

# 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

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**Supplementary material Schulpen *et al.***

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**Supplementary Table S1.** Five-year relative survival<sup>a</sup> of children (0-17 years) and AYAs (18-39 years) diagnosed with non-Hodgkin lymphoma in the Netherlands between 1990-2015 by the most common subtypes

Characteristics	Total			T-LBL			AYAs			Total			BL <sup>b</sup>			AYAs			Total			DLBCL			AYAs			Total			ALCL			AYAs			
	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE				
Overall	360	67.8	2.5	204	77.9	2.9	156	54.7	4.0	569	77.4	1.8	341	86.8	1.8	228	63.4	3.2	2056	73.7	1.0	197	75.0	3.1	1859	73.5	1.0	318	74.4	2.5	101	79.3	4.0	217	72.1	3.1	
Period of diagnosis																																					
1990-1999	153	61.3	4.0	89	71.7	4.8	64	47.1	6.3	221	69.7	3.1	137	83.2	3.2	84	47.8	5.5	724	59.6	1.8	71	61.1	5.9	653	59.5	1.9	120	71.9	4.1	36	69.5	7.7	84	72.9	4.9	
2000-2009	121	72.0	4.1	64	82.9	4.7	57	59.8	6.5	226	80.7	2.6	134	88.9	2.7	92	68.7	4.9	849	77.6	1.4	77	79.3	4.6	772	77.5	1.5	130	70.1	4.0	45	82.3	5.7	85	63.7	5.2	
2010-2015	86	73.4	4.8	51	82.4	5.3	35	60.1	8.3	122	85.4	3.2	70	90.1	3.6	52	79.0	5.7	483	87.7	1.5	49	87.8	4.7	434	87.7	1.6	68	86.9	4.1	20	90.1	6.7	48	85.6	5.1	
P-trend		<b>0.04</b>			0.12			0.12		<b>&lt;0.001</b>			0.12		<b>&lt;0.001</b>		<b>&lt;0.001</b>		<b>&lt;0.001</b>						0.09				0.06					0.39			
Sex																																					
Male	273	67.9	2.8	142	78.9	3.4	131	55.9	4.4	449	79.2	1.9	286	87.1	2.0	163	65.3	3.8	1272	73.4	1.3	121	79.3	3.7	1151	72.7	1.3	183	78.9	3.0	56	82.2	5.1	127	77.5	3.7	
Female	87	67.5	5.1	62	75.5	5.5	25	48.1	10.0	120	70.9	4.2	55	85.5	4.8	65	58.6	6.1	784	74.2	1.6	76	68.1	5.4	708	74.9	1.6	135	68.3	4.0	45	75.6	6.4	90	64.6	5.1	
Ann Arbor stage																																					
I	60	76.8	5.5	35	80.1	6.8	25	72.2	9.0	105	84.0	3.6	58	91.5	3.7	47	74.7	6.4	661	85.3	1.4	60	86.4	4.5	601	85.2	1.5	54	94.7	3.1	11	91.0	8.7	43	95.7	3.2	
II	65	66.3	5.9	43	76.8	6.4	22	45.6	10.7	113	84.2	3.4	72	90.4	3.5	41	73.4	6.9	513	80.1	1.8	49	81.7	5.5	464	79.9	1.9	88	80.8	4.2	33	78.9	7.1	55	82.0	5.2	
III	63	74.7	5.5	41	87.9	5.1	22	50.1	10.7	96	83.4	3.8	76	85.6	4.0	20	75.2	9.7	270	67.8	2.9	26	65.5	9.3	244	68.0	3.0	74	74.5	5.1	25	80.1	8.0	49	71.7	6.5	
IV	133	60.8	4.3	62	67.3	6.0	71	55.1	5.9	237	69.6	3.0	125	84.8	3.2	112	52.8	4.7	563	58.6	2.1	57	61.5	6.5	506	58.3	2.2	90	59.0	5.2	31	74.3	7.9	59	51.0	6.5	
Unknown	39	69.3	7.4	23	87.0	7.0	16	43.9	12.4	18	66.8	11.1	10	70.1	14.5	8	NA		49	57.2	7.1	5	NA		44	54.6	7.6	12	50.2	14.5	1	NA		11	45.7	15.1	
Primary treatment <sup>c</sup>																																					
CT <sup>d</sup>	257	72.0	2.8	183	81.4	2.9	74	48.8	5.8	404	79.3	2.0	310	88.5	1.8	94	49.1	5.2	822	65.3	1.7	133	78.1	3.6	689	62.9	1.9	236	73.5	2.9	91	81.4	4.1	145	68.5	3.9	
CT + RT <sup>e</sup>	28	35.8	9.1	7	NA		21	28.7	9.9	30	65.9	8.8	9	NA		21	62.1	10.6	380	80.6	2.1	13	67.0	13.6	367	81.0	2.1	40	82.8	6.0	6	NA		34	82.6	6.6	
CT + rituximab <sup>f</sup>	0	NA		0	NA		0	NA		62	80.8	5.0	9	NA		53	79.5	5.6	647	87.0	1.3	39	79.6	6.5	608	87.5	1.4	4	NA		0	NA		4	NA		
SCT <sup>g</sup>	67	70.4	5.6	8	NA		59	73.1	5.8	60	75.2	5.6	8	NA		52	77.2	5.9	62	66.2	6.1	3	NA		59	67.8	6.1	25	68.2	9.4	3	NA		22	73.0	9.5	

Abbreviations: AYAs, adolescents and young adults; T-LBL, T-lymphoblastic lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma; SE, standard error; CT, chemotherapy; RT, radiation therapy; SCT, stem cell transplantation; ICC-3, International Classification of Childhood Cancer, 3rd edition.

NA: Estimation of a reliable survival probability was not possible because of N at risk <10.

<sup>a</sup> Expected probabilities of survival were estimated using the Ederer II method.

<sup>b</sup> BL corresponds to ICC-3 diagnostic group IIc.

<sup>c</sup> Survival estimates are not provided for the "Other/no treatment/unknown" treatment group because of the mixed set of patients and the risk of immortal time bias.

<sup>d</sup> CT only, not treated with RT, rituximab or SCT.

<sup>e</sup> Treated with CT and RT; not treated with rituximab or SCT.

<sup>f</sup> 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).

<sup>g</sup> Treated with SCT independent of CT, RT or rituximab.

**Supplementary Table S2.** Multivariable-adjusted associations of age with excess mortality due to non-Hodgkin lymphoma subtypes within 5 years of diagnosis in children and AYAs (0-39 years), the Netherlands, 1990-2015

	N <sub>at risk</sub>	Adjusted 1 <sup>a</sup>			Adjusted 2 <sup>b</sup>		
		Excess HR	95% CI	P-value	Excess HR	95% CI	P-value
<b>T-LBL</b>							
Child	204	1.0 (ref)			1.0 (ref)		
AYA	156	2.4	(1.6-3.6)	<b>&lt;0.001</b>	2.8	(1.9-4.4)	<b>&lt;0.001</b>
0-9 years	117	1.0 (ref)			1.0 (ref)		
10-17 years	87	1.7	(1.0-3.2)	0.07	1.7	(0.9-3.1)	0.10
18-29 years	99	3.3	(1.9-5.6)	<b>&lt;0.001</b>	3.7	(2.1-6.6)	<b>&lt;0.001</b>
30-39 years	57	3.0	(1.6-5.6)	<b>&lt;0.001</b>	3.6	(2.0-6.8)	<b>&lt;0.001</b>
<b>BL<sup>c</sup></b>							
Child	341	1.0 (ref)			1.0 (ref)		
AYA	228	3.4	(2.3-4.9)	<b>&lt;0.001</b>	3.9	(2.6-5.9)	<b>&lt;0.001</b>
0-9 years	204	1.0 (ref)			1.0 (ref)		
10-17 years	137	1.4	(0.8-2.6)	0.25	1.4	(0.8-2.6)	0.25
18-29 years	103	3.0	(1.7-5.3)	<b>&lt;0.001</b>	3.6	(2.0-6.6)	<b>&lt;0.001</b>
30-39 years	125	4.6	(2.8-7.6)	<b>&lt;0.001</b>	5.1	(3.0-8.6)	<b>&lt;0.001</b>
<b>DLBCL</b>							
Child	197	1.0 (ref)			1.0 (ref)		
AYA	1859	1.1	(0.8-1.4)	0.64	1.1	(0.9-1.5)	0.37
0-9 years	42	1.0 (ref)			1.0 (ref)		
10-17 years	155	1.3	(0.7-2.6)	0.45	1.3	(0.7-2.5)	0.46
18-29 years	696	1.1	(0.6-2.1)	0.71	1.2	(0.7-2.3)	0.52
30-39 years	1163	1.4	(0.8-2.6)	0.26	1.5	(0.8-2.7)	0.20
<b>ALCL</b>							
Child	101	1.0 (ref)			1.0 (ref)		
AYA	217	1.8	(1.1-3.0)	<b>0.03</b>	1.9	(1.1-3.3)	<b>0.01</b>
0-9 years	37	1.0 (ref)			1.0 (ref)		
10-17 years	64	2.9	(1.0-8.0)	<b>0.04</b>	3.0	(1.1-8.3)	<b>0.04</b>
18-29 years	110	3.6	(1.4-9.3)	<b>0.01</b>	4.1	(1.6-10.8)	<b>0.004</b>
30-39 years	107	3.5	(1.3-9.2)	<b>0.01</b>	3.8	(1.4-10.1)	<b>0.01</b>

Abbreviations: AYAs, adolescents and young adults; HR, hazard ratio; CI, confidence interval; T-LBL, T-lymphoblastic lymphoma; BL, Burkitt lymphoma; DLBCL, diffuse large B-cell lymphoma; ALCL, anaplastic large cell lymphoma; CT, chemotherapy; RT, radiation therapy; SCT, stem cell transplantation; ICCC-3, International Classification of Childhood Cancer, 3rd edition.

<sup>a</sup> Adjusted for follow-up time (years), period of diagnosis (1990-1999, 2000-2009, 2010-2015), sex (male, female), and Ann Arbor stage (I, II, III, IV, unknown).

<sup>b</sup> Additionally adjusted for primary treatment (CT, CT + RT, CT + rituximab, SCT, other/no treatment/unknown).

<sup>c</sup> BL corresponds to ICCC-3 diagnostic group IIc.

**Supplementary Table S3.** Overview of protocols used in the treatment of non-Hodgkin lymphoma (NHL) in children (0-17 years) and adolescents & young adults (AYAs, 18-39 years) in the Netherlands, 1990-2015

<b>NHL subtype</b>	<b>Age group</b>	<b>Commonly used first-line treatment protocols in the Netherlands</b>
T-lymphoblastic lymphoma	Children	<p><b>1990-1991:</b> ALL-7 protocol (based on ALL-Berlin-Frankfurt-Münster (BFM)-86)<sup>1</sup></p> <p><b>1991-2003:</b> ALL-8 protocol (based on ALL-BFM-90)<sup>2</sup></p> <p><b>2003-2015:</b> Euro-LB02 protocol (based on NHL-BFM90 study)<sup>3</sup></p>
T-lymphoblastic lymphoma	AYAs	<p><b>Acute lymphoblastic leukemia (ALL) regimens</b></p> <p><b>1990-1992:</b> Dutch-Belgian Cooperative Trial Group for Hematology Oncology (HOVON)-5 protocol<sup>4</sup></p> <p><b>1992-1999:</b> HOVON-18 protocol<sup>5</sup></p> <p><b>1999-2005:</b> HOVON-37 protocol<sup>5</sup></p> <p><b>2005-2009:</b> HOVON-70 protocol (based on intensive pediatric French Acute Lymphoblastic Leukaemia study group (FRALLE) 93 high risk protocol)<sup>6</sup></p> <p><b>2009-2015:</b> HOVON-100 protocol (based on HOVON-70 protocol)<sup>7</sup></p> <p>Note: during 1994-2003, a limited number of T-LBL patients with less extensive disease was included in the HOVON-27BL trial<sup>8</sup></p>
Burkitt lymphoma	Children	<p><b>1990-1996:</b> Société Française d'Oncologie Pédiatrique (SFOP) Lymphomes Malins B (LMB) 89 protocol<sup>9</sup></p> <p><b>1996-2008:</b> French-American-British (FAB) LMB96 international protocol<sup>10-12</sup></p> <p><u>Low risk (group A, group B low/intermediate risk)</u>  <b>2008-2015:</b> Dutch Childhood Oncology Group (SKION) B-NHL/B-ALL 2008 protocol (based on the LMB89, 96, and 2001 protocols)</p> <p><u>High risk (group B high risk, group C1, group C3)</u>  <b>2008-2011:</b> SKION B-NHL/B-ALL 2008 protocol</p> <p><b>2011-2015:</b> SKION-Inter-B-NHL ritux 2010 protocol<sup>13</sup></p>
Burkitt lymphoma	AYAs	<p>There was not a standard first-line treatment for adult Burkitt lymphoma in the Netherlands<sup>14</sup>.</p> <p>The following protocols were commonly used:</p> <ul style="list-style-type: none"> <li>• HOVON-27BL protocol<sup>8,14</sup> <ul style="list-style-type: none"> <li>• Treatment was preceded by three courses of dose-dense intensified R-CHOP from approximately 2005 onwards.</li> </ul> </li> </ul>

- Adapted pediatric LMB protocol<sup>15</sup>
- Hoelzer / German Multicenter Study Group for Adult ALL (GMALL) protocol<sup>16</sup>
- (R-)CODOX-M/(R-)IVAC<sup>17</sup>

Note: rituximab was added to the above listed chemotherapy regimens as from 2003 to 2004 onwards<sup>14,18</sup>.

Diffuse large B-cell lymphoma	Children	<p><b>1990-1996:</b> SFOP LMB89 protocol<sup>9</sup></p> <p><b>1996-2008:</b> FAB LMB96 international protocol<sup>10-12</sup></p> <p><u>Low risk (group A, group B low/intermediate risk)</u>  <b>2008-2015:</b> SKION B-NHL/B-ALL 2008 protocol (based on the LMB89, 96, and 2001 protocols)</p> <p><u>High risk (group B high risk, group C1, group C3)</u>  <b>2008-2011:</b> SKION B-NHL/B-ALL 2008 protocol</p> <p><b>2011-2015:</b> SKION-Inter-B-NHL ritux 2010 protocol<sup>13</sup></p>
Diffuse large B-cell lymphoma	AYAs	<p><b>1990-1993:</b> eight courses of standard CHOP-21<sup>19</sup></p> <p><b>1994-2004:</b> multiple variants of CHOP-14/21<sup>20</sup></p> <p><b>2004-2015:</b> variants of R-CHOP-14/21<sup>21,22</sup></p>
Anaplastic large cell lymphoma	Children	<p><b>1990-1999:</b> various strategies</p> <ul style="list-style-type: none"> <li>• For example, LMB regimens for B-NHL<sup>9-12</sup> or an APO regimen for advanced-stage large-cell lymphoma<sup>23</sup></li> </ul> <p><b>1999-2015:</b> ALCL99 protocol (based on NHL-BFM90)<sup>24</sup></p>
Anaplastic large cell lymphoma	AYAs	<p><b>1990-2015:</b> multiple variants of CHOP-14/21<sup>19,20</sup></p> <ul style="list-style-type: none"> <li>• In some cases CHOP was followed by a stem cell transplantation (mainly in patients with anaplastic lymphoma kinase (ALK)-negative disease)</li> </ul>

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