%	79.2%	1342	79.9%	77.5%	82.1%	6.8%	0.00
2.2 Hodgkin lymphoma	813	94.9%	93.1%	96.3%	769	94.4%	92.5%	95.9%	933	96.8%	95.4%	97.8%	1.9%	0.06	8002	92.0%	91.4%	92.6%	8491	93.1%	92.5%	93.6%	10913	94.0%	93.5%	94.4%	2.0%	0.00

	15-19 years														20-24 years											
	2004-2006				2007-2009				2010-2014				Absolute difference 2010-2014 - 2004-2006		2004-2006				2007-2009				2010-2014				Absolute difference 2010-2014 - 2004-2006	
	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Diff.	pvalue	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Diff.	pvalue
1. Leukemias and related disorders	973	61.5%	58.4%	64.5%	1062	67.0%	64.1%	69.7%	1352	71.6%	69.1%	74.0%	10.1%	0.00	882	56.1%	52.7%	59.3%	941	61.5%	58.3%	64.5%	1202	69.1%	66.3%	71.7%	13.0%	0.00
1.1 Acute lymphoblastic leukemia (ALL)	525	62.3%	58.0%	66.2%	575	67.2%	63.1%	71.0%	702	73.4%	69.8%	76.6%	11.1%	0.00	299	45.7%	39.9%	51.4%	292	49.0%	43.1%	54.5%	388	59.2%	54.0%	64.1%	13.5%	0.00
1.1.a ALL, B-cell	62	71.9%	58.6%	81.5%	96	74.2%	64.0%	82.0%	157	76.5%	69.1%	82.4%	4.7%	0.49	32	50.3%	33.0%	65.2%	44	60.8%	44.3%	73.9%	80	53.6%	42.4%	63.6%	3.3%	0.74
1.1.b ALL, T cell	31	55.4%	35.7%	71.2%	45	54.6%	39.5%	67.4%	67	68.2%	54.7%	78.5%	12.8%	0.25	20	66.9%	43.2%	82.5%	34	37.0%	22.2%	51.9%	50	61.5%	46.0%	73.8%	-5.4%	0.66
1.2 Acute myeloid leukemia (AML)	275	53.9%	47.7%	59.7%	302	56.6%	50.9%	61.8%	384	60.1%	54.8%	65.1%	6.2%	0.12	323	50.1%	44.7%	55.3%	348	52.9%	47.5%	57.9%	440	60.6%	55.7%	65.2%	10.5%	0.00
1.2.a Acute promyelocytic leukemia (APL)	29	84.2%	68.2%	92.6%	37	90.9%	74.4%	97.0%	50	80.6%	66.9%	89.1%	-3.6%	0.66	39	91.1%	74.0%	97.1%	40	75.2%	57.6%	86.3%	57	85.1%	73.3%	92.0%	-5.9%	0.39
1.3 Chronic myeloid leukemia (CML)	77	71.6%	59.8%	80.5%	70	87.8%	76.8%	93.8%	91	90.6%	82.5%	95.1%	19.0%	0.00	126	76.8%	68.1%	83.5%	130	90.7%	84.0%	94.7%	149	97.9%	93.3%	99.3%	21.0%	0.00
2. Lymphomas	2036	89.5%	88.1%	90.8%	2128	90.8%	89.4%	91.9%	2653	91.6%	90.5%	92.7%	2.1%	0.02	2711	88.0%	86.7%	89.2%	2824	89.0%	87.8%	90.1%	3676	91.1%	90.1%	92.0%	3.1%	0.00
2.1 Non-Hodgkin lymphomas	507	78.9%	75.1%	82.2%	533	82.8%	79.3%	85.7%	686	83.4%	80.2%	86.0%	4.4%	0.06	697	76.3%	73.0%	79.2%	747	78.3%	75.1%	81.1%	1026	82.3%	79.7%	84.5%	6.0%	0.00
2.1.1 Lymphoblastic	53	68.1%	53.0%	79.3%	59	78.0%	64.9%	86.7%	75	70.3%	58.4%	79.3%	2.2%	0.80	38	74.6%	56.7%	85.9%	40	68.9%	51.3%	81.2%	59	62.6%	48.8%	73.6%	-12.0%	0.22
2.1.2 Burkitt	52	82.7%	70.8%	90.1%	76	79.5%	68.4%	87.1%	95	77.1%	66.4%	84.8%	-5.6%	0.40	54	74.2%	61.0%	83.5%	57	94.0%	82.0%	98.1%	85	84.2%	75.1%	90.2%	10.0%	0.14
2.1.3 Diffuse large B-cell (DLBCL)	143	81.1%	73.5%	86.7%	153	86.0%	79.4%	90.6%	195	86.4%	80.5%	90.7%	5.3%	0.21	212	76.9%	70.8%	81.9%	260	77.8%	72.3%	82.4%	366	81.4%	76.9%	85.1%	4.5%	0.20
2.1.4 Primary mediastinal large B-cell	12	75.5%	37.5%	92.2%	20	86.4%	62.7%	95.5%	33	91.5%	75.7%	97.2%	16.0%	0.26	19	78.3%	51.8%	91.3%	24	96.7%	78.2%	99.6%	51	84.1%	71.4%	91.4%	5.7%	0.60
2.1.5 Anaplastic T- and null-cell excluding NK/T-cell	31	79.7%	60.2%	90.4%	35	83.2%	65.5%	92.3%	52	86.3%	73.4%	93.2%	6.6%	0.46	40	82.2%	67.1%	90.8%	44	63.1%	47.0%	75.6%	59	88.3%	76.9%	94.3%	6.2%	0.39
2.1.6 Follicular	37	92.9%	79.1%	97.7%	36	90.0%	72.1%	96.7%	39	94.2%	78.4%	98.6%	1.3%	0.82	55	94.7%	84.1%	98.3%	61	90.5%	79.7%	95.7%	76	97.3%	89.3%	99.3%	2.6%	0.48
2.1.7 NK/T-cell	33	54.8%	37.5%	69.2%	33	55.1%	36.4%	70.3%	38	63.8%	45.3%	77.5%	9.0%	0.44	29	51.9%	32.8%	68.0%	35	40.7%	25.3%	55.6%	58	63.0%	49.0%	74.1%	11.1%	0.32
2.1.8 Mucosa-associated lymphoid tissue (MALT)	10	83.4%	48.1%	95.6%	16	83.4%	56.8%	94.3%	25	100%	.	.	16.6%	0.12	26	88.1%	67.2%	96.0%	31	94.6%	80.1%	98.6%	46	95.4%	82.7%	98.8%	7.3%	0.31
2.1.9 Other non-Hodgkin lymphoma Not otherwise specified (NOS)	114	78.1%	68.5%	85.0%	91	82.8%	72.9%	89.4%	109	83.0%	73.9%	89.1%	4.9%	0.38	203	69.2%	62.3%	75.1%	177	72.8%	64.8%	79.3%	177	82.3%	75.4%	87.4%	13.1%	0.00
2.2 Hodgkin lymphoma	1448	93.2%	91.8%	94.4%	1523	94.2%	92.9%	95.3%	1885	95.0%	93.9%	95.9%	1.8%	0.03	1897	93.1%	91.9%	94.2%	1983	93.7%	92.5%	94.7%	2543	94.9%	94.0%	95.7%	1.8%	0.01

(*continued on next page*)

Table 3 (*continued*)

	25-39 years													
	2004-2006				2007-2009				2010-2014				Absolute difference 2010-2014 - 2004-2006	
	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Mean N+	RS	RS lower	RS upper	Diff.	pvalue
1. Leukemias and related disorders	3948	65.2%	63.7%	66.6%	4190	67.4%	65.9%	68.8%	5240	72.6%	71.3%	73.8%	7.4%	0.00
1.1 Acute lymphoblastic leukemia (ALL)	600	42.4%	38.2%	46.6%	614	42.3%	38.4%	46.2%	764	50.9%	47.1%	54.5%	8.4%	0.00
1.1.a ALL, B-cell	73	45.0%	30.9%	58.1%	104	52.7%	43.0%	61.6%	155	56.2%	47.9%	63.7%	11.2%	0.17
1.1.b ALL, T cell	34	58.3%	38.2%	73.9%	61	47.2%	35.0%	58.4%	94	46.6%	35.9%	56.5%	-11.7%	0.27
1.2 Acute myeloid leukemia (AML)	1454	48.3%	45.7%	50.9%	1491	50.8%	48.2%	53.3%	1815	55.7%	53.3%	58.0%	7.4%	0.00
1.2.a Acute promyelocytic leukemia (APL)	154	77.5%	70.4%	83.2%	177	82.2%	75.7%	87.2%	242	86.0%	80.7%	89.9%	8.5%	0.03
1.3 Chronic myeloid leukemia (CML)	782	83.1%	80.2%	85.6%	772	86.5%	83.8%	88.8%	924	91.5%	89.5%	93.2%	8.4%	0.00
2. Lymphomas	10098	83.2%	82.5%	84.0%	10736	86.0%	85.3%	86.6%	13771	87.8%	87.2%	88.4%	4.6%	0.00
2.1 Non-Hodgkin lymphomas	4502	77.4%	76.2%	78.6%	4865	80.9%	79.8%	82.0%	6289	83.8%	82.8%	84.7%	6.3%	0.00
2.1.1 Lymphoblastic	103	58.1%	48.3%	66.6%	106	55.2%	45.2%	64.2%	137	62.1%	53.1%	69.9%	4.0%	0.53
2.1.2 Burkitt	193	64.4%	57.4%	70.5%	221	71.0%	64.5%	76.5%	311	70.3%	64.8%	75.2%	6.0%	0.16
2.1.3 Diffuse large B-cell (DLBCL)	1450	75.0%	72.7%	77.1%	1656	79.2%	77.2%	81.1%	2150	82.1%	80.3%	83.7%	7.1%	0.00
2.1.4 Primary mediastinal large B-cell	72	79.1%	68.9%	86.3%	104	87.3%	78.9%	92.5%	194	92.3%	87.5%	95.3%	13.2%	0.01
2.1.5 Anaplastic T- and null-cell excluding NK/T-cell	123	73.1%	64.3%	80.0%	139	73.0%	64.9%	79.5%	168	77.1%	69.6%	83.1%	4.1%	0.44
2.1.6 Follicular	800	90.8%	88.5%	92.6%	874	92.9%	90.9%	94.4%	1168	94.4%	92.8%	95.6%	3.7%	0.00
2.1.7 NK/T-cell	201	53.5%	46.7%	59.9%	235	55.1%	48.5%	61.2%	330	61.2%	55.5%	66.5%	7.7%	0.08
2.1.8 Mucosa-associated lymphoid tissue (MALT)	210	90.5%	85.7%	93.8%	289	91.7%	87.9%	94.4%	438	94.0%	91.2%	96.0%	3.5%	0.13
2.1.9 Other non-Hodgkin lymphoma Not otherwise specified (NOS)	1118	73.5%	70.6%	76.1%	967	76.8%	73.9%	79.5%	1063	79.2%	76.4%	81.7%	5.7%	0.00
2.2 Hodgkin lymphoma	4658	91.2%	90.3%	92.0%	4984	92.4%	91.6%	93.2%	6490	93.3%	92.7%	93.9%	2.1%	0.00

* Based on EUROPEAN pool of 95 registries

+ Mean N is the average number of people alive at the start of the first interval in the cohorts of diagnosis included in the period survival analysis (Supplementary materials Fig. S1)

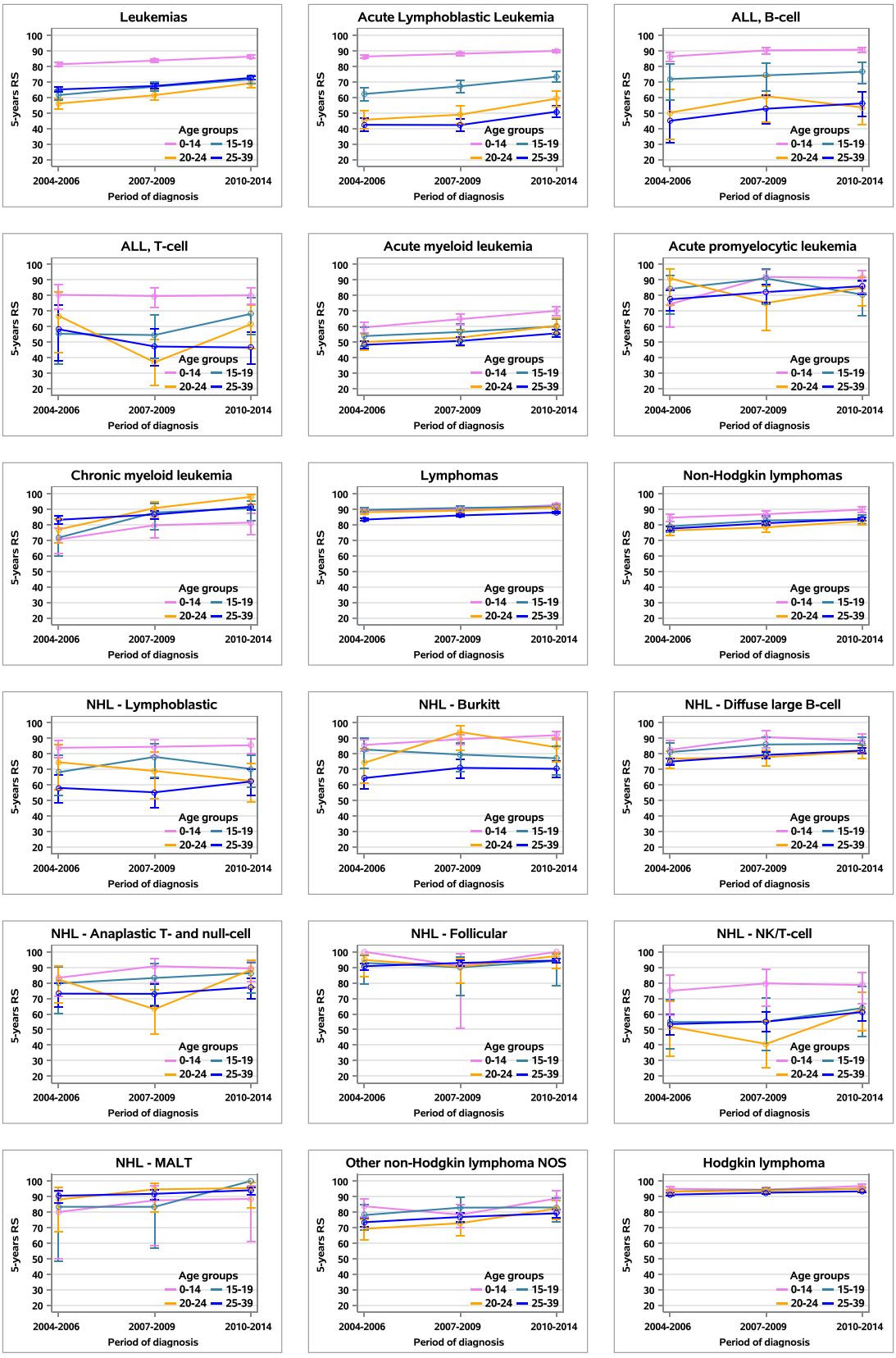

Fig. 2. Trends over time in five-year Relative Survival (RS) of children and AYAs diagnosed with a haematological malignancy in Europe by subtype and age at diagnosis, period estimates of 2004–2006, 2007–2009 and 2010–2014
* Based on EUROPEAN pool of 95 registries.

introduction of imatinib into the therapeutic algorithms of patients with CML at the beginning of the 2000s [24,37], children continue to have a lower survival than AYAs and older patients. Paediatric CML-patients have a slower molecular response when treated with imatinib compared to that of adults [38]. Altogether this suggests that CML is more aggressive in children than in AYAs and older people and may be partially responsible for the poorer survival observed.

Female sex was overall an indicator of better survival when compared to the male sex, in our analysis. Among AYAs, a higher survival was found for females with AML, NHL, NK/T-cell lymphoma, and the overall group of leukaemia and lymphomas. Within the paediatric age group, girls diagnosed with DLBCL and ALL had a higher survival. The reason for these differences in survival between sex is most likely multifactorial, including differences in specific tumour types (e.g., the predominance of boys with T-cell ALL [39]), different tumour genomics, and a differing pharmacological response to therapy as sex may act as a genetic modifier [40].

Our study has a number of limitations, including lack of information on molecular characterization and treatments received, which are not systematically collected by European CRs and the high proportion of ALL cases in which the phenotype information (B or T) is unknown, mainly due to the non-use of more specific codes by registries. Another limitation is the relatively old diagnostic period and end of the follow-up used for the analyses. However, we used the period approach to estimate the most up-to-date 5-year RS based on the available data [14] and our findings are consistent with national studies with more recent included diagnostic periods [11,12,22].

The strengths of this study include being the most up-to-date and providing real-world data (rather than projections or hypothetical models) on haematological cancers in AYAs across Europe. The large dataset considered (nearly 90,000 patients) allowed investigation of RS for different groups with rare haematological cancers. Lastly, population-based survival estimates reflect the survival of all patients with a certain cancer in the population covered by the registry, and thereby reflects overall real-world effectiveness of health care systems.

Despite improvements in survival for children and AYAs with haematological cancers between 2000 and 2013, differences between children and AYAs persist, which highlights the importance of close collaboration between paediatric and adult oncology teams. AYAs with cancer are a diverse group who are defined not simply by their age and particular cancer, but also by the challenges they face regarding access to age-appropriate cancer care, inclusion in clinical trials, short- and long-term health and psychosocial issues that include fertility considerations, transition to survivorship care and psychological support, and adherence to treatment difficulties. Therefore, dedicated AYA services should have environments suited to the age and psychology of AYA patients who should be supported by a multidisciplinary team (MDT) familiar with their needs and with paediatric and adult practices. However, in the EU we do not have a consensus on AYA dedicated programme(1). The upcoming Network of Expertise on AYAs with cancer has among its priorities reaching a consensus on what a program dedicated to AYAs should consist of (https://jane-project.eu/). Future studies are also needed to better understand the needs of this unique patient group and ultimately increase survival.

Ethics approval

We analysed pseudonymized data collected from 95 population-based cancer registries, after approval by the Ethics Committee of the National Cancer Institute of Milan (INT 73/16; April 21, 2016). We hold these data in trust from each participating registry for the statistical analysis agreed on in the EUROCARE-6 protocol, available at http://www.eurocare.it.

Data statement

We are not permitted to share individual data. Aggregated-level data, in the form of counts, rates or survival proportions, can only be shared upon express permission from the participating registries. These data should be requested by contacting the corresponding author or Eurocare Secretariat (eurocare.secretariat@istitutotumori.mi.it).

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CRediT authorship contribution statement

Annalisa Trama: Conceptualization, Project administration, Supervision, Writing – original draft, writing – review and editing. **Emma E. Geerdes:** Writing – original draft, writing – review and editing. **Elena Demuru:** Data curation, Formal analysis, Writing – original draft, writing – review and editing. **Roberta De Angelis:** Supervision, Writing – original draft, writing – review and editing. **Henrike Karim-Kos:** Supervision, Writing – review and editing. **Xavier Troussard:** Writing – review and editing. **Damien Bennett:** Writing – review and editing. **Rafael Marcos-Gragera**: Writing – review and editing. **Claudia E. Kuehni:** Writing – review and editing. **Hanhua Liu:** Writing – review and editing. **Alice Bernasconi:** Writing – review and editing. **Claudia Vener:** Writing – review and editing. **Marcela Guevara:** Writing – review and editing. **Christian M. Zwaan:** Writing – review and editing. **Alexandra Mayer-da-Silva:** Writing – review and editing. **Keiu Paapsi:** Writing – review and editing. **Rosalia Ragusa:** Writing – review and editing. **Owen P. Smith:** Conceptualization, Writing – original draft, writing – review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115336.

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