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Original Research

Progress against non-Hodgkin's lymphoma in children and young adolescents in the Netherlands since 1990: Stable incidence, improved survival and lower mortality

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Abstract ***Background:*** With epidemiologic analyses of population-based trends in incidence and outcomes, we ascertained progress against non-Hodgkin's lymphoma (NHL) in children and young adolescents in the Netherlands since 1990.
Methods: Tumour characteristics were extracted from the Netherlands Cancer Registry for patients aged <18 years at diagnosis, between 1990 and 2015. Mortality data for 1980–2016 were derived from Statistics Netherlands. NHL subtypes comprised lymphoblastic lymphoma (LBL), Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL) and anaplastic large cell lymphoma (ALCL). Time trends in incidence and mortality rates and 5-year overall survival (OS) rates were evaluated by average annual percentage change (AAPC) analyses and parametric survival models, respectively.
Results: Overall incidence of NHL remained stable at 11 per million person-years (AAPC -0.2%, $p = 0.68$), with a marked decrease among children of 5–9 years (AAPC -2.6%, $p < 0.01$), especially among those with BL. Treatment regimens comprised less radiotherapy

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over time, especially for LBL and BL. Since 2004, most 15–17-year-old patients with NHL have been treated at a paediatric oncology centre. Five-year OS improved from 71% in 1990–94 to 87% in 2010–15 ($p < 0.01$), the most gain has been achieved in patients with DLBCL and ALCL from 60% and 73%, respectively, to both 90%. Population-based mortality from NHL decreased significantly towards 1.4 per million person-years (AAPC -4.2%, $p < 0.01$).

Conclusions: This population-based epidemiological study exhibited significant progress against childhood and young adolescent NHL in the Netherlands since 1990, before the advent of a national paediatric oncologic centre in 2018: incidence decreased among children of 5–9 years, survival improved, and mortality steadily decreased over time.

1. Introduction

Non-Hodgkin's lymphoma (NHL) is the third most common cancer in children and young adolescents in the Netherlands [1], comprising immature and mature B- or T-cell NHL: Burkitt lymphoma (BL), diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma (LBL: precursor T- and B-cell or immature NHL) and anaplastic large cell lymphoma (ALCL, a mature T-NHL), as major subtypes [2]. These subtypes account for approximately 90% of NHL cases. Incidence rates for NHL in Western countries are 5–6 per million children younger than 15 years and 10–17 per million at age 15–19 years [3–5]. Prognosis for NHL depends on subtype, stage of disease, somatic genetic aberrations and response [6,7].

Few publications exist of the combined trends in incidence, survival and mortality for children (<15 years) and young adolescents (15–17 years) diagnosed with NHL. In the Netherlands, these children were mostly treated in seven specialised centres for paediatric oncology according to standardised (inter)national treatment protocols [8]. Treatment of NHL depends on the cell type involved. Initiated in the 1970s, application of acute lymphoblastic leukaemia (ALL)-based regimens for LBL proved to be most effective [9,10]. For mature B-NHL, a 4-drug regimen (including cyclophosphamide, vincristine, doxorubicin and corticosteroids) was more effective than the 10-drug ALL regimen. In the 1980s, high-dose methotrexate and cytarabine were incorporated into treatment regimens for children with B-cell NHL, as exemplified by the total B-regimen [11,12]. Treatment of ALCL was based on mature B cell-like treatment protocols during 4–6 months. In 1999, the ALCL99 protocol was implemented with a prephase, six courses and for high-risk ALCL, followed by randomised administration of vinblastine maintenance [13,14].

Given all these therapeutic changes and tendency towards centralisation in centres for paediatric haemato-oncology, we assessed progress made against NHL in children and young adolescents in the Netherlands by performing epidemiologic analyses of trends in incidence, survival and mortality based on data from the population-based Netherlands Cancer Registry (NCR). Detailed trend analyses were made by NHL subtypes (i.e. LBL, BL, DLBCL and ALCL), stage at diagnosis, centre and type of treatment.

The results of this study will provide an up-to-date nationwide and population-based overview of children and young adolescents with NHL diagnosed and treated before the centralisation of paediatric haemato-oncology care in one single centre in the Netherlands. Future studies should therefore be able to evaluate the effects of concentration of care for children with cancer.

2. Patients and methods

2.1. Patient selection and data sources

Patients aged <18 years and diagnosed with NHL during 1990–2015 were extracted from the NCR which registers all newly diagnosed cancers in the Netherlands, irrespective of patients' age or hospital [15], based on case notification through the National Network and Registry of Histopathology and Cytopathology (PALGA) and the National Registry of Hospital Discharges (inpatient and outpatient). Trained registrars of the NCR extract data on basic patient and tumour characteristics and primary therapy through extensive medical records review. Information on vital status (alive, dead or emigrated) is obtained through annual linkage with the Nationwide Personal Record Database (BRP) that holds vital statistics on all Dutch residents. The last linkage was on 1st February 2019.

Disease-specific mortality data from 1980 to 2016 were derived from Statistics Netherlands [16], using the NHL-specific International Classification of Diseases (ICD)-9 codes 200 and 202 and ICD-10 codes C82–C85 presented per 5-year age groups at death. Mortality data included patients who died from NHL up to age 19.

2.2. Defining subgroups

We distinguished LBL, BL, DLBCL and ALCL, being defined according to the 2008 World Health Organisation (WHO) classification scheme, which also incorporated the International Classification of Diseases for Oncology (ICD-O) [17,18] and the International Classification of Childhood Cancers (ICCC-3) [19] (Supplementary Table S1). The total group of NHL corresponds to the ICCC-3 diagnostic groups IIb, IIc and IIe, and BL refers to ICCC-3 diagnostic group IIc. The number of cases in ICCC-3 diagnostic group IIe, the so-called unspecified lymphomas, was very low during the whole study period (<5 cases in total). Stage was classified using the Ann Arbor staging system for lymphomas [20]. Advanced stage of NHL was defined as Ann Arbor stage IV [21]. NCR data further included primary therapy codes for, that is, surgery, radiotherapy (RT) and systemic chemotherapy (CT). Central review of pathological specimens was not standard practice in the Netherlands. Therefore, we have used the morphology codes as entered in the NCR database. The accuracy of these morphology codes was assessed by checking the pathology reports and medical files from a sample of the patient population. One-fifth of the patients were checked, and in 98% of the patients, these codes were matching.

Incidence and survival analyses of time trends were performed for age groups 0–4, 5–9, 10–14 and 15–17 years, categorised by aforementioned NHL subtypes. Mortality analyses were performed for age groups 0–4, 5–9, 10–14 and 15–19 only. Period of diagnosis was defined in five intervals: 1990–94, 1995–99, 2000–04, 2005–09 and 2010-15, the latter covering six years. Patients with an unknown stage (N = 59, 6% of the total study population) were excluded in stage-specific analysis. Patients could have been primarily treated in a University Medical Centre (UMC) setting or a non-academic setting. From 2004 onwards, we could split the UMC treated patients in paediatric oncology or adult haematology ward [8]. Primary treatment was defined as CT-only or CT+RT. Twelve patients without or unknown treatment (1%) were excluded from the treatment analysis. The 22 patients who received autologous stem cell transplantations (2%) were included in the CT-only group. Rituximab was given to patients with $CD20^+$ lymphoma on individual basis since 2004 [22,23] and implemented in a mature B-cell protocol that started in the Netherlands in 2014. Addition of immunotherapy (IT) is considered a third treatment group CT + IT (n = 47).

2.3. Statistical analyses

Characteristics of the study population by period, age or NHL subtypes were proportionally tested with chi-square tests and differences in median age by subgroup with Kruskall-Wallis.

Annual incidence and mortality rates were calculated per 1 million person-years, using mid-year population size from Statistics Netherlands. Rates were age-adjusted according to the World Standard Population for 0–17 years for estimation of incidence rates and 0–19 years for mortality rates [24].

Average annual percent changes (AAPCs) of incidence rates during 1990–2015 were estimated from linear regression modelling, calendar year being a continuous variable [24]. AAPC analyses also include 95% confidence interval (CI) and p-values. AAPCs of mortality rates were analysed from 1980 onwards per 5-year periods. The last period, 2010–2016, included 7 years. Joinpoint regression analysis was used to check for trend transitions during the study period (Joinpoint program, version 4.7.0.0).

Survival time was calculated as the time elapsed between the date of diagnosis and the date of death of any cause (event) or date at last follow-up (alive, censored). Two patients with an NHL diagnosis were discovered at autopsy and excluded from survival analyses. Traditional cohort-based survival analysis was used to calculate observed survival at 5 and 10 years after diagnosis instead of relative survival, because competing causes of death among childhood and young adolescent cancer patients were rare in the Netherlands [25]. Time trends in observed 5- and 10-year survival were evaluated by using parametric survival models (*streg*). To estimate improvement over time, risk of dying by period of diagnosis was modelled, adjusted for follow-up time (in years). Age, gender, stage at diagnosis and therapeutic strategy were entered in the model to evaluate the effect of period of diagnosis. A p-value <0.05 was considered statistically significant. Statistical analyses were performed with STATA/SE 16.1 (StataCorp LP, College Station, Texas, USA).

2.4. Ethical consideration

Use of data obtained without explicit consent for this study was approved by the Privacy Review Board of the NCR, after the principles of a Code of Good conduct of the Dutch Federation of Medico-scientific Societies, www.federa.org.

3. Results

3.1. Patient and tumour characteristics

Between 1990 and 2015, NHL was diagnosed in 1001 children and young adolescents aged <18 years. Mature B-NHL was most common with 599 patients and 60% of all patients with NHL, comprised 350 BL (58%), 180 DLBCL (30%) and 69 mature B-NHL (i.e. marginal zone and follicular lymphoma, 12%) diagnoses. Immature NHL (LBL) accounted for 241 patients (24% of all

patients with NHL), T-LBL being the most predominant (80%) within this group. Patients with mature T-NHL (n = 161, 10% of all patients with NHL) comprised ALCL (61%) and other mature T-NHL (predominantly peripheral T/natural killer-cell lymphoma, not otherwise specified, 39%) (Table 1; Supplementary Table S1).

Median age of patients significantly differed from nine years for LBL to 10 for mature B-NHL and 12 for mature T-NHL ($p < 0.01$) (Table 1). During this 26-year diagnostic period, only 11 infants (<1 year, 1%) were diagnosed with NHL. Fig. 1 shows the distribution of NHL subtypes per age group. BL is more common in children (<15 years), whereas DLBCL is diagnosed most in young adolescents. The male:female ratio was about 3 for mature B-NHL, 2 for immature NHL and 1.5 for mature T-NHL ($p < 0.01$). No differences in stage distribution were observed between the various NHL subtypes.

Regarding the stage distribution over time, an increase in unknown stages was seen in the latest period for the total NHL group, from 4% in 1990–94 to 12% in 2010–15 ($p = 0.003$). After excluding unknown stages, no significant changes were observed ($p = 0.25$). The same pattern was seen for LBL (Fig. 2). For BL, a significant shift towards Ann Arbor stages III and IV was seen after excluding unknown stages ($p = 0.03$). Advanced stage BL increased from 33% in 1990–94 to

Table 1
Characteristics of patients with non-Hodgkin's lymphoma (NHL) aged <18 years diagnosed in the Netherlands, 1990–2015.

	All lymphomas[a]		Annual average N	Immature NHL		Mature B-NHL		Mature T-NHL		*p*-value[b]
	N	%		N	%	N	%	N	%	
Row, N %	1001	100%	38	241	24%	599	60%	161	16%	
Age (yrs)										
0–4	173	17%	6	59	24%	93	16%	21	13%	**<0.01**
5–9	291	29%	11	75	31%	181	30%	35	22%	
10–14	311	31%	12	79	33%	177	30%	55	34%	
15–17	226	23%	9	28	12%	148	25%	50	31%	
Median age (IQR;yrs)	10 (6–14)			9 (5–12)		10 (6–14)		12 (8–15)		**<0.01**
Gender										**<0.01**
Male	702	70%	27	162	67%	443	74%	97	60%	
Female	299	30%	11	79	33%	156	26%	64	40%	
Period of diagnosis										0.10
1990–94	199	20%	40	63	26%	103	17%	33	20%	
1995–99	190	19%	38	42	17%	124	21%	24	15%	
2000–04	177	18%	35	32	13%	113	19%	32	20%	
2005–09	196	20%	39	45	19%	119	20%	32	20%	
2010–15[c]	239	24%	40	59	24%	140	23%	40	25%	
Stage										0.61
I	205	22%	8	44	20%	138	24%	23	17%	
II	217	24%	8	51	24%	130	23%	36	27%	
III	189	21%	7	45	21%	113	20%	31	23%	
IV	307	33%	12	76	35%	186	33%	45	33%	
Unknown (N = 59, 6%)	59[d]	(6%)		25	(10%)	32	(5%)	2[d]	(1%)	
Treatment in UMC										0.08
No	110	11%	4	18	8%	76	13%	16	10%	
Yes	891	89%	34	223	92%	523	87%	145	90%	
Histologic category										
precursor B-cell LBL	49	5%	**2**	49	20%					
precursor T-cell LBL	192	19%	**7**	192	80%					
Burkitt lymphoma[e]	350	35%	13			350	58%			
DLBCL	180	18%	**7**			180	30%			
Other mature B-cell lymphoma[f]	69	7%	3			69	12%			
ALCL	98	10%	4					98	61%	
Other mature T-cell lymphoma[f]	63	6%	2					63	39%	

LBL, lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma; ALCL, anaplastic large cell lymphoma; IQR, InterQuartile Range; UMC, University Medical Centre.
Note: Because of rounding-off, average annual numbers may not add up to total number.
Bold values indicate statistical significance.
Source: Netherlands Cancer registry.
[a] The total group of NHL corresponds to the ICCC-3 diagnostic groups IIb, IIc and IIe.
[b] p-values based on the chi-square test for differences across categories and Kruskall-Wallis for median age.
[c] 6-year period.
[d] Stage is not recorded for cutaneous T-cell lymphomas in the Netherlands Cancer Registry, N = 24.
[e] BL corresponds to the ICCC-3 diagnostic group IIc.
[f] Other types of mature lymphomas in supplementary table 1.

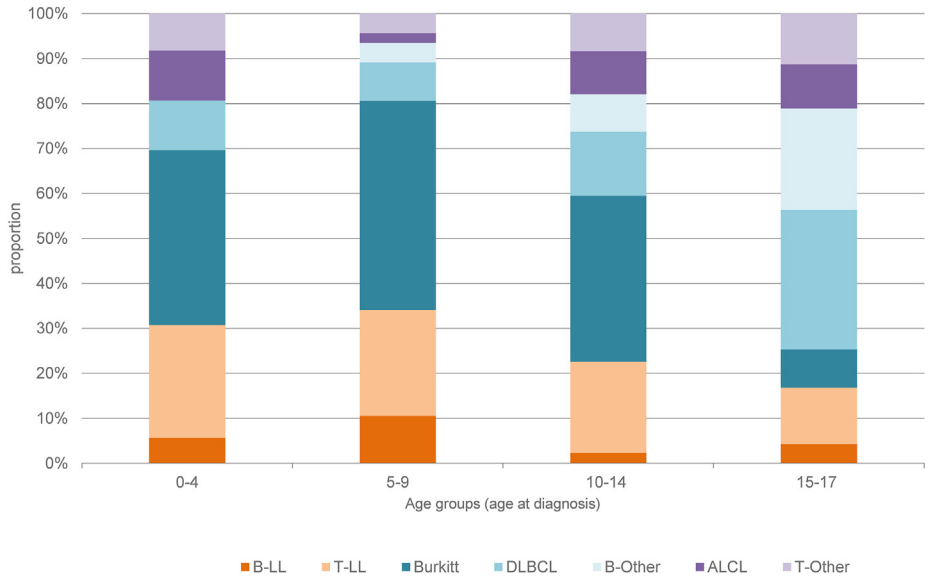

Fig. 1. Distribution of non-Hodgkin's lymphoma subtypes by age group in patients aged <18 years diagnosed in the Netherlands, 2010–2015. B-LBL, B-cell lymphoblastic lymphoma; T-LBL, T-cell lymphoblastic lymphoma; BL, Burkittlymphoma; DLBCL, diffuse large B-cell lymphoma; B-Other other mature B-cell non-Hodgkin's lymphoma morphologies; ALCL, anaplastic large cell lymphoma, T-Other other mature T-cell non-Hodgkin's lymphoma morphologies, Source: Netherlands Cancer Registry.

47% in 2010–15, although this trend was not significant ($p = 0.17$).

3.2. Trends in incidence

On average, thirty-eight children and young adolescents were newly diagnosed with NHL annually (range 28–48). The overall NHL incidence rate (age-adjusted rate 0–17 years) remained stable over time at about 11 per million person-years. The same pattern was seen for all NHL subtypes (Fig. 3). However, age-specific incidence rates significantly decreased at age 5–9 years, from 15 per million person-years in 1990–94 to 8 in 2010–15 (AAPC -2.6%, $p < 0.01$), mainly observed in boys (AAPC -2.7%,

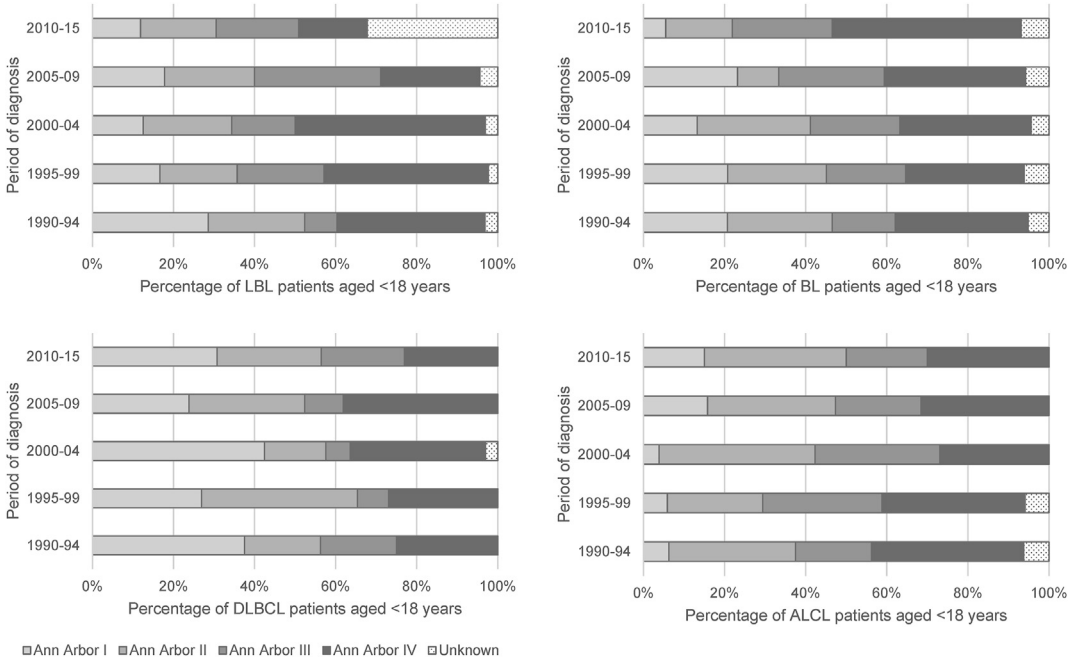

Fig. 2. Time trends in stage at diagnosis by non-Hodgkin's lymphoma subtypes in patients aged <18 years diagnosed in the Netherlands, 1990–2015. Distribution of stage at diagnosis changed significantly over time for LBL owing to the increase of unknown stages, $p < 0.01$. After excluding unknown stages, no significant changes were observed for LBL, $p = 0.11$. For BL a significant shift towards Ann Arbor stages III/IV was seen after excluding unknown stages, $p = 0.03$. The increase in advanced stage BL (i.e. Ann Arbor stage IV) was not significant ($p = 0.17$). BL, Burkitt lymphoma; LBL, lymphoblastic lymphoma.

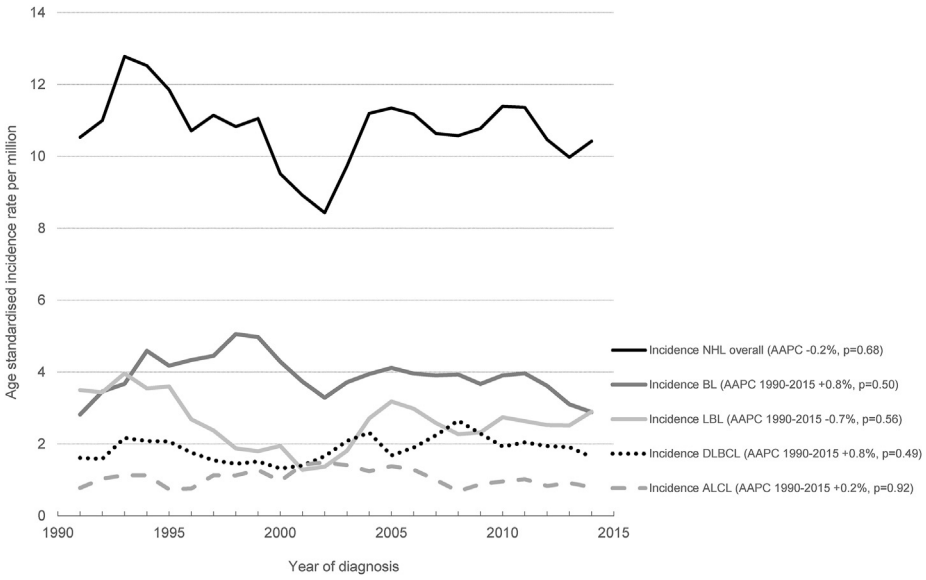

Fig. 3. Time trends in age-standardised incidence rates of non-Hodgkin's lymphoma by subtype in patients aged <18 years diagnosed in the Netherlands, 1990–2015. Three-year moving averages are shown. Incidence rates were standardised as per the World Standard Population [22]. Incidence of NHL corresponds to the ICCC-3 diagnostic groups IIb, IIc and IIe. Incidence of BL corresponds to the ICCC-3 diagnostic group IIc. AAPC, average annual percentage change; NHL, non-Hodgkin's lymphoma; LBL, lymphoblastic lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma. Source: Netherlands Cancer Registry

$p = 0.01$) and children with BL (AAPC-3.2%, $p = 0.01$). Incidence rates of stage I lymphomas decreased from 2 to 1 per million person-years (AAPC -2.6%, $p = 0.03$), whereas stage III seemed to increase (AAPC +5.6%, $p = 0.05$). Other age and sex-specificincidence rates showed minimal changes (Supplementary Table S2). In joinpoint analysis, no trend transitions were observed for any (sub)group of patients with NHL during the study period.

3.3. Trends in primary treatment and site of treatment

For patients with LBL, BL, DLBCL and ALCL (n = 867), the proportion of patients treated with RT decreased in favour of more patients treated with CT-only (p for trend = 0.01) (Fig. 4). On introduction of IT (rituximab) in 2004, the proportion of patients with BL and DLBCL receiving CT and IT substantially increased. A fluctuating proportion of patients with ALCL received CT-only over time, probably owing to low numbers of patients (i.e. about 20 per diagnostic period). Overall, less than 5% of patients with ALCL received CT and RT.

Over time, more patients were treated in a UMC, increasing from 74% in 1990 to 99% after 2010 (Fig. 5). After 2003, about 95% of patients were treated at a paediatric oncology centre within the UMC. In the last two years of this study, only four patients were treated in the haematology department in a UMC, all 17 years old at diagnosis.

3.4. Trends in overall survival

The median follow-up for all patients with NHL was 11 years (p25-p75: 4–19 years). From the 867 included NHL cases in the survival analyses, only six cases were lost to follow-up within five years after diagnosis. Five-year OS improved from 71% in 1990––94 to 87% in 2010–15 ($p < 0.01$) (Table 2). Five-year OS for LBL improved from 68% in 1990–94 to 83% in 2010––15 ($p = 0.10$). Five-year OS for BL was already above 80% in 1990–94 and slightly improved to 89% in 2010–15 ($p = 0.20$). Significant improvements were seen in patients with DLBCL (5-year OS of 60% in 1990–94 vs 90% in 2010–15, $p < 0.01$) and in patients with ALCL (5-year OS of 73% in 1990–94 vs 90% in 2010–15 $p = 0.03$) (Fig. 6; Table 2). Five-year OS improved in patients of 15–17 years only and diagnosed with subtypes BL and DLBCL ($p = 0.046$ and $p < 0.01$, respectively). Gender-specific improvements in 5-year OS were only seen for both sexes with DLBCL. Stage-specific improvements in 5-year OS were only manifest among patients with DLBCL, stage II and higher.

3.5. Determinants of death

Multivariable analysis of the risk of dying from DLBCL within 5-years after diagnosis showed a significant decrease in the hazard ratio (HR) during the periods 2005–09 and 2010–15 (HR 0.3, $p = 0.01$ and HR 0.1,

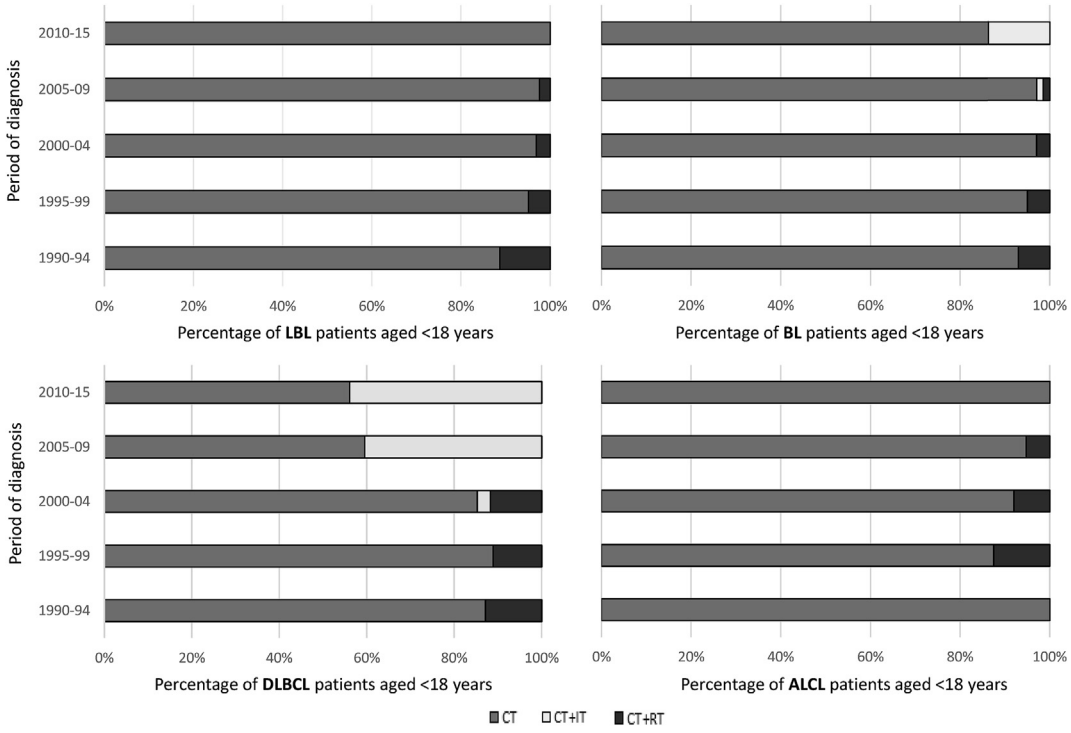

Fig. 4. Time trends in primary treatment by non-Hodgkin's lymphoma subtypes in patients aged <18 years diagnosed in the Netherlands, 1990–2015. Proportions of patients receiving CT or CT+IT significantly increased over time for LBL and BL, both p < 0.01. LBL, lymphoblastic lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma; CT, chemotherapy; CT+IT, chemotherapy and immunotherapy; CT+RT, chemotherapy and radiotherapy. Source: Netherlands Cancer Registry.

$p < 0.01$) compared with 1990–94, adjusted for follow-up time, age and gender, stage at diagnosis and site of treatment (Table 3). Female patients had a higher risk of dying from DLBCL than male patients (HR 2.0, $p = 0.04$). Patients with stage III or IV also had a higher risk of dying from DLBCL than patients with stage I (HR 5.2, $p = 0.01$ and HR 5.5, $p < 0.01$, respectively). Patients treated outside a UMC had a borderline significant higher risk of dying compared with patients treated in a UMC (HR 2.6, $p = 0.05$).

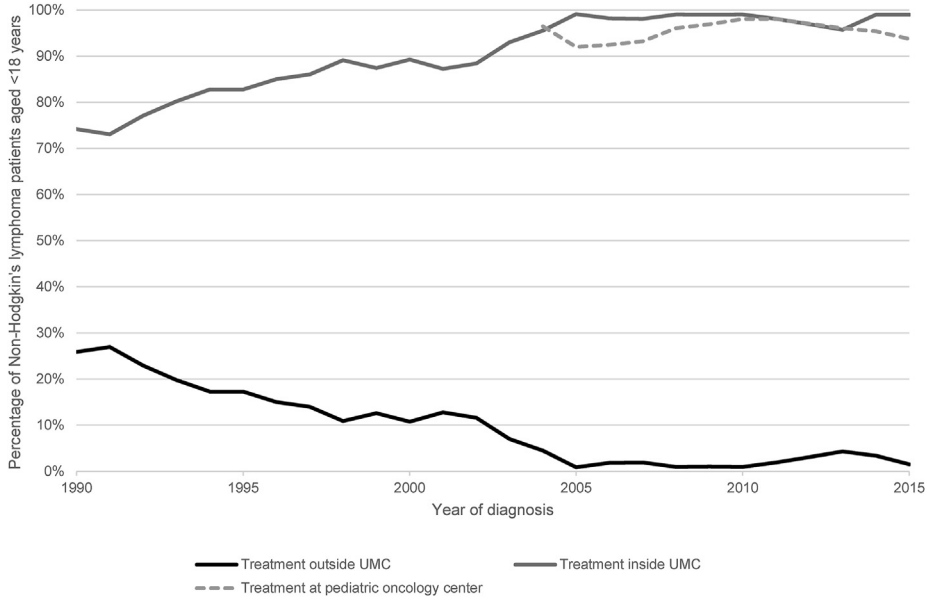

Fig. 5. Time trend in site of primary treatment of patients with non-Hodgkin's lymphoma aged <18 years diagnosed in the Netherlands, 1990–2015. UMC, University Medical Centre. Source: Netherlands Cancer Registry and the Registry of the Dutch Childhood Oncology Group for site of treatment as used in Reedijk et al. [8].

Table 2
Five-year observed survival of patients with non-Hodgkin's lymphoma aged <18 years diagnosed in the Netherlands, 1990–2015.

		N at risk	5-yr OS (%)	SE (%)	p-trend[b]
All patients[a]		999	81	1	**< 0.01**
Period	1990–94	198	71	3	
	1995–99	190	77	3	
	2000–04	177	84	3	
	2005–09	195	85	3	
	2010–15	239	87	2	

By NHL subtype		LBL				BL[c]				DLBCL				ALCL			
		N at risk	5-yr OS (%)	SE (%)	p-trend[b]	N at risk	5-yr OS (%)	SE (%)	p-trend[b]	N at risk	5-yr OS (%)	SE (%)	p-trend[b]	N at risk	5-yr OS (%)	SE (%)	p-trend[b]
All patients		240	78	3	0.10	350	86	2	0.20	180	76	3	**<0.01**	97	78	4	0.03
Period of diagnosis	1990–94	63	68	6		58	83	5		33	60	9		15	73	11	
	1995–99	42	81	6		82	83	4		28	64	9		17	65	12	
	2000–04	32	88	6		68	90	4		34	73	8		26	73	9	
	2005–09	44	77	6		69	87	4		43	86	5		19	95	5	
	2010–15	59	83	5		73	89	4		42	90	5		20	90	7	
Age (yrs)	0–4	59	78	5	0.32	72	90	4	0.54	14	ND			11	ND		
	5–9	74	85	4	0.94	138	87	3	0.91	26	77	8	0.05	24	83	8	0.70
	10–14	79	77	5	0.41	104	85	3	0.22	61	80	5	0.94	36	75	7	0.13
	15–17	28	65	9	0.07	36	77	7	0.05	79	75	5	**<0.01**	26	72	9	0.25
Gender	Male	161	79	3	0.32	290	86	2	0.27	118	80	4	**0.02**	54	81	5	0.15
	Female	79	86	5	0.17	60	85	5	0.51	62	69	6	**<0.01**	43	74	7	0.08
Stage	I	44	79	6	0.60	58	91	4	0.35	55	87	5	0.28	9	ND		
	II	51	80	6	0.43	73	89	4	0.63	43	81	6	**0.02**	32	78	7	0.08
	III	45	89	5	0.71	76	86	4	0.82	22	64	10	**0.03**	24	78	9	0.11
	IV	76	67	5	0.55	123	85	3	0.32	51	64	7	**<0.01**	31	74	8	0.24
	Unknown	24				20				9				1			
Treatment in UMC	No	17	82	8		30	83	7		27	67	9		8	ND		
	Yes	223	78	3	0.08	320	86	2	0.32	153	78	3	**<0.01**	89	79	4	0.05

LBL, lymphoblastic lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma; ALCL, anaplastic large cell lymphoma; UMC, University Medical Centre; OS, overall survival; SE, standard error; ND, 5-year OS not determined owing to <15 patients in a category.
Bold values indicate statistical significance.
Source: Netherlands Cancer Registry and the Registry of the Dutch Childhood Oncology Group for site of treatment as used in Reedijk et al. [8].
[a] The total group of NHL corresponds to the ICCC-3 diagnostic groups IIb, IIc and IIe.
[b] p-values represent significance of improvements in 5-year OS over time. Time trends were evaluated using parametric survival models including period of diagnosis and follow-up time.
[c] BL corresponds to the ICCC-3 diagnostic group IIc.

Insignificant changes over time in the risk of dying were observed for subtypes LBL, BL and ALCL in multivariable analyses (data not shown).

3.6. Trends in mortality rates

The average annual number of deaths owing to NHL in the population younger than 20 years decreased from 20 during 1980–84 to 11 in 1990–94 and 6 in 2010–16. Time trend analyses over 1980–2016 revealed an AAPC of −4.2% ($p < 0.01$) (Supplementary Table S3), remaining significant during 1990–2016 (AAPC -4.1%, $p < 0.01$). In joinpoint analysis, no trend transitions were observed for mortality rates during the study period.

4. Discussion

This first comprehensive population-based study on trends in incidence, primary treatment, survival and mortality for children and young adolescents with NHL in the Netherlands showed stable incidence rates, albeit decreasing among 5–9 year-olds. The use of RT combined with CT as treatment strategy for LBL and BL decreased over time in favour of CT only. Survival improved over time, mostly for subtypes DLBCL and ALCL. These findings are supported by steadily decreasing, independently assessed, mortality rates for this young patient group.

The stable incidence rate of NHL of 11 per million person-years was in accordance with rates in other European countries, as is shown in a selected overview in Supplementary Table S4. Moreover, these incidence rates were also comparable with other non-European high-income countries [3,4,26,27]. The decreasing incidence trend at age 5–9 years is, to our knowledge, not reported in other studies. Analyses by subgroups revealed a clear decrease for BL, possibly owing to a decline in the prevalence of Epstein-Barr virus (EBV)

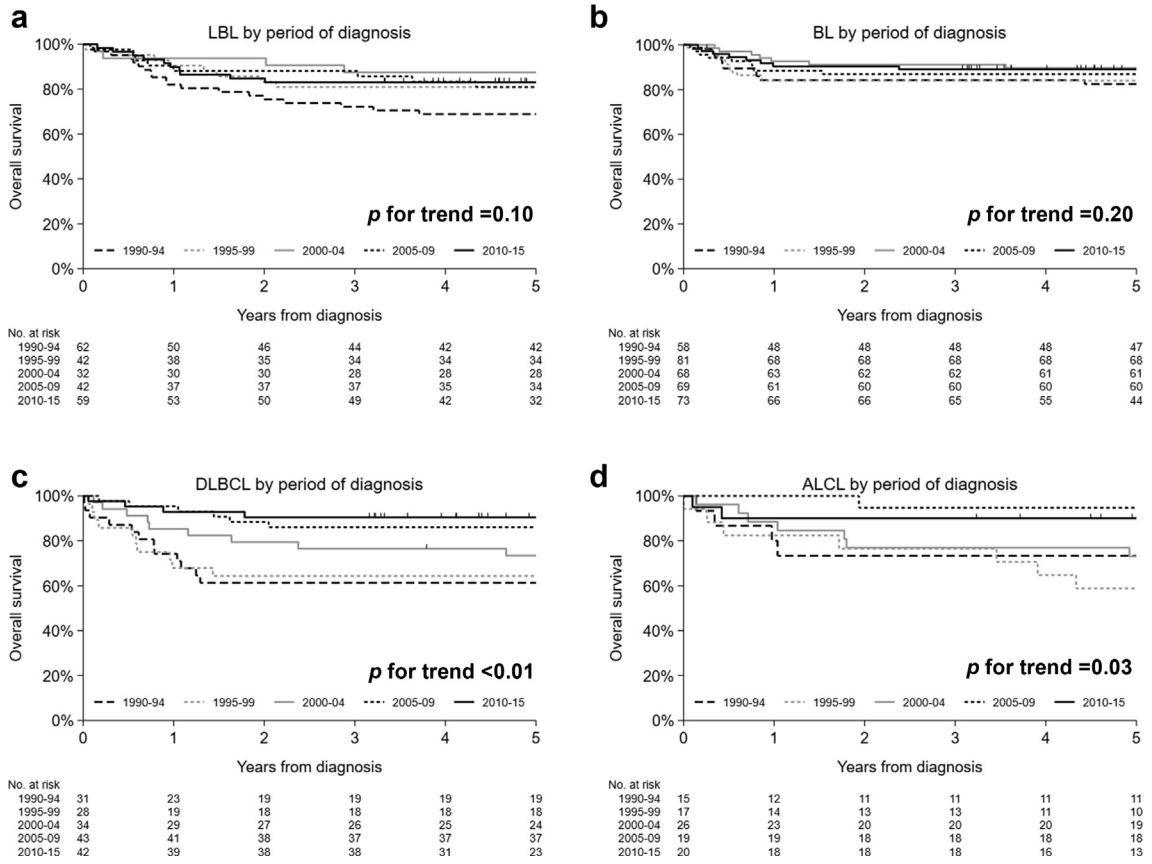

Fig. 6. Time trend of 5-year observed survival by non-Hodgkin's lymphoma subtypes in patients aged <18 years diagnosed in the Netherlands, 1990–2015, The p for trend was tested by parametric survival models adjusted for follow-up time. LBL, lymphoblastic lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma. Source: Netherlands Cancer Registry.

[28]. Unfortunately, no information was available on EBV infections in the Netherlands. Furthermore, a shift towards Ann Arbor stage III and IV has been observed, although the increase in advanced stage BL was not significant. The exact reason(s) behind these trends remains unknown and needs to be monitored in the future.

Treatment of children and young adolescents with each of the four common types of paediatric NHL changed into predominantly 'CT-only' or CT plus IT for BL and DLBCL. In a paediatric setting, RT as part of the upfront treatment of NHL was mainly applied in children with overt central nervous system involvement. In adult oncology, RT has been used in the treatment of NHL located in the central nervous system (CNS), residual disease during treatment and was part of conditioning for allogeneic stem cell transplantation during primary treatment of resistant NHL. Less use of RT over time in children with NHL may reflect the reduction of the use of RT as part of the primary treatment of CNS disease and an increase of young adolescents treated in a paediatric setting instead of adult oncology since 2004 (i.e. 95% in 2010––15). This contrasts with similarly aged patients with Hodgkin's lymphoma or ALL of whom 75%–87% were treated in a paediatric oncology centre during 2010–15 [30,37].

Five-year overall survival (OS) for patients with NHL increased from 71% in 1990–94 to 87% in 2010–15. Improvements were mainly seen for patients with DLBCL and ALCL, most likely owing to new standardised treatment protocols by the end of the 1990s [9]. Addition of rituximab for patients with high-risk DLBCL since 2004 improved survival for these patients as well [9]. Five-year OS rates for children with BL and LBL were already above 80% in 1995–99. Similar 5-year OS rates for children with NHL were found in Australia (82% for NHL and 91% for BL in 1997–2006), Europe (84% for NHL and 90% for BL in 2000–06; Supplementary Table S4) and the United States of America (84% in 2003–09) [28,31,32]. In the group of patients with DLBCL, we found worse outcomes for girls than those for boys. In a German study [33], inferior outcomes for female adolescents with DLBCL were explained by high serum lactate dehydrogenase concentration (as surrogate for tumour mass). In our study, female patients with mature B-NHL were slightly older at diagnosis than boys (median age of 13 vs 9 years), but with similar stages at diagnosis. Gender differences in

Table 3
Univariate and multivariate analyses on the risk of dying within five years after diagnosis of patients with DLBCL aged <18 years in the Netherlands, 1990–2015.

NHL subtype		n at risk	DLBCL					
			Univariate analysis			Multivariable analysis		
			HR	95% CI	*p*-value	HR	95% CI	*p*-value
Period of diagnosis	1990–94	32	Ref.			Ref.		
	1995–99	26	0.9	0.4–2.1	0.80	1.3	0.5–3.2	0.62
	2000–04	32	0.6	0.2–1.3	0.19	0.5	0.2–1.4	0.20
	2005–09	42	**0.3**	**0.1–0.7**	**0.01**	**0.3**	**0.1–0.8**	**0.01**
	2010–15	39	**0.1**	**0.0–0.5**	**<0.01**	**0.1**	**0.0–0.5**	**<0.01**
Age (yrs)	0–4	11	Ref.			Ref.		
	5–9	25	0.6	0.2–2.2	0.48	0.5	0.1–1.7	0.25
	10–14	59	0.5	0.2–1.5	0.21	0.4	0.1–1.4	0.16
	15–17	76	0.6	0.2–1.8	0.38	0.5	0.1–1.6	0.23
Gender	male	115	Ref.			Ref.		
	female	56	1.7	0.9–3.1	0.11	**2.0**	**1.0–3.9**	**0.04**
Stage	I	55	Ref.			Ref.		
	II	43	0.5	0.6–4.2	0.42	2.1	0.7–6.0	0.18
	III	22	**3.2**	**1.2–8.9**	**0.02**	**5.2**	**1.6–16**	**0.01**
	IV	51	**3.4**	**1.4–8.1**	**0.01**	**5.5**	**2.1–14**	**<0.01**
Treatment in UMC	yes	144	Ref.			Ref.		
	no	27	1.6	0.8–3.4	0.20	2.6	1.0–6.5	0.05

HR, hazard ratio; DLBCL, diffuse large B-cell lymphoma; UMC, University Medical Centre; CI, confidence interval.
In the multivariate analysis, each covariate is simultaneously adjusted for all other covariates, including follow-up time. Hazard ratios represent the risk of dying within 5 years from diagnosis compared with the reference category.
Patients with missing stage (N = 9; 5%) in total, were excluded.
Bold values indicate statistical significance.
Source: Netherlands Cancer Registry and the registry of the Dutch Childhood Oncology Group for site of treatment as used in Reedijk et al. [8].

survival need further investigation, taking into account the unequal male to female ratio between different subgroups of NHL as shown in Table 1.

In agreement with other studies in Europe [34,35], population-based mortality rates have declined constantly in each age group (Supplementary Table S4). Against the background of stable incidence and no large changes in disease severity, improvements in therapy are most likely responsible for the progress made against NHL in the Netherlands. Increased intensity of both induction and re-induction therapies were the first important components of successful NHL treatment protocols at the end of the 1970s and in the 1980s [12].

A major strength of this study is the use of high-quality, population-based data from the NCR without age or hospital limits. Despite the lack of detailed information on treatment schemes (also of relapses) and trial inclusion in the NCR, non-lethal serious adverse events or late effects of treatment, this cancer registry population-based study is uniquely able to demonstrate the notion of progress. Besides facilitating a variety of analyses of clustering and trends in detection, incidence, primary treatment, long term survival and aspects of survivorship in the general patient population, the registry can also act as sampling frame for etiological and more detailed clinical research [36]. Limitations of this study are the missing information on stage and treatment for about 6% and 1% of the study population, respectively. Missing stage was especially seen for LBL in the latest period 201–015, but the reason(s) remains unclear. Furthermore, the NCR used the Ann Arbor staging system instead of the Toronto staging guidelines which are based on the Murphy/St. Jude staging system. However, Ann Arbor stage IV corresponds to advanced-stage disease in the Toronto staging guidelines [21]. To define the most common NHL subgroups, to increase the clinical relevance of this study, the 2008 WHO classification was used. This classification is more detailed than the ICCC-3 classification, and incidence and survival rates of the total NHL group and BL group are comparable with the diagnostic groups IIb-c, IIe and IIc, respectively. Finally, mortality data also included 18- and 19-year-old patients at time of death. These data could be affected by patients who were diagnosed at age 18 and 19 years with a short survival time but also include patients diagnosed before the age of 18 years.

5. Conclusion

This population-based epidemiological study exhibited significant progress against NHL diagnosed in children and young adolescents in the Netherlands since 1990, before the advent of a national paediatric oncologic centre in 2018. Progress is demonstrated by a stable incidence, but decreasing in 5–9-year old, improved

survival and a decreasing mortality. This comprehensive assessment reveals real treatment improvements in paediatric and young adolescent NHL in the Netherlands.

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Author contributions

AMJR, AB, JWWC, LCK, RP, JLCL and HEKK conceived and designed the study. AMJR did the literature search. AMJR prepared the database and carried out the analysis. AMJR, AB, JWWC, JLCL and HEKK drafted the article. All authors contributed to the interpretation of the results and critically revised the article. AMJR and HEKK directly accessed and verified the raw data and took 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 article for publication.

Data statement

The data sets generated during and/or analysed for the present study are not publicly available owing to the potential identifiable nature of the data. However, deidentified data can be made available from the corresponding author.

Conflict of interest statement

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.

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Appendix A. Supplementary data

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