Improved relative survival in older patients with acute myeloid leukemia over a 30-year period in the Netherlands

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ACUTE MYELOID LEUKEMIA

Improved relative survival in older patients with acute myeloid leukemia over a 30-year period in the Netherlands: a long haul is needed to change nothing into something

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TO THE EDITOR:

It was somewhat disheartening to read Martínez-Cuadrón and colleagues' article about the general lack of improvement in the overall survival (OS) of 3637 older patients (≥60 years) diagnosed with acute myeloid leukemia (AML) in Spain during 1999–2013 [1]. This finding is rather unexpected since AML management has gradually evolved over the past decades, particularly in recent years [2]. The authors acknowledged that their study's major limitation was using a cooperative group registry instead of a population-based registry, thereby impeding their study findings' generalizability.

To complement and extend their observations, we here report the results of a nationwide, population-based study that describes trends in primary therapy and relative survival (RS) among more than 12,000 older patients diagnosed with AML in the Netherlands during a 30-year period.

We selected all patients with AML aged ≥60 years diagnosed during 1989-2018—with survival follow-up through December 31, 2020—from the nationwide Netherlands Cancer Registry (NCR) using International Classification of Diseases for Oncology morphology codes as described in the Supplemental [3]. Patients diagnosed with acute promyelocytic leukemia ($n = 303$) and blastic plasmacytoid dendritic cell neoplasms ($n = 39$), and patients diagnosed with AML at autopsy ($n = 57$) were excluded. Information on demographics, disease morphology, and primary therapy—i.e., best supportive care (BSC) only, anti-neoplastic therapy ± stem cell transplantation (SCT), and other/unknown therapy—was available in the NCR and obtained via retrospective medical records review. Information on the exact therapeutic regimen was available for patients diagnosed from 2014 onwards. The Privacy Review Board of the NCR approved the use of anonymous data for this study.

Patients were categorized into five calendar periods (i.e., 1989–1994, 1995–2000, 2001–2006, 2007–2012, and 2013–2018) and five age groups at diagnosis (i.e., 60–64, 65–69, 70–74, 75–79, and ≥80 years). RS was calculated up to five years post-diagnosis until death, emigration, or end of follow-up (December 31, 2020), whichever occurred first. RS was defined as the ratio of observed to expected survival in the general population, matched for age, sex, and calendar year using national annual life tables [4]. Poisson regression was used to assess trends in RS between the first and last calendar period across the five age groups and to model the effect of calendar period on the excess mortality rate ratio (EMRR) during the first five years after diagnosis according to the five age groups, with adjustment for sex, prior malignancy, and years of follow-up. An additional adjustment was made for treatment to assess its effect on the EMRR of each calendar period [5]. A P value of <0.05 implies statistical significance. A detailed description of the statistical analyses is given in the Supplemental.

A total of 12,229 patients with AML ≥ 60 years were included in the analyses (57% males; median age, 73 years; 18% prior malignancy; Supplemental Table 1).

The application of anti-neoplastic therapy followed by an SCT increased with each calendar period in patients aged 60–64 years (from 1% to 48% between 1989–1994 and 2013–2018; $P < 0.001$; Fig. 1A). This treatment approach was gradually introduced for patients aged 65–69 and 70–74 years during the 2000s, ultimately reaching 27% and 10% during 2013–2018, respectively (Fig. 1A). The application of anti-neoplastic therapy started to increase from 2007 onwards among patients aged 75–79 and ≥80 years ($P < 0.001$; Fig. 1A). Overall, the use of BSC only increased with advancing age across all calendar periods ($P < 0.001$; Fig. 1A).

Detailed data on primary therapy among 3160 patients diagnosed during 2014–2018 showed that 75% of patients aged 60–64 years received intensive, potentially curative therapy (Fig. 1B). The use of this treatment approach decreased dramatically after the age of 70, following a broader application of hypomethylating agents and/or BSC only (Fig. 1B). In the overall cohort, an SCT was applied in 15% of the patients.

Figure 2A–C shows that the 1-, 3-, and 5-year RS improved significantly between the first and last calendar period across all age groups ($P < 0.001$). The improvements were most pronounced among patients aged 60–64 and 65–69 years, particularly regarding the 3- and 5-year RS. Consequently, the age differential in RS widened over time.

The primary age-stratified models for RS showed that the EMRR was lower for patients diagnosed during 2013–2018 compared to 2007–2012 (Supplementary Fig. 1A). After additional adjustment for primary therapy, the prognostic effect of calendar period lost statistical significance (Supplemental Fig. 1B). This finding hints that changes in the application of primary therapy contributed to the improved RS between 2007–2012 and 2013–2018.

In contrast to Martínez-Cuadrón and colleagues' study [1], the population-level survival of AML patients across all older age groups improved over time in the Netherlands. We could link this improvement to changing treatment practices over time. Differences in study populations might account for the survival

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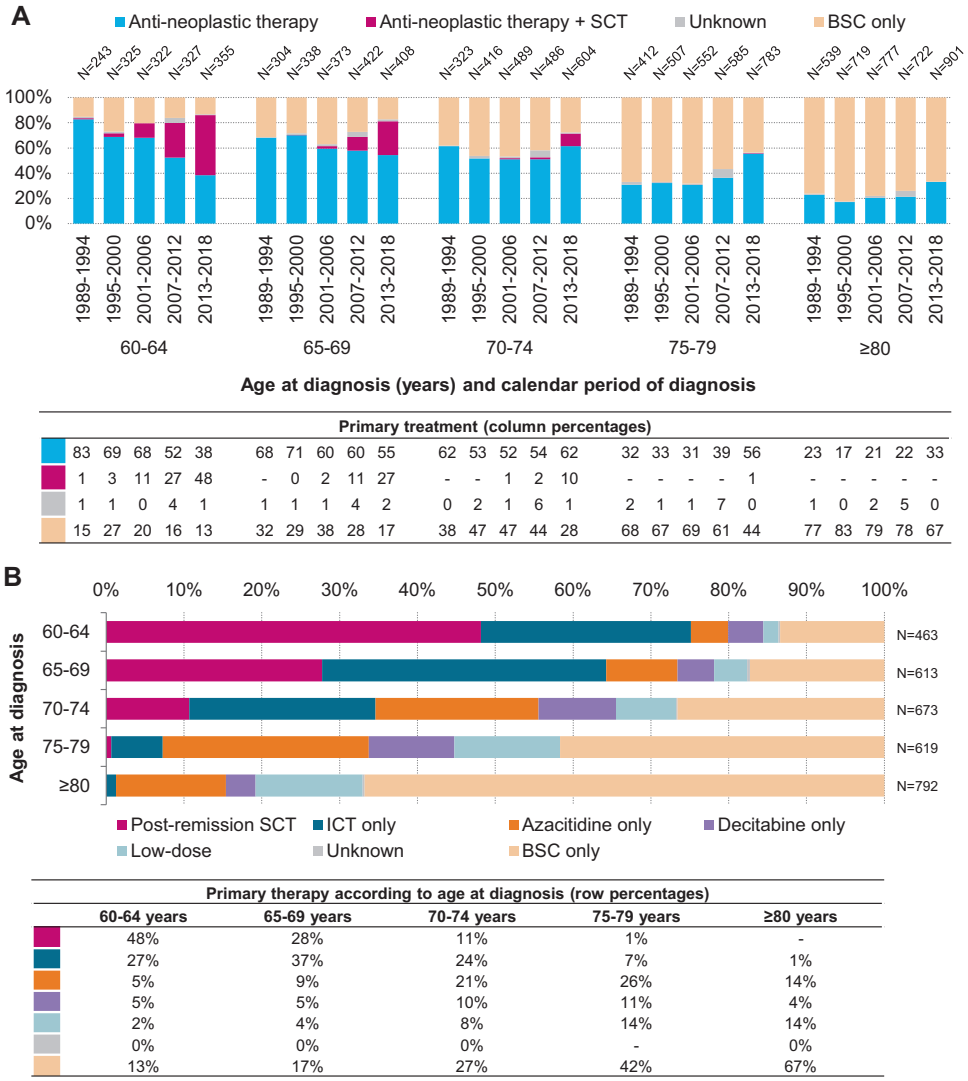
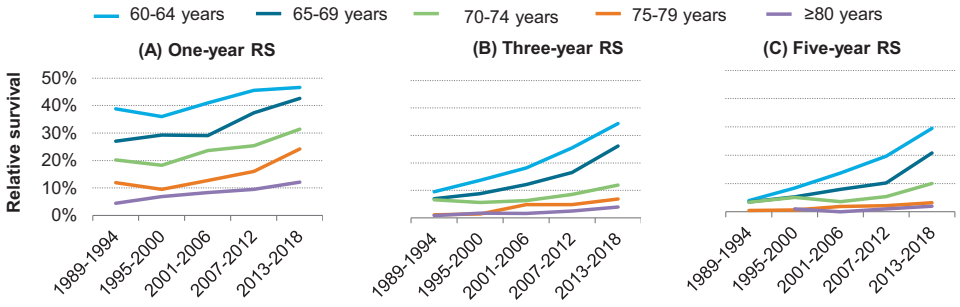


Fig. 1 Primary therapy of older (≥60 years) patients with AML in the Netherlands. Panel **A** shows the results of primary therapy in broad categories for patients diagnosed during the calendar period 1989–2018 according to age at diagnosis and calendar period of diagnosis. The table presents the proportion of patients receiving a particular treatment within a specific age group and calendar period. The absolute number of patients within a specific age group is shown above the graph bars. Before the calendar period 2014, the exact type of anti-neoplastic therapy was not registered in the Netherlands Cancer Registry. This also holds for the type of stem cell transplantation (i.e., allogeneic or autologous). The anti-neoplastic therapy group collectively includes treatment with low-dose approaches (e.g., hydrea), hypomethylating agents, and intensive remission induction chemotherapy. Panel **B** shows the specific type of primary therapy according to age at diagnosis for patients diagnosed during the calendar period 2014–2018. The table presents the proportion of patients receiving a particular treatment within a specific age group. The absolute number of patients within a specific age group is shown on the right of the graph bars. Low-dose chemotherapy includes oral treatment with hydrea, mercaptopurine, or melphalan. A stem cell transplantation (88% allogeneic and 12% autologous) was frequently applied after intensive remission induction chemotherapy (83%) or after decitabine (14%) and azacitidine (1%). *BSC* best supportive care, *SCT* stem cell transplantation, *ICT* intensive remission induction chemotherapy.

differences between Spain and the Netherlands because we used a population-based cancer registry that overcomes issues regarding generalizability and selection biases inherent to cooperative group registries as used in the Spanish study. Regarding the applied treatment approaches, the use of SCT increased in the Netherlands—of which its use was restricted to patients aged 60–74 years—reaching an overall rate of 15% in all elderly (≥60 years) patients in 2013–2018. That rate was around 5% in Spain during 1999–2013 [1]. Furthermore, in contrast to Spain, patients aged ≥75 years in the Netherlands more often received anti-neoplastic therapy [1]. The overall use of anti-neoplastic therapy (i.e., intensive and non-intensive) remained unchanged in Spain. Also, the use of intensive chemotherapy—which has a curative potential, especially when followed by post-remission therapy [6]—decreased over time in Spain, following a broader application of non-intensive therapies [1].

Limitations of our study include the lack of detailed clinical and treatment information throughout most of the registry. Notwithstanding these limitations, this nationwide, population-based showed that the survival of older AML patients gradually increased over time concurrently with changing treatment practices. Therefore, our subtitle "*a long haul is needed to change nothing into something*" provides optimism in the progress against AML. Nevertheless, continuous efforts are warranted to further improve the outlook of older AML patients because contemporary diagnosed patients still experience substantial excess mortality.



Age at diagnosis (years) and calendar period of diagnosis

Age	Calendar period and RSR (with 95% CI)				
	89-94	95-00	01-06	07-12	13-18
60-64	39 (33-45)	36 (31-41)	41 (36-46)	46 (41-50)	47 (41-51)
65-69	27 (22-32)	29 (24-34)	29 (25-34)	37 (33-42)	43 (39-46)
70-74	20 (16-25)	18 (15-22)	24 (20-28)	25 (22-29)	31 (28-35)
75-79	12 (9-16)	10 (7-13)	13 (10-16)	16 (13-19)	24 (21-28)
≥80	4 (3-7)	7 (5-10)	8 (6-11)	10 (8-12)	12 (10-14)

	Calendar period and RSR (with 95% CI)				
	89-94	95-00	01-06	07-12	13-18
	9 (6-14)	14 (10-18)	18 (14-23)	25 (21-30)	34 (30-39)
	7 (4-10)	9 (6-12)	12 (9-16)	17 (13-20)	26 (23-30)
	7 (4-10)	6 (4-8)	6 (4-9)	9 (6-11)	12 (10-15)
	1 (0-3)	1 (1-3)	5 (3-7)	5 (3-7)	7 (5-9)
	2 (1-4)	2 (1-4)	2 (1-3)	3 (1-4)	4 (3-6)

	Calendar period and RSR (with 95% CI)				
	89-94	95-00	01-06	07-12	13-18
	4 (2-7)	8 (6-12)	14 (10-18)	20 (16-24)	30 (25-34)
	4 (2-6)	5 (3-8)	8 (6-11)	10 (8-13)	21 (17-24)
	3 (2-6)	5 (3-8)	4 (2-6)	5 (4-8)	10 (8-13)
	0 (0-2)	1 (0-2)	2 (1-4)	2 (1-4)	3 (2-6)
NA	1 (0-3)	0 (0-0)	1 (1-3)	2 (1-5)	

Fig. 2 Relative survival of older (≥60 years) patients with AML in the Netherlands, 1989–2018. One-, three-, and five-year relative survival according to the calendar period of diagnosis and age at diagnosis are shown in panels **A**, **B**, and **C**, respectively. The table presents the projected 1-, 3-, and 5-year relative survival, with 95% confidence intervals, according to the calendar period of diagnosis and age at diagnosis. *P* values for the likelihood ratio test assessing linear trends in relative survival between the first (1989–1994) and last (2013–2018) calendar period were statistically significant with values of less than 0.0001 across all age groups for the 1-, 3-, and 5-year relative survival. NA (not applicable) indicates subgroups that did not survive five years post-diagnosis. *RS* relative survival, *RSR* relative survival rate, *CI* confidence interval.

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AUTHOR CONTRIBUTIONS

AGD designed the study; ZLRK analyzed the data; OV was responsible for the data collection; ZLRK wrote the manuscript with contributions from all authors, who also interpreted the data, and read, commented on, and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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