Survival disparities between children and adolescents and young adults for the major subtypes of non-Hodgkin lymphoma in the Netherlands: a large population-based study

Non-Hodgkin lymphoma (NHL) is a relatively common type of cancer in children and adolescents and young adults (AYA).[1,2] The most prevalent histological subtypes occurring in both groups are T-lymphoblastic lymphoma (T-LBL), Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), and anaplastic large cell lymphoma (ALCL).[3,4]

AYA with NHL have poorer survival compared with pediatric patients.[5-7] The causes for this survival gap may be related to differences in disease biology, treatment, therapy-related toxicities, and sociological and psychosocial factors.[3] Although NHL is a heterogeneous disease, subtype-specific survival disparities between children and AYA have solely been reported in a few US population studies.[4,5,8,9] Findings may, however, differ for the Netherlands and other highly developed countries with compulsory health insurance and complete coverage of costs related to treatment. In the Netherlands, the age cutoff for treatment at a pediatric oncology center is 18 years. Therefore, we aimed to investigate potential survival disparities between all children (age, 0-17 years) and AYA (age, 18-39 years) diagnosed with NHL in the Netherlands between 1990-2015 for the major histological subtypes occurring in both age groups.

Data were retrieved from the nationwide population-based Netherlands Cancer Registry (NCR), which contains basic data regarding patient, tumor, and primary treatment started within 1 year of diagnosis.[10] Registration of rituximab use has been complete since 2007. Patients were selected using International Classification of Childhood Cancer (3rd edition) diagnostic groups IIb, IIc, and IIe. The histological subtypes were defined according to the 2008 World Health Organization classification[11] using International Classification of Diseases for Oncology (3rd edition) morphology codes: T-LBL - 9727, 9729, 9837; BL - 9687; DLBCL - 9678-9680, 9684, 9688, 9712, 9735, 9737-9738; ALCL - 9714-9715. The NCR data are extensively validated conforming to the comprehensive and standardized list of data quality checks from the European Network of Cancer Registries. Data quality checks were the same for children and AYA.

All analyses were stratified by histological subtype. Survival time was calculated from diagnosis until death or last follow-up (emigration or February 1, 2021). Five-year relative or disease-specific survival was determined by taking the ratio of the patients' overall survival to the expected survival of an age-, sex-, and calendar year-matched cohort from the general population. Poisson regression was used to test for linear trends in relative survival across the diagnostic periods (1990-1999, 2000-2009, 2010-2015) and to evaluate the association between age and excess mortality within 5 years of diagnosis while adjusting for patient mix. Patients diagnosed by autopsy were excluded from the survival analyses (n=7). Patients who died on the day of diagnosis were included with a follow-up of 1 day (n=18).

Between 1990-2015, 1,031 children and 4,608 AYA were diagnosed with NHL in the Netherlands. The distribution of the subtypes (i.e., T-LBL, BL, DLBCL, and ALCL) varied considerably, with BL being most common among children (33%) and DLBCL among AYA (41%). Additionally, large differences in initial treatment were observed across the age groups regardless of subtype (Table 1). In 2010-2015, rituximab was given to 67% of AYA with BL and 93% of AYA with DLBCL compared to only 11% and 49% of children, respectively (*data not shown*).

For T-LBL, 5-year relative survival was 23 percent-points higher in children than AYA (78% *vs*. 55%; Figure 1A; *Online Supplementary Table S1*). Survival improved over time by a fairly equal extent in both age groups, reaching 82% in children and 60% in AYA. In 2010-2015, survival progressively worsened with age from 92% in 0-9 year-olds to 54% in 30-39 year-olds (Figure 2A).

Overall, children with BL had a 24 percent-point higher 5-year relative survival than AYA (87% *vs*. 63%; Figure 1B; *Online Supplementary Table S1*). The survival gap decreased considerably over time due to the marked survival improvement among AYA from 48% to 79%. Survival of children also increased, albeit more modest from 83% to 90%. In 2010-2015, only survival of 30-39 year-olds remained lagging behind that of the other age groups (67% *vs*. 88-92%; Figure 2B).

Regarding DLBCL, 5-year relative survival was approximately 75% in children and AYA (Figure 1C; *Online Supplementary Table S1*). Survival improved significantly over time in both age groups from about 60% to 88%. Detailed analyses did not reveal any survival disparities in 2010-2015 either (Figure 2C).

Five-year relative survival of ALCL was 79% in children, which was not significantly higher than the 72% observed in AYA (Figure 1D; *Online Supplementary Table S1*). Increasing survival trends were noted, resulting in survival probabilities of 90% in children and 86% in AYA. Moreover, survival did not significantly differ across the more detailed age categories in 2010-2015 (Figure 2D).

Sensitivity analyses using an alternative age cutoff of 15 years to delineate children and AYA retrieved similar results (*data not shown*).

Table 1. Characteristics of children (0-17 years old) and adolescents and young adults (18-39 years old) diagnosed with non-Hodgkin lymphoma in the Netherlands between 1990-2015 by the most common subtypes.

Characteristics	T-LBL							BL[a]							DLBCL							ALCL						
	Total		Children		AYA			Total		Children		AYA			Total		Children		AYA			Total		Children		AYA		
	N	%	N	%	N	%	$P(\chi^2)$[b]	N	%	N	%	N	%	$P(\chi^2)$[b]	N	%	N	%	N	%	$P(\chi^2)$[b]	N	%	N	%	N	%	$P(\chi^2)$[b]
Overall	361		205		156			569		341		228			2,061		197		1,864			319		102		217		
Period of diagnosis							0.62							0.68							0.80							0.69
1990-1999	153	42.4	89	43.4	64	41.0		221	38.8	137	40.2	84	36.8		728	35.3	71	36.0	657	35.3		121	37.9	37	36.3	84	38.7	
2000-2009	122	33.8	65	31.7	57	36.5		226	39.7	134	39.3	92	40.4		849	41.2	77	39.1	772	41.4		130	40.8	45	44.1	85	39.2	
2010-2015	86	23.8	51	24.9	35	22.4		122	21.4	70	20.5	52	22.8		484	23.5	49	24.9	435	23.3		68	21.3	20	19.6	48	22.1	
Median age at diagnosis in years (IQR)	14	(8-25)	9	(5-12)	27	(21-33)	-	13	(7-27)	8	(5-12)	31	(24-35)	-	31	(24-36)	14	(10-16)	32	(26-36)	-	24	(15-32)	12	(8-15)	29	(24-34)	-
Sex							0.002							<0.001							0.88							0.66
Male	274	75.9	143	69.8	131	84.0		449	78.9	286	83.9	163	71.5		1,276	61.9	121	61.4	1,155	62.0		184	57.7	57	55.9	127	58.5	
Female	87	24.1	62	30.2	25	16.0		120	21.1	55	16.1	65	28.5		785	38.1	76	38.6	709	38.0		135	42.3	45	44.1	90	41.5	
Ann Arbor stage							0.04							<0.001							0.98							0.16
I	60	16.6	35	17.1	25	16.0		105	18.5	58	17.0	47	20.6		661	32.1	60	30.5	601	32.2		54	16.9	11	10.8	43	19.8	
II	65	18.0	43	21.0	22	14.1		113	19.9	72	21.1	41	18.0		513	24.9	49	24.9	464	24.9		88	27.6	33	32.4	55	25.4	
III	63	17.5	41	20.0	22	14.1		96	16.9	76	22.3	20	8.8		270	13.1	26	13.2	244	13.1		74	23.2	25	24.5	49	22.6	
IV	133	36.8	62	30.2	71	45.5		237	41.7	125	36.7	112	49.1		563	27.3	57	28.9	506	27.2		90	28.2	31	30.4	59	27.2	
Unknown	40	11.1	24	11.7	16	10.3		18	3.2	10	2.9	8	3.5		54	2.6	5	2.5	49	2.6		13	4.1	2	2.0	11	5.1	
Primary treatment							<0.001							<0.001							<0.001							0.001
CT[c]	257	71.2	183	89.3	74	47.4		404	71.0	310	90.9	94	41.2		822	39.9	133	67.5	689	37.0		236	74.0	91	89.2	145	66.8	
CT + RT[d]	28	7.8	7	3.4	21	13.5		30	5.3	9	2.6	21	9.2		380	18.4	13	6.6	367	19.7		40	12.5	6	5.9	34	15.7	
CT + rituximab[e]	0	0.0	0	0.0	0	0.0		62	10.9	9	2.6	53	23.3		647	31.4	39	19.8	608	32.6		4	1.3	0	0.0	4	1.8	
SCT[f]	67	18.6	8	3.9	59	37.8		60	10.5	8	2.4	52	22.8		62	3.0	3	1.5	59	3.2		25	7.8	3	2.9	22	10.1	
Other/no treatment/ unknown	9	2.5	7	3.4	2	1.3		13	2.3	5	1.5	8	3.5		150	7.3	9	4.6	141	7.6		14	4.4	2	2.0	12	5.5	
Other[g]	0	0.0	0	0.0	0	0.0		4	0.7	2	0.6	2	0.9		77	3.7	4	2.0	73	3.9		8	2.5	0	0.0	8	3.7	
No treatment	7	1.9	5	2.4	2	1.3		8	1.4	2	0.6	6	2.6		63	3.1	5	2.5	58	3.1		6	1.9	2	2.0	4	1.8	
Unknown	2	0.6	2	1.0	0	0.0		1	0.2	1	0.3	0	0.0		10	0.5	0	0.0	10	0.5		0	0.0	0	0.0	0	0.0	

T-LBL: T-lymphoblastic lymphoma; BL: Burkitt lymphoma; DLBCL: diffuse large B-cell lymphoma; ALCL: anaplastic large cell lymphoma; AYA: adolescents and young adults; IQR: interquartile range; CT: chemotherapy; RT: radiation therapy; SCT: stem cell transplantation; ICCC-3: International Classification of Childhood Cancer, 3rd edition. [a]BL corresponds to ICCC-3 diagnostic group IIc. [b]Fisher's exact test was used instead of Pearson's χ^2 test when N≤5 in 1 or more categories. [c]CT only, not treated with RT, rituximab or SCT. [d]Treated with CT and RT; not treated with rituximab or SCT. [e]Treated with CT and rituximab independent of RT; not treated with SCT (patients treated with rituximab, who did not receive CT, were also included in this category). [f]Treated with SCT independent of CT, RT or rituximab. [g]"Other treatment" encompassed all patients who did receive any type of therapy, but could not be classified in 1 of the other treatment groups, e.g., patients who only received RT or surgery.

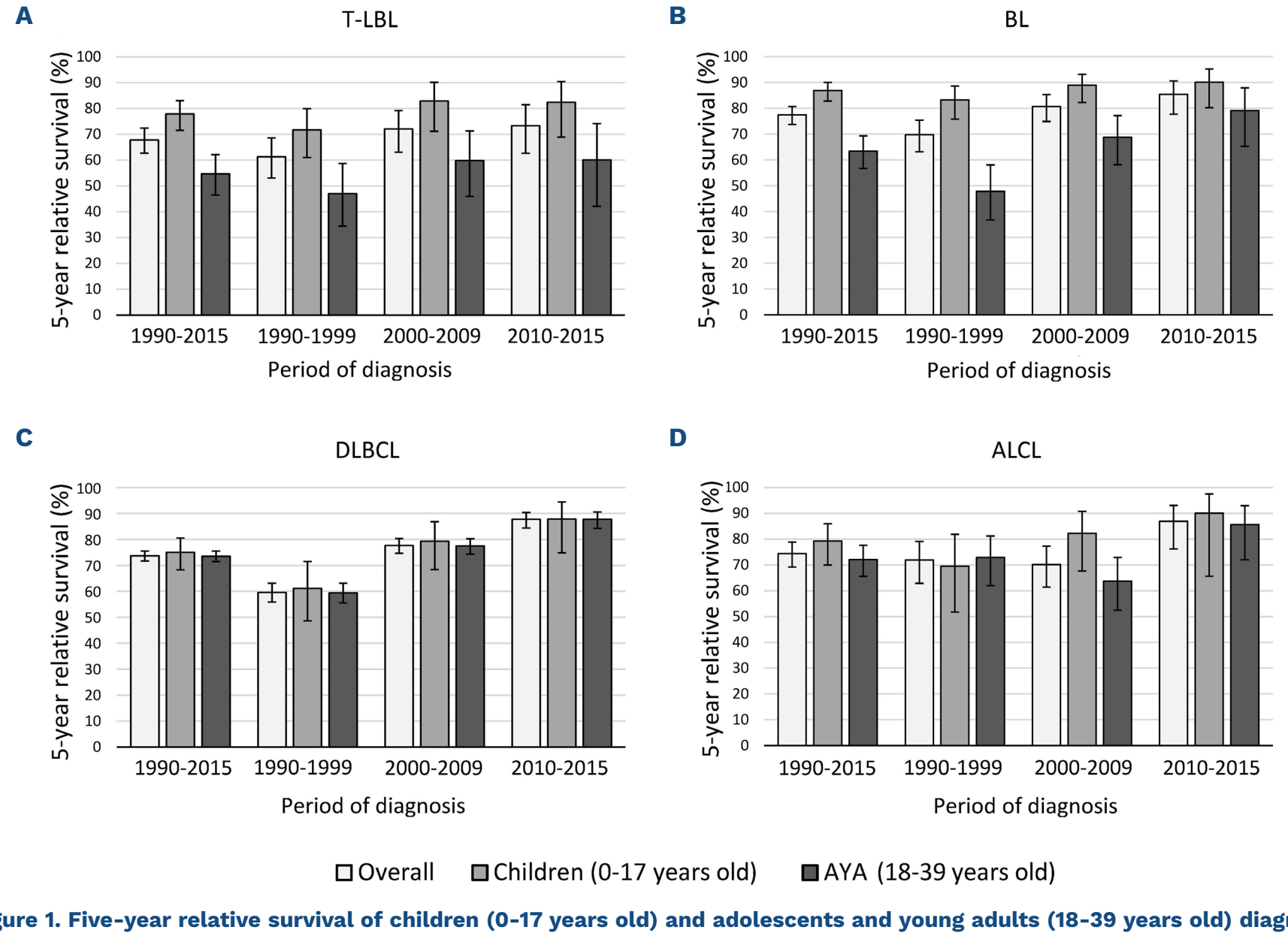

Figure 1. Five-year relative survival of children (0-17 years old) and adolescents and young adults (18-39 years old) diagnosed with the most common subtypes of non-Hodgkin lymphoma in the Netherlands between 1990-2015, overall and by diagnostic period. (A) T-lymphoblastic lymphoma (T-LBL); (B) Burkitt lymphoma (BL); (C) diffuse large B-cell lymphoma (DLBCL); (D) anaplastic large cell lymphoma (ALCL). The error bars depict 95% confidence intervals of the survival estimates. AYA: adolescents and young adults.

Multivariable regression analyses adjusting for patient mix confirmed the findings for T-LBL, BL, and DLBCL showing a significantly increased excess mortality in AYA compared with children during 1990-2015 for T-LBL and BL, but not DLBCL (*Online Supplementary Table S2*). Although 5-year relative survival of AYA with ALCL was not significantly lower than that of children in 1990-2015, the multivariable-adjusted excess mortality was significantly increased.

In this Dutch population study spanning 26 years, AYA with T-LBL and BL had a worse prognosis than children. Nonetheless, the survival disadvantage for BL solely persisted for 30-39 year-olds in 2010-2015. AYA with ALCL had an increased excess risk of dying after patient-mix adjustment. Children and AYA with DLBCL had similar outcomes.

The inferior prognosis of AYA with T-LBL is in line with US SEER data showing a substantial survival gap between children and AYA with LBL.[4] Nowadays, children and AYA with T-LBL in the Netherlands are treated according to intensive acute lymphoblastic leukemia-based chemotherapy regimens. Before 2005, pediatric protocols contained higher doses of non-myelotoxic chemotherapy, were more strictly timed, and had a longer total duration than adult protocols (*Online Supplementary Table S3*). One crucial difference that persists is the substantial use of stem cell transplantation (SCT) in AYA in first complete remission, while SCT is reserved for very high-risk patients in pediatric protocols. Biological differences are likely to have contributed to the inferior survival of AYA as well, though the understanding of the molecular characteristics of T-LBL is still limited.

Similar to our overall findings, AYA with BL were reported to have inferior survival in the US population.[4,5,9] Nonetheless, we showed that worse outcome was restricted to AYA aged 30-39 years in 2010-2015. Children with BL in the Netherlands are treated with risk-adjusted dose-intensive multi-agent chemotherapy. Treatment of adult BL is generally less dose-intensive, though there was no standard first-line therapy during 1990-2015 (*Online Supplementary Table S3*). As of 2003-2004, rituximab was incorporated into adult regimens, a major step in improving outcomes.[12] Rituximab was included in pediatric regimens for mature B-NHL almost 10 years later, and only for high-risk patients.[13] A decrease in treatment tolerability with increasing age

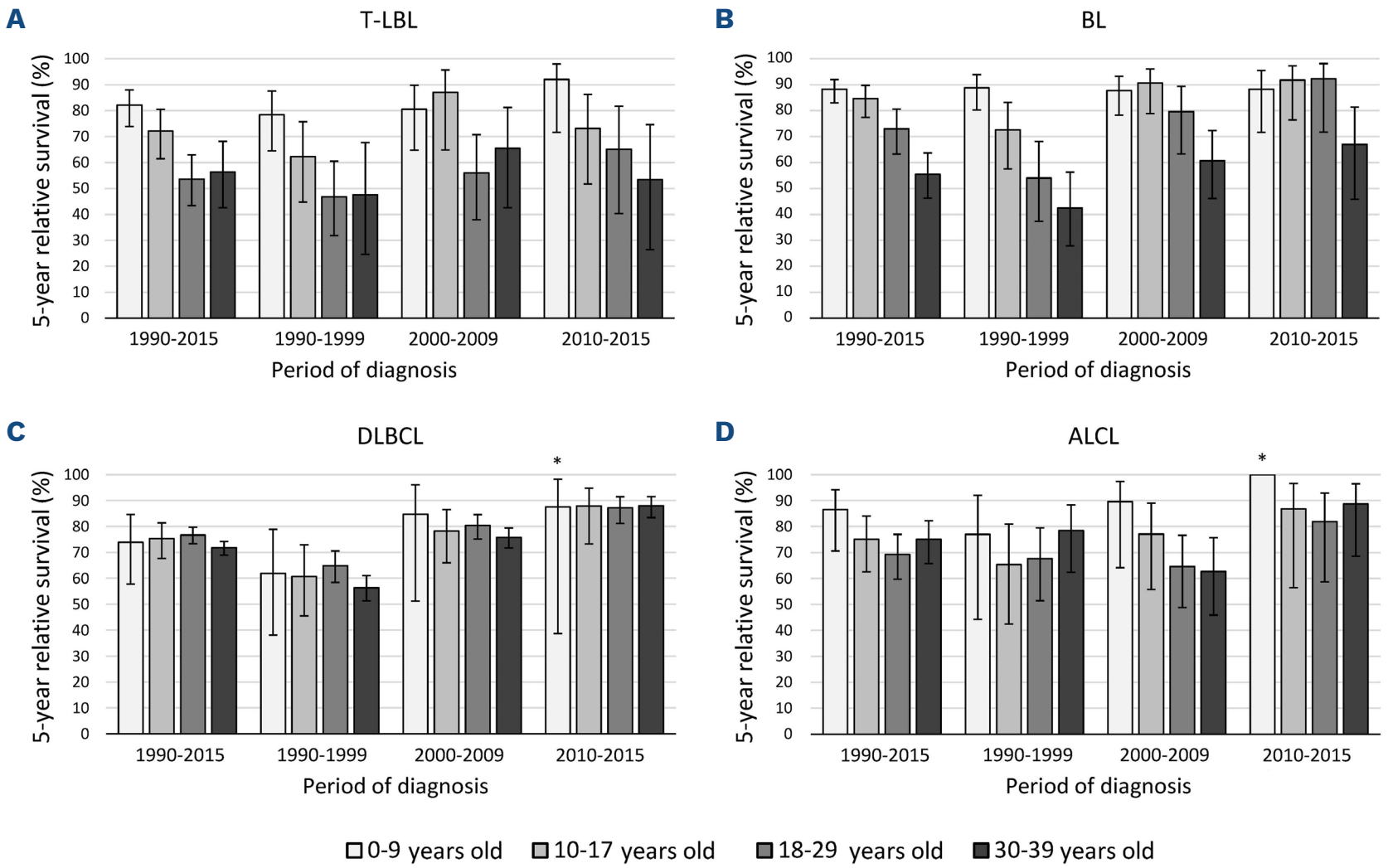

Figure 2. Age-specific 5-year relative survival of children and adolescents and young adults (0-39 years old) diagnosed with the most common subtypes of non-Hodgkin lymphoma in the Netherlands between 1990-2015, overall and by diagnostic period. (A) T-lymphoblastic lymphoma (T-LBL); (B) Burkitt lymphoma (BL); (C) diffuse large B-cell lymphoma (DLBCL); (D) anaplastic large cell lymphoma (ALCL). The error bars depict 95% confidence intervals of the survival estimates. *N at risk <10.

could explain why survival of older AYA with BL continued to lag behind. Furthermore, the study by Burkhardt *et al.*[14] revealed a transition in the mutational profile of BL between the ages of 25 and 40 years.

In contrast to US data,[5,8] survival of children and AYA with DLBCL in the Netherlands was comparable. Insurance barriers may negatively affect survival of AYA in the US, while costs of cancer treatments are entirely covered in the Netherlands. Dutch children with DLBCL are treated with the same intensive chemotherapy protocols as pediatric BL patients. Since the early 2000s, less dose-intensive rituximab-containing cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) protocols have been the standard of care for adult DLBCL (*Online Supplementary Table S3*). As mentioned above, rituximab just became available for high-risk pediatric mature B-NHL in the latest period of our study. Additionally, central nervous system (CNS) prophylaxis is standard part of pediatric regimens, but is only added to R-CHOP for adult patients at high risk for CNS relapse.[3] Although we had no individual details available concerning chemotherapy intensity, based on the commonly used treatment protocols it is likely that AYA with DLBCL received less chemotherapy than children. The similar survival estimates therefore raise the question whether chemotherapy intensity could safely be reduced for children with (early-stage) DLBCL without impacting cure. Considering the lower risk of acute toxicities and late adverse effects, treatment reduction for pediatric DLBCL should be further studied.

Our findings regarding ALCL were inconclusive, but may indicate a slightly worse outcome for AYA, which would be in agreement with US data.[4] Dutch children with ALCL have been treated uniformly since 2000 using a short intensive B-NHL-derived regimen (ALCL99 protocol), while adult treatment generally consisted of CHOP sometimes followed by SCT (*Online Supplementary Table S3*). Two subgroups of systemic ALCL are distinguished depending on anaplastic lymphoma kinase (ALK) protein expression.[11,15] The relative frequency of the less favorable ALK-negative variant increases with age,[2,3,15] which might explain the modestly increased excess risk of dying among AYA with ALCL in our study. Unfortunately, ALK expression status was not registered in the NCR before 2014. The population-based nature (i.e., the inclusion of trial and non-trial participants) and relatively large cohort size pose important strengths of our study. More detailed information on treatment, therapy-related toxicities, molecular characteristics, and cause of death would be of value in future investigations.

Studies like ours, comparing survival of children and AYA, may serve as a bridge and point towards aspects of therapy regimens that justify further investigation. Our observation

that dose-intensively treated children with DLBCL have similar survival as AYA, who are likely to have been treated less intensively, suggests that it might be worth investigating treatment reductions for (early-stage) pediatric DLBCL, while keeping age-related differences in disease biology in mind.

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Contributions

HEKK, AB and JLCL conceived and designed the study. MS did the literature search. HEKK and MS prepared the database and carried out the analysis. MS drafted the manuscript. All authors contributed to the interpretation of the results and critically revised the manuscript. HEKK and MS directly accessed and verified the raw data and take responsibility for the integrity and accuracy of the analyses. All authors had full access to all the data reported in the study and accept responsibility to submit the paper for publication.

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Data-sharing statement

The data that support the findings of our study are available on request from the Netherlands Cancer Registry. To obtain data of children diagnosed with cancer in the Netherlands since 2014, an additional permission from the Biobank and Data Access Committee of the Princess Máxima Center for Pediatric Oncology is required. Further information is available from the corresponding author.

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