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Increased survival disparities among children and adolescents & young adults with acute myeloid leukemia: A Dutch population-based study

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Abstract

For many cancers, adolescents and young adults (AYAs) have a poorer prognosis than pediatric patients. Our study evaluates survival outcomes of children (0-17 years) and AYAs (18-39 years) diagnosed with acute myeloid leukemia (AML) in the Netherlands between 1990 and 2015 (N = 2058) utilizing the population-based Netherlands Cancer Registry, which includes information on therapy and site of primary treatment. Five- and 10-year relative (disease-specific) survival were estimated for all patients, children and AYAs. Multivariable analyses were performed using generalized linear models (excess mortality) and logistic regression (early mortality). AYAs with AML had a substantially lower 5- and 10-year relative survival than children (5-year: 43% vs 58%; 10-year: 37% vs 51%). The gap in 5-year relative survival was largest (nearly 20 percent-points) in 2010 to 2015, despite survival improvements over time across all ages. The multivariable-adjusted excess risk of dying was 60% higher in AYAs (95% CI: 37%-86%). Early mortality (death within 30 days of diagnosis) declined over time, and did not differ between children and AYAs. In conclusion, AYAs diagnosed with AML in the Netherlands had a worse prognosis than pediatric patients. The survival gap seemed most pronounced in recent years, suggesting that improvements in care resulting in better outcome for children have not led to equal benefits for AYAs.

KEYWORDS
acute myeloid leukemia, adolescents and young adults, children, early mortality, relative survival

What's new?

For many cancers, children under 18 have better survival outcomes than adolescents and young adults, age 18-39. Here, the authors evaluated long-term survival of young people diagnosed with acute myeloid leukemia in the Netherlands. When they compared outcomes, they found that adolescents and young adults had a worse prognosis than children. Although survival has improved across all age groups, the disparity between children and adolescents and young adults has widened. Treatments that improved outcomes for children, therefore, do not appear to have benefited adolescents and young adults to the same degree.

1 | INTRODUCTION

Acute myeloid leukemia (AML) comprises 15% to 20% of all pediatric leukemias. AML is a life-threatening disease and accounts disproportionately for about one-third of the deaths from childhood leukemia. After a peak in infants, the incidence of AML declines, reaching a minimum in 1 to 9 year old children, which is followed by a gradual increase through adolescence and (young) adulthood.[1,2] The prognosis of pediatric AML patients has improved in the past decades with 5-year survival rates currently about 70% to 75% in Europe and the United States.[2-6] The favorable trend in survival of pediatric AML has been attributed to better supportive care, optimization of risk stratification, intensification of chemotherapy, improvements in stem cell transplantation (SCT) and higher salvage rates at relapse.[2,7,8]

Adolescent and young adult (AYA) cancer patients are often reported to have an inferior prognosis compared to children with the same disease. Although the higher rate of survival improvement among AYAs since the early 1990s narrowed the survival gap in Europe, AYAs with cancer still had a worse prognosis than pediatric patients in the mid-2000s. In the same period, survival of AYAs with cancer in the United States increased at a similar rate as that of children and remained to lag behind.[9] Age at diagnosis is an important prognostic factor for AML and is inversely associated with the probability of survival.[1]

So far, population-based survival of children and AYAs diagnosed with AML has been investigated in a limited number of studies from Europe and the United States.[10-14] In general, AYAs experienced lower long-term survival compared to pediatric patients; however, the observed differences did not always reach statistical significance, perhaps because of small sample sizes. Moreover, results were generally not specified by cytogenetic risk group, therapy or site of treatment.

Long-term survival of children and AYAs with AML in the Netherlands has not been compared yet, despite the availability of high-quality data collected by the Netherlands Cancer Registry (NCR). According to a recent study focusing on Dutch pediatric AML patients, 5-year overall survival for the period 2010 to 2015 was 84% for younger children (1-9 years) and 66% for older children and adolescents (10-17 years).[15] So, increasing age was already associated with worse survival outcome within the pediatric AML population.

In the present study, we investigated long-term survival of children and AYAs (0-39 years) diagnosed with AML in the Netherlands between 1990 and 2015 using population-based, nationwide data from the NCR including information on therapy and site of primary treatment. Our primary objective was to determine whether AYA AML patients (18-39 years) also have a worse prognosis than pediatric AML patients (0-17 years) in the Netherlands and if differences in prognosis have changed over time due to improved survival.

2 | PATIENTS AND METHODS

2.1 | Data collection

All patients aged 0 to 39 years who were diagnosed with AML in the Netherlands between 1990 and 2015 were identified using the NCR. The NCR is a population-based cancer registry with national coverage since 1989 and has an estimated completeness of at least 96%.[16,17] The NCR receives information concerning all incident cancers diagnosed in the Netherlands from the Nationwide Network and Registry of Histopathology and Cytopathology (PALGA) and the National Registry of Hospital Discharges. After notification, trained registration clerks of the NCR collect data on patient, tumor and treatment characteristics from medical records. Annual linkage with the nationwide Personal Records Database (BRP) is performed to check vital status (last linkage: 1 February 2020).

AML was defined based on International Classification of Childhood Cancer, third edition (ICCC-3), diagnostic group Ib "Acute myeloid leukemias". AML diagnoses were selected from the NCR using International Classification of Diseases for Oncology, third edition (ICD-O-3), morphology codes 9840, 9841 (ICD-O-2), 9861, 9864 (ICD-O-2), 9865 to 9867, 9869 to 9874, 9877 to 9879, 9891, 9895 to 9898, 9910 to 9912, 9920, 9930, 9931 and 9932 (ICD-O-2). Since 2001, core-binding factor (CBF) leukemia (t[8;21][q22;q22], inv[16] [p13.1;q22] or t[16;16][p13.1;q22]) has consistently been registered in the NCR based on morphology code. To obtain information regarding CBF leukemia for children diagnosed during the entire study period, linkage was performed with the database of the Dutch Childhood Oncology Group (DCOG), which includes all patients treated at pediatric oncology centers in the Netherlands.[15] Cytogenetic testing for CBF leukemia has been performed more structurally since 2001. Acute promyelocytic leukemia (APL, ICD-O-3 code 9866) and myeloid leukemia associated with Down syndrome (ML-DS, ICD-O-3 code 9898) have a much better prognosis than the other AML subtypes and are treated differently. Therefore, APL patients (N = 202) were analyzed separately. ML-DS patients (N = 28) were excluded from the relative survival, excess mortality and early mortality analyses,

because ML-DS was not diagnosed in AYAs. Depending on their age at diagnosis, patients were classified as either children (0-17 years) or AYAs (18-39 years). Patients were followed from their date of diagnosis until death, emigration, loss to follow-up or 1 February 2020 (end of follow-up), whichever occurred first.

2.2 | Statistical analyses

Descriptive statistics were used to assess characteristics of the study population. Statistical significance of differences between children and AYAs was tested by Pearson's X^2 tests or Fisher's exact tests (N ≤ 5 in one or more categories) for categorical variables.

Five- and 10-year relative survival rates were estimated utilizing the traditional cohort approach by applying the strs procedure in Stata[18] using 6-month intervals during the first year of follow-up and annual intervals thereafter. Relative survival estimates disease-specific survival by correcting for mortality due to competing causes and is calculated by dividing the observed patient survival by the expected survival of a comparable cohort from the general population.[18] Expected probabilities of survival were determined by the Ederer II method[19] using Dutch population life tables stratified by age, sex and calendar year, which were obtained from Statistics Netherlands (CBS). Linear trends in relative survival over the diagnostic periods (1990-1999, 2000-2009 and 2010-2015) were assessed by generalized linear models (GLMs) using a Poisson assumption for the observed number of deaths.[18] GLMs were also utilized to investigate the relation between age at diagnosis and excess mortality, which is the mortality analogue of relative survival. To adjust for potential confounding, multivariable models were run including sex, diagnostic period, SCT (only for AML) and site of primary treatment. Patients were classified as being treated at an academic hospital when they had received chemotherapy or a SCT at such type of hospital. All GLMs were adjusted for follow-up time in years. The 1 to 9 year age group was used as reference when modeling excess mortality for more detailed age categories, because infants (0 years) with AML have a clearly worse prognosis than older children and the main aim of our study was to compare survival outcomes of children and AYAs. Patients who died on the day of diagnosis were included in the survival models with a follow-up time of 1 day.

Early mortality (death within 30 days of diagnosis) was examined as a secondary outcome to evaluate whether the potentially worse long-term survival of AYAs compared to children could be the result of higher mortality among AYAs shortly after diagnosis. Patients who died on the day of diagnosis were therefore included in the early mortality analyses. Logistic regression analyses were performed to investigate univariable and multivariable associations of age at diagnosis with early mortality. Multivariable analyses were adjusted for sex, diagnostic period and site of primary treatment. Furthermore, diagnostic period was entered as a continuous term into logistic regression models to obtain P-values for linear trends in early mortality over time. Patients diagnosed by autopsy were excluded from the relative survival, excess mortality and early mortality analyses (AML: N = 7, 0.4%; APL: N = 0). Death certificate only (DCO) cases are not

included in the NCR as there is no linkage with the cause-of-death registry at an individual basis due to legislation.

CBF leukemia has more consistently been tested and registered since 2001. To evaluate the potentially confounding effect of this favorable risk subtype on the excess mortality estimates, GLMs with and without adjustment for CBF leukemia (no vs yes) were compared for the period 2001 to 2015. Furthermore, relative survival was estimated in children and AYAs diagnosed with CBF leukemia after 2001.

Statistical analyses were executed using Stata 16 (StataCorp LLC, College Station, Texas). Two-sided P-values <.05 were considered statistically significant.

3 | RESULTS

3.1 | Characteristics study population

In the period 1990 to 2015, 2058 patients aged below 40 years were diagnosed with AML in the Netherlands, of whom 675 were children (0-17 years) and 1383 were AYAs (18-39 years). Patient characteristics are presented in Table 1. The median age at diagnosis was 6 years in children and 31 years in AYAs. Pediatric AML patients were more commonly boys compared to girls, whereas both sexes were fairly equally represented among AYAs. With respect to the AML subtypes, APL occurred more frequently in AYAs (12% vs 5%), whereas the opposite pattern was observed for ML-DS (0% vs 4%) and CBF leukemia (6% vs 14%). The proportion of patients treated at a nonacademic hospital was almost three times higher among AYAs compared to children (21% vs 8%). Of the patients who were treated at a nonacademic hospital, 82% received primary treatment at a teaching hospital. Furthermore, AYAs were nearly twice more likely to receive SCT than children (43% vs 23%). Patients with AML (excluding APL and ML-DS) and APL were further analyzed separately. After exclusion of diagnoses based on autopsy, 1821 AML patients and 202 APL patients could be included in the analyses. ML-DS patients (N = 28) were excluded.

3.2 | Acute myeloid leukemia

3.2.1 | Relative survival

The 5-year relative survival of AML patients younger than 40 years in the Netherlands increased by 22 percent-points during 1990 to 2015 from 40% to 62% (P_{trend} < .001, Table 2). Similarly, the 10-year relative survival improved from 37% to 47% between 1990 and 2009. Children (N = 612) had a better prognosis than AYAs (N = 1209, Table 2; Figure 1). Overall, 5- and 10-year relative survival were approximately 15 percent-points higher in children compared to AYAs. The rise in 5-year relative survival between 1990 and 2015 was more pronounced among children (+25%, P_{trend} < .001) than AYAs (+19%, P_{trend} < .001), causing the survival gap to be largest in the latest period. In 2010 to 2015, the 5-year relative survival of

TABLE 1 Characteristics of children (0-17 years) and AYAs (18-39 years) diagnosed with AML in the Netherlands between 1990 and 2015

Characteristics	Total		Children (0-17 years)		AYAs (18-39 years)		$P (\chi^2)$[a]
	N	%	N	%	N	%	
Overall	2058		675		1383		
Median age at diagnosis in years, IQR	26	21	6	12	31	11	
Sex							.001
Male	1040	50.5	377	55.9	663	47.9	
Female	1018	49.5	298	44.2	720	52.1	
Period of diagnosis							.04
1990-1999	833	40.5	247	36.6	586	42.4	
2000-2009	769	37.4	270	40.0	499	36.1	
2010-2015	456	22.2	158	23.4	298	21.6	
Subtype							<.001
APL	202	9.8	34	5.0	168	12.2	
ML-DS	28	1.4	28	4.2	0	0.0	
Myeloid sarcoma	21	1.0	9	1.3	12	0.9	
CBF leukemia: t(8;21) or inv(16)/t(16;16)[b]	174	8.5	95	14.1	79	5.7	
AML other	1633	79.4	509	75.4	1124	81.3	
Site of primary treatment							<.001
Nonacademic hospital	346	16.8	51	7.6	295	21.4	
Academic hospital	1711	83.2	624	92.4	1087	78.7	
Therapy							
Chemo	1946	94.7	645	95.8	1301	94.1	.11
SCT	744	36.2	155	23.0	589	42.6	<.001

Notes: The % missing values was <1% for all variables included in this table. Statistically significant *P* values (*P* < .05) are displayed in bold.
Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AYAs, adolescents and young adults; CBF, core-binding factor; IQR, interquartile range; ML-DS, myeloid leukemia associated with Down syndrome; SCT, stem cell transplantation.
[a]Fisher's Exact test was used instead of Pearson's X^2 test when N ≤ 5 in one or more categories.
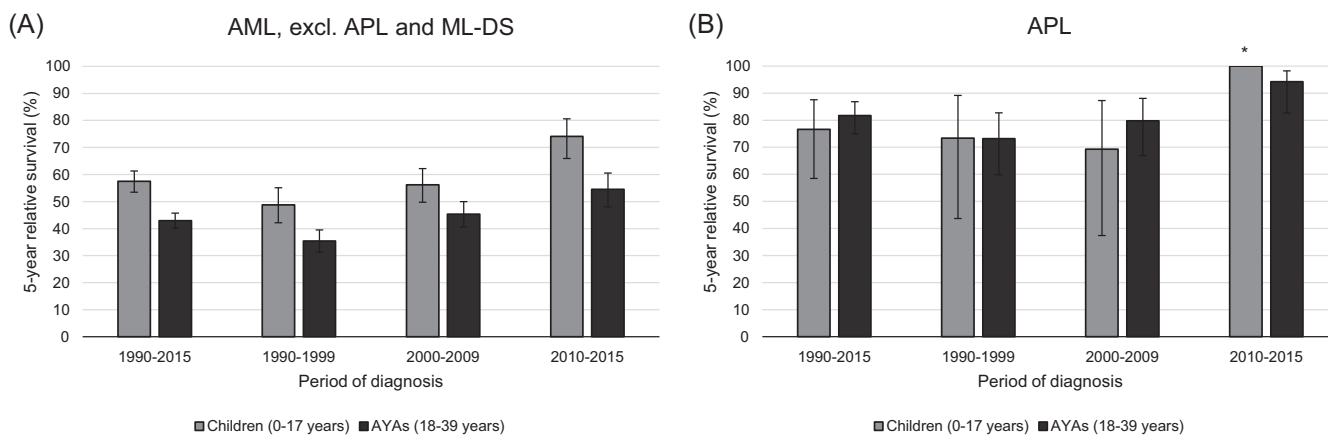[b]CBF leukemia was more consistently tested and registered as from 2001.

FIGURE 1 Five-year relative survival of children (0-17 years) and AYAs (18-39 years) diagnosed with AML (excl. APL and ML-DS, A) and APL (B) in the Netherlands between 1990 and 2015, overall and by diagnostic period. The error bars depict 95% CI of the survival estimates. *N at risk <10. AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AYAs, adolescents and young adults; ML-DS, myeloid leukemia associated with Down syndrome

children was 74%, which was nearly 20 percent-points higher than the corresponding estimate for AYAs (55%). Furthermore, the survival advantage of children over AYAs generally remained present when considering subgroups based on sex, site of primary treatment and therapy (Table 2). Regarding the AML subtypes, CBF leukemia was more structurally tested and registered as from 2001. Within the group of patients diagnosed with CBF leukemia since 2001 (children: N = 68, AYAs: N = 68), children also had a better 5-year relative

TABLE 2 Five-year and 10-year relative survival[a] of children (0-17 years) and AYAs (18-39 years) diagnosed with AML (excl. APL and ML-DS) in the Netherlands between 1990 and 2015, overall and by subgroup

| | 5-year relative survival (1990-2015) | | | | | | | | | 10-year relative survival (1990-2009)[b] | | | | | | | | |
| | Total | | | Children (0-17 years) | | | AYAs (18-39 years) | | | Total | | | Children (0-17 years) | | | AYAs (18-39 years) | | |
	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE	N	%	SE
Overall	1821	47.8	1.2	612	57.5	2.0	1209	42.9	1.4	1435	41.8	1.3	473	51.2	2.3	962	37.1	1.6
Sex																		
Male	935	46.9	1.6	341	55.5	2.7	594	42.0	2.0	738	40.4	1.8	270	48.3	3.0	468	35.7	2.2
Female	886	48.8	1.7	271	60.0	3.0	615	43.8	2.0	697	43.3	1.9	203	55.1	3.5	494	38.5	2.2
Period of diagnosis																		
1990-1999	751	39.5	1.8	229	48.8	3.3	522	35.4	2.1	751	36.9	1.8	229	47.1	3.3	522	32.4	2.1
2000-2009	684	49.3	1.9	244	56.2	3.2	440	45.4	2.4	684	47.1	1.9	244	55.0	3.2	440	42.7	2.4
2010-2015	386	61.6	2.5	139	74.1	3.7	247	54.5	3.2	NA	NA	NA	NA	NA	NA	NA	NA	NA
P_{trend}		**<.001**			**<.001**			**<.001**			**<.001**			**.04**			**.001**	
Site of primary treatment																		
Nonacademic hospital	287	35.0	2.8	44	36.4	7.3	243	34.7	3.1	249	29.4	2.9	43	37.3	7.4	206	27.7	3.1
Academic hospital	1534	50.2	1.3	568	59.1	2.1	966	45.0	1.6	1186	44.4	1.5	430	52.6	2.4	756	39.7	1.8
Therapy																		
Chemo	1731	49.7	1.2	587	59.3	2.0	1144	44.8	1.5	1357	43.6	1.4	451	53.0	2.4	906	38.9	1.6
SCT	732	53.3	1.9	150	53.4	4.1	582	53.2	2.1	551	48.0	2.1	130	51.7	4.4	421	46.8	2.5

Note: Statistically significant *P* values (*P* < .05) are displayed in bold.

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AYAs, adolescents and young adults; ML-DS, myeloid leukemia associated with Down syndrome; SCT, stem cell transplantation; SE, standard error.

[a]Expected probabilities of survival were estimated using the Ederer II method.

[b]10-year relative survival could not be estimated for the most recent period 2010 to 2015 due to incomplete follow-up.

survival than AYAs (84% vs 75%), though this difference did not reach statistical significance.

Age-specific 5-year relative survival of AML is displayed in Figure 2. In the most recent time period, young children (1-9 year olds) had the best prognosis (5-year relative survival 84%). After a decline to 65% to 70% in 10 to 17 year olds, the 5-year relative survival continued to drop to just over 50% in 18 to 24 year olds. Thereafter, 5-year relative survival remained stable at 50% to 60% in older patients up to 39 years. Table S1 contains 5-year relative survival estimates of AML for some alternative categories of age.

3.2.2 | Regression excess mortality due to AML

Table 3 shows associations of age with excess mortality due to AML until 5 years of follow-up. After adjustment for follow-up time, sex, diagnostic period, SCT and site of primary treatment, AYAs experienced a 60% (95% confidence interval [CI]: 37%-86%) higher excess mortality compared to children. Using the 1 to 9 year age category as reference, excess hazard ratios (HRs) of mortality were almost two times increased in 18 to 29 and 30 to 39 year olds (both $P < .001$). Patients aged 10 to 17 years did not have a significantly higher excess risk of dying than 1 to 9 year olds (excess HR = 1.2). Although being present in all diagnostic periods, the higher excess mortality associated with adolescence and young adulthood was most evident in the latest period (Table S2). In 2010 to 2015, the excess risk of dying was almost 2.5 times increased in 10 to 17 year olds ($P = .02$) and 4 to 5 times in 18 to 29 and 30 to 39 year olds (both $P < .001$), when compared to 1 to 9 year olds. Excess HR estimates obtained using

alternative cut-offs for age are shown in Table S3. A sensitivity analysis including patients diagnosed after 2001 showed that additional adjustment for CBF leukemia did not relevantly affect the effect estimates of age (data not shown). Finally, diagnosis in 2000 to 2009 and 2010 to 2015 was associated with a significantly decreased excess mortality when compared to diagnosis in 1990 to 1999 in multivariable analyses (data not shown).

3.2.3 | Early mortality

One patient was censored alive at a follow-up of less than 30 days and therefore excluded from the early mortality analyses. In total, 114 patients (6%) died within 30 days of diagnosis between 1990 and 2015. During the study period, early mortality decreased by 5 percent-points reaching 4% in 2010 to 2015 ($P_{trend} = .001$), which was largely the result of the marked decline from 9% to 5% that occurred between 1990 to 1999 and 2000 to 2009. The frequency of early death was comparable among children (N = 39, 6%) and AYAs (N = 75, 6%, Figure 3). Figure 4 reveals that early mortality was lowest among 1 to 9 year olds, of whom 3% (N = 9) experienced early death between 1990 and 2015, and increased to 6% to 8% in older age categories.

Multivariable-adjusted associations of age with early mortality after AML diagnosis are presented in Table 4. The risk of early mortality did not significantly differ between children and AYAs (odds ratio [OR] AYAs vs children, 95% CI: 0.7, 0.4-1.0) after adjustment for sex, diagnostic period and site of primary treatment. When compared to 1990 to 1999, significantly reduced ORs of early death were observed for the two more recent time periods (ie, 2000-2009 and 2010-2015, data not shown).
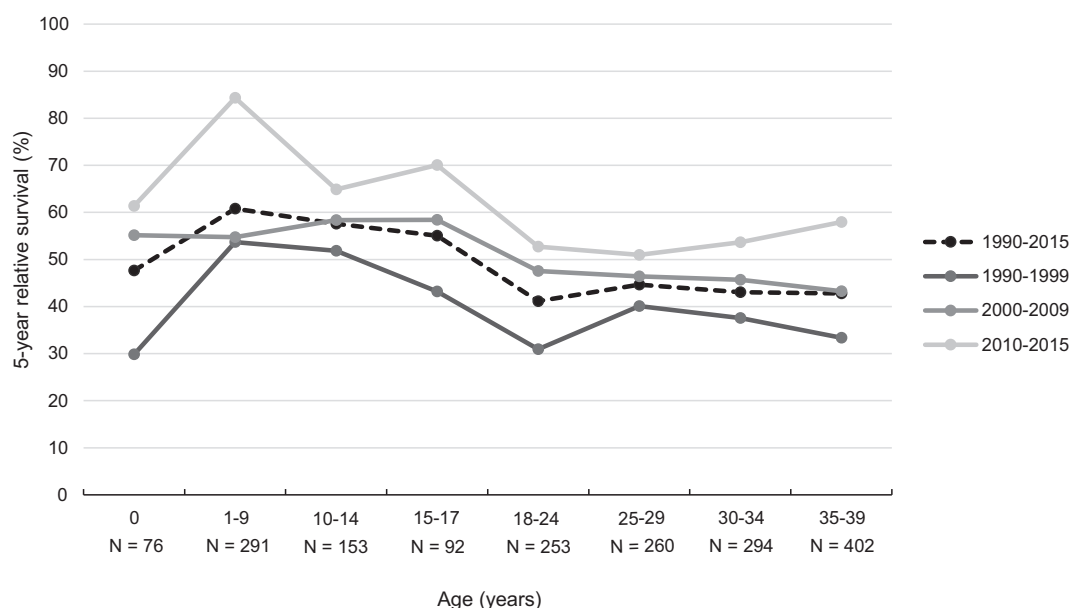

FIGURE 2 Age-specific 5-year relative survival of children and AYAs (0-39 years) diagnosed with AML (excl. APL and ML-DS) in the Netherlands between 1990 and 2015, overall and by diagnostic period. For each age category, the number of patients at risk in the entire period 1990 to 2015 is displayed. AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AYAs, adolescents and young adults; ML-DS, myeloid leukemia associated with Down syndrome

TABLE 3 Univariable and multivariable associations[a] of age with excess mortality due to AML (excl. APL and ML-DS) in children and AYAs (0-39 years) until 5 years of follow-up, the Netherlands, 1990-2015

Variable	$N_{at\ risk}$	Until 5 years of follow-up (1990-2015)								
		Univariable			Adjusted 1[b]			Adjusted 2[c]		
		Excess HR	95% CI	P-value	Excess HR	95% CI	P-value	Excess HR	95% CI	P-value
Age										
Children (0-17 years)	612	1.00 (ref)			1.00 (ref)			1.00 (ref)		
AYAs (18-39 years)	1209	1.50	(1.30-1.73)	**<.001**	1.47	(1.28-1.70)	**<.001**	1.60	(1.37-1.86)	**<.001**
Age (years)										
0	76	1.72	(1.20-2.47)	**.003**	1.83	(1.27-2.63)	**.001**	1.81	(1.26-2.60)	**.001**
1-9	291	1.00 (ref)			1.00 (ref)			1.00 (ref)		
10-17	245	1.17	(0.90-1.53)	.24	1.20	(0.92-1.56)	.18	1.24	(0.95-1.62)	.11
18-29	513	1.69	(1.36-2.10)	**<.001**	1.68	(1.35-2.08)	**<.001**	1.82	(1.45-2.28)	**<.001**
30-39	696	1.73	(1.40-2.13)	**<.001**	1.73	(1.40-2.13)	**<.001**	1.93	(1.55-2.40)	**<.001**

Note: Statistically significant P values (P < .05) are displayed in bold.

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AYAs, adolescents and young adults; CI, confidence interval; excess HR, excess hazard ratio; ML-DS, myeloid leukemia associated with Down syndrome; SCT, stem cell transplantation.

[a]All models were adjusted for follow-up time (years).

[b]Additionally adjusted for sex (male, female) and period of diagnosis (1990-1999, 2000-2009, 2010-2015).

[c]Additionally adjusted for sex (male, female), period of diagnosis (1990-1999, 2000-2009, 2010-2015), SCT (no, yes) and site of primary treatment (nonacademic hospital, academic hospital).
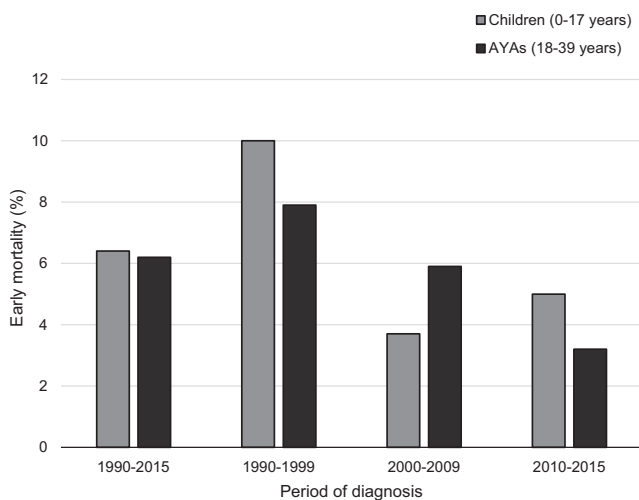

FIGURE 3 Early mortality (death within 30 days of diagnosis) in children (0-17 years) and AYAs (18-39 years) diagnosed with AML (excl. APL and ML-DS) in the Netherlands between 1990 and 2015, overall and by diagnostic period. AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AYAs, adolescents and young adults; ML-DS, myeloid leukemia associated with Down syndrome
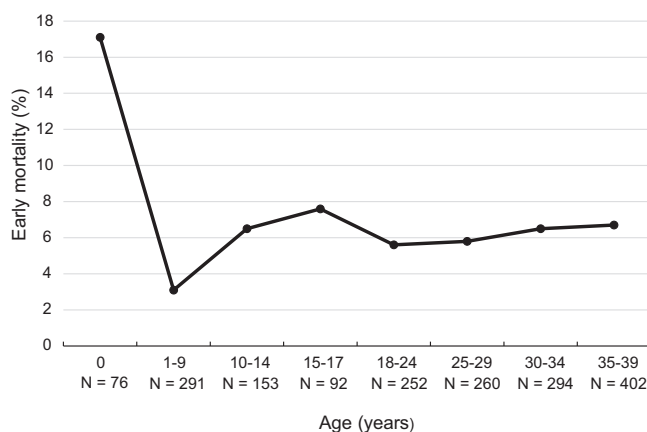

FIGURE 4 Age-specific early mortality (death within 30 days of diagnosis) in children and AYAs (0-39 years) diagnosed with AML (excl. APL and ML-DS) in the Netherlands between 1990 and 2015. For each age category, the number of patients at risk in the entire period 1990 to 2015 is displayed. AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AYAs, adolescents and young adults; ML-DS, myeloid leukemia associated with Down syndrome

3.3 | Acute promyelocytic leukemia

Children and AYAs diagnosed with APL in the Netherlands had a 5- and 10-year relative survival of 81% (1990-2015) and 74% (1990-2009), respectively (Table S4). A striking rise in 5-year relative survival from 78% to 95% (+17 percent-points) was observed

between 2000 to 2009 and 2010 to 2015. The prognosis of children (N = 34) and AYAs (N = 168) with APL seemed roughly comparable with 5-year relative survival estimates of 77% and 82%, respectively (Figure 1; Table S4). Moreover, the excess risk of mortality until 5 years of follow-up did not significantly differ between the groups after adjustment for follow-up time, sex, diagnostic period and site of primary treatment (excess HR AYAs vs children, 95% CI: 0.7, 0.3-1.5).

TABLE 4 Univariable and multivariable associations of age with early mortality[a] due to AML (excl. APL and ML-DS) in children and AYAs (0-39 years), the Netherlands, 1990-2015

Variable	N_early death	Univariable			Adjusted 1[b]			Adjusted 2[c]		
		OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age										
Children (0-17 years)	39	1.00 (ref)			1.00 (ref)			1.00 (ref)		
AYAs (18-39 years)	75	0.97	(0.65-1.45)	.89	0.95	(0.63-1.42)	.80	0.68	(0.44-1.04)	.07
Age (years)										
0	13	6.47	(2.65-15.79)	**<.001**	7.23	(2.93-17.86)	**<.001**	6.74	(2.67-17.00)	**<.001**
1-9	9	1.00 (ref)			1.00 (ref)			1.00 (ref)		
10-17	17	2.34	(1.02-5.34)	**.04**	2.40	(1.05-5.51)	**.04**	2.12	(0.91-4.93)	.08
18-29	29	1.88	(0.88-4.03)	.10	1.86	(0.86-3.99)	.11	1.19	(0.54-2.63)	.66
30-39	46	2.22	(1.07-4.59)	**.03**	2.26	(1.09-4.70)	**.03**	1.57	(0.74-3.34)	.24

Note: Statistically significant P values (P < .05) are displayed in bold.

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AYAs, adolescents and young adults; CI, confidence interval; ML-DS, myeloid leukemia associated with Down syndrome; OR, odds ratio.

[a]Early mortality was defined as death within 30 days of diagnosis.

[b]Adjusted for sex (male, female) and period of diagnosis (1990-1999, 2000-2009, 2010-2015).

[c]Adjusted for sex (male, female), period of diagnosis (1990-1999, 2000-2009, 2010-2015) and site of primary treatment (nonacademic hospital, academic hospital).

In total, 19 APL patients (9%) died within 30 days of diagnosis among which were 4 children (12%) and 15 AYAs (9%). Early mortality markedly decreased between 2000 to 2009 and 2010 to 2015 from 13% to 4%. These results should, however, be interpreted with caution as the number of early deaths among APL patients was small.

4 | DISCUSSION

In this nationwide population-based study among Dutch AML patients, we showed that AYAs (18-39 years) had a worse 5-year relative survival compared to children (0-17 years) in the period 1990 to 2015. The survival gap was consistently present across the calendar periods of diagnosis, but was most pronounced in the latest period 2010 to 2015. These findings were supported by multivariable analyses in which we showed that excess mortality due to AML in AYAs was 60% higher in the total study period and more than 160% higher in 2010 to 2015. Early mortality did not differ between children and AYAs. Overall, favorable trends over time were observed for both 5-year relative survival (increase) and early mortality (decline).

In contrast to AML, 5-year relative survival did not seem to differ between children and AYAs diagnosed with APL. The prognosis of APL patients improved considerably between 2000 to 2009 and 2010 to 2015 reaching a 5-year relative survival of 95%.

Similar to our findings for the Netherlands, several population-based studies from Europe have consistently reported lower long-term survival for AYAs with AML compared to pediatric patients.[11,13,14] According to the EUROCARE-5 study (2000-2007), 5-year relative survival after AML diagnosis was 61% in European children (0-14 years), which was 11 percent-points higher than the corresponding estimate for AYAs (15-39 years,

P < .001).[11] In the Nordic countries, 5-year relative survival estimates (2000-2013) were 74% for 0 to 14 year olds, 69% for 15 to 24 year olds and 62% for 25 to 34 year olds.[14] The 5-year relative survival of children (0-17 years) in our study was 74% in 2010 to 2015, which was almost 20 percent-points higher than the 55% observed among AYAs. Besides the European studies, two US studies have evaluated the prognosis of children and AYAs with AML in the general population between the 1970s/1980s and early 2010s.[10,12] Five-year overall survival was 35% to 40% among AYAs compared to 45% to 52% among children. In addition to the lower survival, AYAs also experienced higher early mortality.

Currently, the outcome of young Dutch APL patients is excellent. We estimated a 5-year relative survival of 95% in the most recent time period. The prognosis of APL strongly improved between 2000 to 2009 and 2010 to 2015, most likely as the result of the combined use of all-*trans* retinoic acid (ATRA), initially with chemotherapy and later with arsenic trioxide (ATO), which has made APL the most curable form of AML in children and adults.[20-23] In line with the present results, previous publications have also reported similar population-based survival in pediatric and AYA patients with APL.[12,24]

Several factors have been proposed in the literature that could potentially contribute to the inferior prognosis of AYAs with cancer compared to pediatric patients, including differences in cancer biology, the lack of standardized treatment (not valid for AML), increased treatment-related toxicity or transplant-procedure related mortality with older age, longer delays in diagnosis and treatment, problems with adherence to treatment plans, lower participation rates in clinical trials and insurance barriers.[14,25-27]

Additional research efforts are essential in the endeavor to improve the management of AYAs with AML and to narrow the currently existing survival gap. Future studies should, for instance,

focus on disease biology and treatment characteristics. Differences in disease biology and disease-specific therapies are suggested to be more important contributors to the survival disparity between pediatric and AYA AML patients than social issues.[12] Moreover, the inclusion of information concerning cause of death (eg, refractory disease, relapse, infection, treatment-related toxicity, etc) could add valuable information as contributions of the various causes of death may differ depending on age at diagnosis.

AYAs with AML are thought to have different biological disease characteristics compared to children. Pediatric AML seems to differ cytogenetically and molecularly from adult AML.[10,28-30] For instance, the favorable risk subtype CBF AML has a higher relative frequency among children and adolescents. On the other hand, adult AML patients present more often with abnormalities of chromosomes 5 and 7, and internal tandem duplication mutations of fms-related tyrosine kinase 3 (FLT3-ITD), which are associated with a worse prognosis. Contrastingly, adverse risk translocations involving the gene nucleoporin 98 kD (NUP98) are almost exclusive to those of younger age and are more prevalent in children.[10,28-30] In children, single gene abnormalities are almost absent. Furthermore, Creutzig et al observed a gradual decline in the relative frequency of favorable cytogenetics from the age of 2 years, while the opposite seemed to apply to poor risk features.[31] Studies specifically focusing on cytogenetic and molecular abnormalities occurring in childhood and adolescence/young adulthood AML are, however, rather scarce.

The subtype information available in our study primarily related to morphology, which is of little prognostic value. Since 2001, CBF leukemia has consistently been registered in the NCR and patients have more structurally been tested for this subtype.[15] To investigate the role of CBF leukemia in the survival disparity that we observed between pediatric and AYA AML, we performed several sensitivity analyses in patients diagnosed after 2001. First, these analyses showed that adjustment for CBF leukemia in the multivariable models did not substantially alter the HR estimates of age. Second, within the subgroup of CBF leukemia patients, the survival gap remained present. The abovementioned findings indicate that the worse prognosis of AYA AML patients cannot (fully) be explained by differences in the relative frequency of CBF leukemia. Therefore, differences in other disease biological characteristics, diagnostic- and treatment-related factors or, for example, retrieval at relapse, are likely to be involved as well.

For acute lymphoblastic leukemia (ALL), most AYAs fare better by adherence to pediatric(-inspired) treatment regimens instead of adult ALL protocols.[26,32-34] Only a few studies have investigated the potential benefits of a similar approach in AYA AML with somewhat contradictory findings.[26] Generally, pediatric AML protocols include higher-intensity chemotherapy cycles compared to adult protocols and SCT is given more restrictively[26,35]; however, differences may be subtle in some settings. According to Woods et al, overall survival was significantly higher in 16 to 21 year old AML patients treated on pediatric trials (Children's Oncology Group) compared to adult trials (Cancer and Leukemia Group B and Southwest Oncology Group)[36]; however, participants of the pediatric trials were significantly younger. An Australian study has reported 5-year overall survival of 84% and

64% among AML patients aged 15 to 24 years treated on pediatric and adult protocols, respectively ($P_{log-rank}$ = .08).[37] In the Nordic countries, 5-year overall survival did not significantly differ between 15 to 18 year old AML patients treated in pediatric (51%) and adult (70%) settings,[38] although the inclusion of patients in the pediatric cohort started earlier. Two additional studies also reported comparable outcomes for pediatric and adult AML protocols, but each of these studies had its limitations (ie, large timespan of the data and large variety of institutional protocols included, and homogeneity of the pediatric and adult treatment regimens, respectively).[26,39,40]

During our study period, pediatric AML patients in the Netherlands were treated according to one of six consecutive DCOG treatment protocols (ANLL-87, ANLL-92/94, ANLL-97, AML 15, DB AML-01 and NOPHO-DBH AML 2012),[15] which generally consisted of four to five chemotherapy courses. The induction phase usually encompassed two cycles of an anthracycline, cytarabine and a third drug, which was followed by consolidation using high-dose cytarabine as a single agent or in combination with, for example, mitoxantrone or etoposide. In the 1990s, it was standard of care to proceed with allogeneic SCT (alloSCT) after attaining first complete remission (CR1). Subsequently, use of upfront alloSCT became restricted to specific risk groups and was even completely omitted from the DB AML-01 protocol. In the current NOPHO-DBH AML 2012 protocol, alloSCT in CR1 has been reintroduced for poor risk patients.[15] For a nice schematic overview of the active DCOG AML protocols, we refer to Figure S1 of a previously published article by Reedijk et al.[15] AYAs with AML were treated according to protocols designed by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) and Swiss Group for Clinical Cancer Research (SAKK) (HOVON-4(A), -29, -42(A), -92, -102 and -132). The remission-induction regimens consisted of two chemotherapy cycles including an anthracycline, cytarabine and generally a third drug if the patient was included in a clinical trial and randomized into the treatment arm. Patients achieving CR were subsequently treated with alloSCT, autologous SCT (autoSCT) or a third chemotherapy cycle, depending on their prognostic risk profile.[41-47]

AYA AML patients in the present study were almost twice more likely to receive SCT in CR1 compared to children, whereas only subtle differences in chemotherapy use were observed. In AML treatment, SCT is generally reserved for high-risk patients and was used with a lot of restriction in pediatric patients in the given time period because of the associated long-term toxicity. Pediatricians therefore often only transplanted as salvage therapy in CR2 rather than in CR1. Consequently, the relative frequency of SCT could possibly be a proxy for the proportion of high-risk patients, but also reflects specific concerns among pediatricians.[48] In our multivariable analysis, the excess HR of dying for AYAs vs children did not attenuate after adjustment for SCT, suggesting that differences in the appliance of SCT are not responsible for the lower relative survival of AYA AML patients in the Netherlands; however, it should be noted that the available treatment information was very general and possibly not sufficiently detailed to reveal meaningful differences between children and AYAs. We had, for example, no details concerning type of SCT (autologous/allogeneic) or salvage therapy. In contrast to alloSCT, which is standard in

higher risk AML, autoSCT is used in AYA patients with a more favorable prognosis.

Similar to other countries, AYAs diagnosed with AML in the Netherlands are less likely to enroll in clinical trials than pediatric patients (AYAs, 18-40 years: 68% vs children: 87%).[15,49] Higher participation rates of AYAs in and better compliance with clinical trials may advance the development of successful treatments for this specific patient group. Health insurance is obligatory in the Netherlands ensuring equal access to health care for all inhabitants. Therefore, insurance issues cannot have played a role in the worse outcome of AYAs in the present study.

Our study evaluated population-based survival of children and AYAs diagnosed with AML in the Netherlands using nationwide, high-quality data of the NCR, which has no restrictions regarding age or hospital of treatment. The relatively large number of patients is a major advantage of our investigation that allowed separate analysis for specific subgroups and the evaluation of survival trends over time. An additional strength includes the estimation of relative survival, instead of observed survival, to take the higher background mortality among AYAs into account. A weakness is the lack of detailed information regarding (cyto)genetic abnormalities and treatment. Moreover, the classification and registration of AML by the NCR has changed during the investigated period. The ICD-O-3 is based on the World Health Organization (WHO) classification of hematological malignancies and has been used for case ascertainment since 2001, whereas the ICD-O-2 (applied from 1993 to 2000) used the French-American-British classification of AML.[49]

In cancer research, no international consensus has been reached on the definition of AYAs yet, resulting in considerable variability in age ranges used to delineate AYAs across studies.[11,14] An age range of 15 to 39 years has been proposed by the US National Cancer Institute (NCI) and has been accepted by the European Network for Cancer in Children and Adolescents.[11,50] In the present study, we slightly deviated from the NCI definition by considering AYAs as those aged 18 to 39 years at diagnosis, because 18 years is the upper age limit for treatment at a pediatric oncology center in the Netherlands and almost all AML patients below this age (>95%) are treated at such center.[51] In addition to the comparison of children vs AYAs, we also estimated relative survival for smaller age intervals to gain more insight into the specific age at which the survival of young AML patients starts to decline.

In conclusion, AYAs diagnosed with AML in the Netherlands between 1990 and 2015 had a worse prognosis than pediatric patients. The survival disparity between children and AYAs seemed most pronounced in the latest period, suggesting that improvements in care leading to better outcome for younger children have not resulted in equal benefits for AYAs yet.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY 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 upon request.

ETHICS STATEMENT

According to the Central Committee on Research Involving Human Subjects (CCMO), this observational study does not require approval from an ethics committee in the Netherlands. Use of the anonymous data for our study was approved by the Privacy Review Board of the Netherlands Cancer Registry and the Biobank and Data Access Committee of the Princess Máxima Center for pediatric oncology, following the principles of the Code of Good Conduct of the Federa (https://www.federa.org/codes-conduct).

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