BMJ Oncology

Regional disparities in the use of intensive chemotherapy for AML in the Netherlands: does it influence survival?

Z L Rana Kaplan ,[1,2] Nikki van Leeuwen,[1] David van Klaveren,[1] Otto Visser,[3] Eduardus F M Posthuma,[4,5] Danielle van Lammeren-Venema,[6] Tjeerd J F Snijders,[7] Catharina H M J van Elssen,[8] Anna van Rhenen,[9] Peter A von dem Borne,[5] Nicole M A Blijlevens,[10] Jan J Cornelissen,[11] Marc H G P Raaijmakers,[11] Arjan A van de Loosdrecht,[12] Gerwin Huls,[13] Valery E P P Lemmens,[1,2] Hester F Lingsma,[1] Avinash G Dinmohamed[1,2,13]

To cite: Kaplan ZLR, van Leeuwen N, van Klaveren D, *et al*. Regional disparities in the use of intensive chemotherapy for AML in the Netherlands: does it influence survival? *BMJ Oncology* 2024;**3**:e000264. doi:10.1136/bmjonc-2023-000264

Received 16 November 2023
Accepted 13 May 2024

For numbered affiliations see end of article.

Correspondence to
Dr Z L Rana Kaplan;
z.kaplan@erasmusmc.nl

ABSTRACT

Objective Acute myeloid leukaemia (AML) prognosis is enhanced with intensive remission induction chemotherapy (ICT) in eligible patients. However, ICT eligibility perceptions may differ among healthcare professionals. This nationwide, population-based study aimed to explore regional variation in ICT application and its relation with overall survival (OS).

Methods and analysis We compared nine Dutch regional networks using data from the Netherlands Cancer Registry. Regional variance was assessed for the entire population and age subgroups (ie, ≤60 years and >60 years) using multivariable mixed effects logistic and Cox proportional hazard regression analyses, expressed via median OR (MOR) and median HR (MHR).

Results Including all adult AML patients from 2014 to 2018 (N=4060 patients; 58% males; median age, 70 years), 1761 (43%) received ICT. ICT application varied from 36% to 57% (MOR 1.36 (95% CI 1.11 to 1.58)) across regions, with minor variations for patients aged ≤60 years (MOR 1.16 (95% CI 1.00 to 1.40)) and more extensive differences for those aged >60 years (MOR 1.43 (95% CI 1.16 to 1.63)). Median OS spanned 4.9–8.4 months across regions (MHR 1.11 (95% CI 1.00 to 1.15)), with pronounced differences in older patients (MHR 1.12 (95% CI 1.08 to 1.20)) but negligible differences in the younger group (MHR 1.02 (95% CI 1.00 to 1.14)). Survival differences for the total population and the older patients decreased to respectively, MHR 1.09 (95% CI 1.00 to 1.13) and 1.10 (95% CI 1.04 to 1.18), after additional adjustment for the probability of receiving ICT within a region, indicating approximately 10% unexplained differences.

Conclusion Regional disparities in ICT application and survival exist, especially in older AML patients. However, ICT application differences partially explain survival disparities, indicating the need for more standardised ICT eligibility criteria and a better understanding of underlying causes of outcome disparities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Swedish Acute Leukaemia Registry Group revealed differences in acute myeloid leukaemia (AML) management across regional cancer networks using nationwide, population-based data from Sweden. Their studies showed better overall survival (OS) for patients with AML in regional cancer networks where first-line treatment with intensive therapy was more prevalent. The remaining studies mainly focused on integrating patient characteristics and prognostic features to inform uniform treatment decisions, with an absence of studies examining the association between regional differences in AML management and patient outcomes.

WHAT THIS STUDY ADDS

⇒ Our study fills a notable gap in the existing literature. In this nationwide population-based, we addressed practice variation in AML management across nine regional cancer networks in the Netherlands. Our study is the first to quantify practice variation in induction chemotherapy (ICT) application and assess its effect on OS. We showed significant between-region differences in the application of ICT and OS, most pronounced among older AML patients. However, variations in ICT application only partially account for survival disparities.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study provides insights into the AML care practices in the Netherlands and highlights the importance of uniform care delivery to enhance patient outcomes. The evidence presented in this study adds to the existing knowledge and shows the urgency to create understanding into the disparities in treatment and outcomes.

INTRODUCTION

Acute myeloid leukaemia (AML) is a clonal haematopoietic stem cell malignancy characterised by an aggregation of immature progenitor cells that fail to differentiate, resulting in ineffective haematopoiesis.[1] It is a rare malignancy with an age-standardised incidence rate of approximately 3–5 per

100 000 person-years. AML affects a broad age spectrum of individuals; however, it has a predilection to affect individuals above age 60.[2–4] Furthermore, this malignancy is known for its heterogeneity in cytomorphology, immunophenotype, cytogenetics, molecular genetics, epigenetic signatures and treatment responses.[1 2 4–12]

AML is a rapidly fatal malignancy when not recognised and managed promptly.[2 4 10] Intensive remission induction chemotherapy (ICT) with the so-called 7+3 regimen (ie, cytarabine combined with anthracycline), followed by consolidation therapy, currently offers a curative potential for patients with AML.[8 13] However, its application is restricted to medically fit patients who can tolerate intensive treatment. Patient eligibility for intensive treatment is based on disease-specific (eg, cytogenetics) and patient-related factors (eg, age and physical and mental health status). Discussing patients within multidisciplinary tumour boards is essential to ensure uniformity in ICT application.[14] In the Netherlands, regional cancer networks collectively manage AML to ensure integrated care over multiple care processes—that is, diagnosis, treatment, post-treatment follow-up care and palliative care—across regional healthcare providers.[15]

Over the past decades, the population-level survival of patients with AML improved considerably, particularly among those below age 70.[4 16] This improvement can be linked to an increased provision of treatment with ICT over time, leading to consecutive increases in of allogeneic stem cell transplantation (alloSCT) and advances in supportive care measures, postremission therapies and targeted agents. The population-level survival in AML may be further improved when the provision of treatment is uniformly distributed across regional cancer networks.[16 17] This notion stems from earlier population-based studies conducted in Sweden during the late 2000s and early 2010s.[9 17 18] While Sweden is a country that provides its citizens with equal access to healthcare services, these studies revealed that the overall survival (OS) of patients with AML was higher in regional cancer networks with a higher rate of first-line treatment with intensive therapy.[18]

At present, studies on regional disparities in AML management and its relation with OS are inherently scarce and dated. Furthermore, the current literature on this topic does not concurrently consider the variability in baseline patient and AML characteristics (ie, casemix) and variation due to chance (ie, random variation). Therefore, in this nationwide, population-based study, we aimed to assess the between-region variation in (1) the application of ICT and (2) OS in the Netherlands.

MATERIALS AND METHODS

The Netherlands Cancer Registry

We used data from the Netherlands Cancer Registry (NCR) for this study. Founded in 1989, the NCR is maintained and hosted by the Netherlands Comprehensive Cancer Organisation and covers at least 95% of all malignancies in the Netherlands.[19] The Nationwide Network of Histopathology and Cytopathology and the National Hospital Discharge Registry (ie, inpatient and outpatient discharges) notify the NCR of newly diagnosed malignancies in the Netherlands. After case notification, trained registrars retrospectively collect data from the medical records within 12 months postdiagnosis. These data include the date of birth and diagnosis, sex, disease topography and morphology, primary treatment, and hospital of diagnosis and treatment. The last known vital status for all patients (ie, alive, dead or emigration) is obtained through the annual linkage of the NCR with the Nationwide Population Registries Network that holds this information of all residents in the Netherlands.

Study population

We selected all adult (≥18 years) patients diagnosed with AML between 1 January 2014 and 31 December 2018—with survival follow-up through 1 February 2022—using morphology codes of the International Classification of Disease for Oncology as described elsewhere.[16] We chose to include patients diagnosed from 2014 onwards due to the availability of more detailed information on prognostic factors and the availability of data on the exact therapeutic regimens from this year onwards. Patients diagnosed with acute promyelocytic leukaemia (n=172) and blastic plasmacytoid dendritic cell neoplasms (n=37), as well as those diagnosed at autopsy (n=5) and who received treatment outside of the Netherlands (n=17) were excluded. All patients were followed from diagnosis until death, emigration or last follow-up, whichever occurred first.

Reporting patient and public involvement in research

In this study, it was not possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Regional networks

Haemato-oncological care in the Netherlands is divided into 10 regional networks as designated by the Hemato-Oncology Foundation for Adults in the Netherlands (HOVON).[15] Each regional network, except for two, includes a university hospital responsible for clinical consultations for non-university hospitals within that region. A non-academic teaching hospital provides clinical consultations to other hospitals in one regional network. This regional network was considered a separate network in these analyses. The other regional network, in which a non-academic teaching hospital also provides clinical consultations to other hospitals, is geographically located in the catchment area of a regional network with a university hospital. In addition, non-academic teaching hospital collaborates with that regional network to ensure integrated care. Therefore, these two regional networks were merged based on these two factors. Collectively, this study discerns nine regional networks. The regional

network corresponds with the region where the patient was diagnosed.

The Netherlands has a well-established healthcare system where all residents have equal access to high-quality healthcare services, irrespective of their socioeconomic position and place of residence.[20] Furthermore, all patients with AML in the Netherlands are diagnosed and managed in non-private hospitals. Therefore, treatment decision-making is solely based on patient-related and disease-related characteristics in concert with patient preference. The regional networks in the Netherlands have all the required expertise and facilities to manage AML properly.

Definition of primary therapy

Primary therapy was divided into ICT and non-intensive therapy. Treatment with ICT is applied in hospitals qualified for intensive haematological care.[15] Patients with AML were generally classified as eligible for ICT during our study period based on their age and physical and mental health status.[1 12 21 22] Furthermore, intensive postremission therapy consists of a third cycle with ICT, autologous SCT (autoSCT) or alloSCT. The choice for a particular postremission strategy is generally guided by AML genetics and the patient's fitness and preference.[1] However, practice variation in postremission therapy was not further explored since its application depends on the outcome of the initial treatment with ICT. Of note, alloSCTs in the Netherlands are only applied in academic hospitals. As for autoSCTs, they can be applied in academic hospitals and three large, non-academic teaching hospitals. The regional network without a university hospital in their catchment area refers patients for an alloSCT outside their network. Patients not eligible for ICT can be managed with best supportive care (BSC) only, hydroxyurea, low-dose cytarabine, azacitidine or decitabine. These modalities comprise the group of non-intensive therapy.

Statistical analyses

Descriptive analyses

Descriptive statistics were used to present patient and treatment characteristics across the nine regional networks. The Pearson's χ^2 test was used to compare categorical covariates, and the Kruskal-Wallis test to compare non-normally distributed continuous covariates. The Kaplan-Meier method was applied to estimate OS for each regional network. We used the log-rank test to test whether the OS distribution of the regional networks was statistically equivalent.

Between-region variance in the application of intensive chemotherapy

Differences in casemix and random variation should be accounted for when assessing between-region variation.[23 24] Therefore, we employed mixed effects modelling with a random effect for the regional network. The between-region variation in ICT application was assessed using a mixed effects logistic regression model. Fixed-effect terms for important baseline characteristics were added to the mixed effects model to account for differences in casemix. Casemix adjustment was performed for the following baseline characteristics: age on a continuous scale, sex, socioeconomic status (SES), secondary AML and hyperleucocytosis.[7 25 26] The SES indicator ranks neighbourhoods by postal code using the aggregated value of houses and household income. This indicator provided an aggregated level of SES for each postal code and was categorised as low (deciles 1–3), medium (deciles 4–7) and high (deciles 8–10). Hyperleucocytosis, defined as a white cell count $\geq 100\times10^9$/L, was included in the model as a dichotomous variable. The variance of the random effects in this model indicates the differences between regions in the outcome of interest beyond what can be explained by the differences in case mix. For example, a larger variance indicates a higher between-region variation. To convert this regional-level variance to a more interpretable measure, we estimated the median OR (MOR).[24] The MOR is the median value of the OR between the area at the highest risk and the area at the lowest risk and can be interpreted as the median of the increased odds on outcome when comparing two patients with identical baseline characteristics who are selected from two random regions. For example, an MOR of 1.5 for ICT application indicates that if two AML patients with the same baseline characteristics present at two random regions in our sample, one of the patients will have a 50% higher probability of receiving ICT than the other patient.

Between-region variance in OS

We used mixed effects Cox proportional regression analysis to assess regional differences in OS. We developed and compared two models: a model with (1) casemix adjustment as denoted above and (2) with additional adjustment for the likelihood of treatment with ICT within a region. This likelihood of treatment with ICT was estimated by applying a logistic regression model wherein we adjusted for relevant casemix variables and included the region as a fixed effect. To assess the extent to which variations in treatment regimens contribute to the observed survival differences, the regional fixed effects (ie, the natural logarithm of the odds of treatment with ICT per region) were consecutively included in the analysis of the between-region variance in OS. In both models, a random effect for the regional network was added. Also, both models included an adjustment for the 2010 AML classification of the European LeukemiaNet (ELN) and participation in first-line treatment trials. The ELN 2010 risk classification is a prognostic tool of patient outcome and stratifies patients into the following categories: favourable, intermediate I, intermediate II and adverse risk. Patients in whom cytogenetic risk profiling was not performed were categorised as unclassifiable ELN. These patients were not excluded from the analysis to ensure an objective representation

of AML practices in the Netherlands. Trial participation, defined as a dichotomous variable, was included because it could affect the OS of patients as it may act as a proxy for their health condition. After all, patients are generally enrolled in trials based on their physical and mental health state.[27] Model 2 was established to illustrate how practice variation in AML management between regions affects the between-region variance in the OS. Of note, all baseline characteristics were selected based on prior research that showed the prognostic value of these characteristics on OS.[1 7 14] The between-region variance was expressed as a median HR (MHR). This estimate can be interpreted similarly to the MOR. For example, an MHR of 1.3 indicates that if two AML patients with the same baseline characteristics present at two random regions in our sample, one of the patients will have a 30% higher mortality risk than the other. Since the allocation of ICT and patient outcome is highly dependent on age, all analyses were performed for the total AML population and age subgroups, including patients ≤60 years and >60 years. CIs for the MOR and MHR were estimated using a parametric bootstrap methodology.[28]

All analyses were performed using R statistical software V.1.4.1103.[29] Mixed effects modelling was applied using the lme4 package for logistic regression analysis and the coxme package for proportional hazards regression analysis.[30 31] P values <0.05 were considered statistically significant.

RESULTS

Patient characteristics

Our analytical cohort included 4060 adult (≥18 years) patients diagnosed with AML in the Netherlands between 2014 and 2018 (median age, 70 years; IQR age range, 61–78 years; 60% males; table 1). The number of patients in each region ranged between 181 and 775, owing to differences in population density across the regions. Patients' age and socioeconomic distribution, as well as the AML risk profile as per the ELN 2010 classification, varied significantly between the regions (p<0.001 for all covariates). As for the latter, the regional disparity in ELN risk classification is mainly driven by the unclassifiable ELN category due to unperformed cytogenetic testing. A total of 670 patients (17%) participated in a trial, of whom 90% were treated with ICT and 10% with hypomethylating agents (9% decitabine and 1% azacitidine). Lastly, the sex distribution and the distribution of secondary AML and hyperleucocytosis were comparable between the regions (p>0.05 for all covariates).

Regional differences in the application of intensive chemotherapy

Overall, the average application of ICT was 43% (N=1761), with substantial variation across the regional networks (range 36%–57%, table 1). As expected, patients receiving ICT were younger than those receiving non-intensive therapy (median age, 61 years; IQR age range, 51–67 years vs 76 years; IQR age range, 70–82 years; p<0.001) (online supplemental table 1). In the overall cohort, 26% of patients received SCT, of whom 80% and 20% received an alloSCT and autoSCT, respectively. An SCT was frequently applied after ICT (92%), followed by decitabine (6%) and azacitidine (1%). The remaining (2%) patients received an alloSCT upfront. Of note, from the total population, 254 patients (11%) received hydroxyurea, 62 patients (3%) were treated with low-dose cytarabine and 1200 patients (30%) only received BSC.

In the mixed effect logistic regression model, the MOR of the between-region variation in the application of ICT was 1.36 (95% CI 1.11 to 1.58) for the overall population. This estimate indicates that AML patients with the same measured baseline characteristics from a random region have a 36% higher chance of receiving ICT when they would have presented to another random region (figure 1A). Regional differences in the application of ICT were smaller in patients aged ≤60 years, with an MOR of 1.16 (95% CI 1.00 to 1.40) (figure 1B). Differences were larger in patients aged >60 years, with an MOR of 1.43 (95% CI 1.16 to 1.63). This finding indicates that an AML patient aged >60 years has a 43% higher chance of receiving ICT when presented to another random region (figure 1C).

Regional differences survival

The median OS ranged between 4.9 months (95% CI 3.5 to 6.4 months) to 8.4 months (95% CI 6.6 to 10.0 months) and was significantly different between the regional networks (figure 2; p=0.008). Also, OS significantly differed according to the treatment regimen in patients aged above 60 years (online supplemental figure 1).

In the initial mixed effects Cox proportional regression model, which only adjusted for random variation, casemix and trial participation, we found an MHR for between-region variation in OS of 1.11 (95% CI 1.00 to 1.15) (figure 3A). This estimate indicates that AML patients with the same measured baseline characteristics from a random region have an 11% higher chance of mortality when they present to another random region. After additional adjustment for the chance of receiving ICT within a regional network in the second model, the estimate of the MHR decreased to 1.09 (95% CI 1.00 to 1.13), with remaining differences between regions (figure 3B). This finding indicates that the between-region variation in OS may partially be explained by variations in the application of ICT across the regional networks. No significant survival variation was found in patients aged ≤60 years (figure 3C,D). However, in patients aged >60 years, we found between-region variation in OS with an MHR of 1.12 (95% CI 1.08 to 1.20) (figure 3E). After adjustment for the likelihood of ICT within a regional

Table 1 Baseline patient characteristics of AML patients treated in regional networks in the Netherlands

	Total population		Regional network-level range			P value
Characteristics	No.	(%)	Percentage			
Total no. of patients	4060	(100)	181	–	775	
Sex						0.938
Male	2342	(58)	(54)	–	(60)	
Female	1718	(42)	(40)	–	(46)	
Age, years						
Median (IQR)	70 (61–78)		67 (58–75)	–	71 (63–79)	<0.001
18–40	196	(5)	(3)	–	(7)	0.006
41–60	808	(20)	(17)	–	(24)	
61–70	1123	(28)	(25)	–	(33)	
71–80	1245	(31)	(25)	–	(34)	
80+	688	(17)	(12)	–	(19)	
Socioeconomic status *						<0.001
Low	1341	(33)	(14)	–	(61)	
Mid	1602	(40)	(28)	–	(51)	
High	1114	(27)	(8)	–	(46)	
Secondary AML	641	(16)	(11)		(16)	0.097
ELN 2010 classification						<0.001
Favourable	610	(15)	(8)	–	(17)	
Intermediair I	624	(15)	(11)	–	(19)	
Intermediair II	643	(16)	(11)	–	(20)	
Adverse	449	(11)	(7)	–	(15)	
Unclassifiable	1734	(43)	(33)		(56)	
Hyperleukocytosis†						0.488
No	3623	(89)	(86)	–	(91)	
Yes	431	(11)	(9)	–	(14)	
Primary therapy						<0.001
Intensive chemotherapy	1761	(43)	(36)	–	(57)	
Non-intensive therapy	2299	(57)	(43)	–	(64)	
Stem cell transplantation				–		<0.001
No transplantation	3009	(74)	(68)	–	(83)	
AutoSCT	215	(5)	(3)	–	(10)	
AlloSCT	836	(21)	(12)	–	(28)	
Trial participation						<0.001
No	3390	(83)	(75)	–	(90)	
Yes	670	(17)	(10)	–	(25)	

*Three patients had missing data on socioeconomic status at diagnosis.
†Six had missing white cell count data. These patients were excluded from the regression analyses.
Allo-SCT, allogeneic SCT; AML, acute myeloid leukaemia; Auto-SCT, autologous SCT; ELN, European LeukemiaNet risk classification; SCT, stem cell transplantation.

network, the MHR decreased to 1.10 (95% CI 1.04 to 1.18) (figure 3F), with remaining differences between regions. This indicates that the variation in the application of ICT may only partly explain OS differences in elderly patients.

DISCUSSION

This nationwide, population-based study in AML shows that between-region differences in the application of ICT and OS are present. However, differences in ICT management only partially account for the regional differences

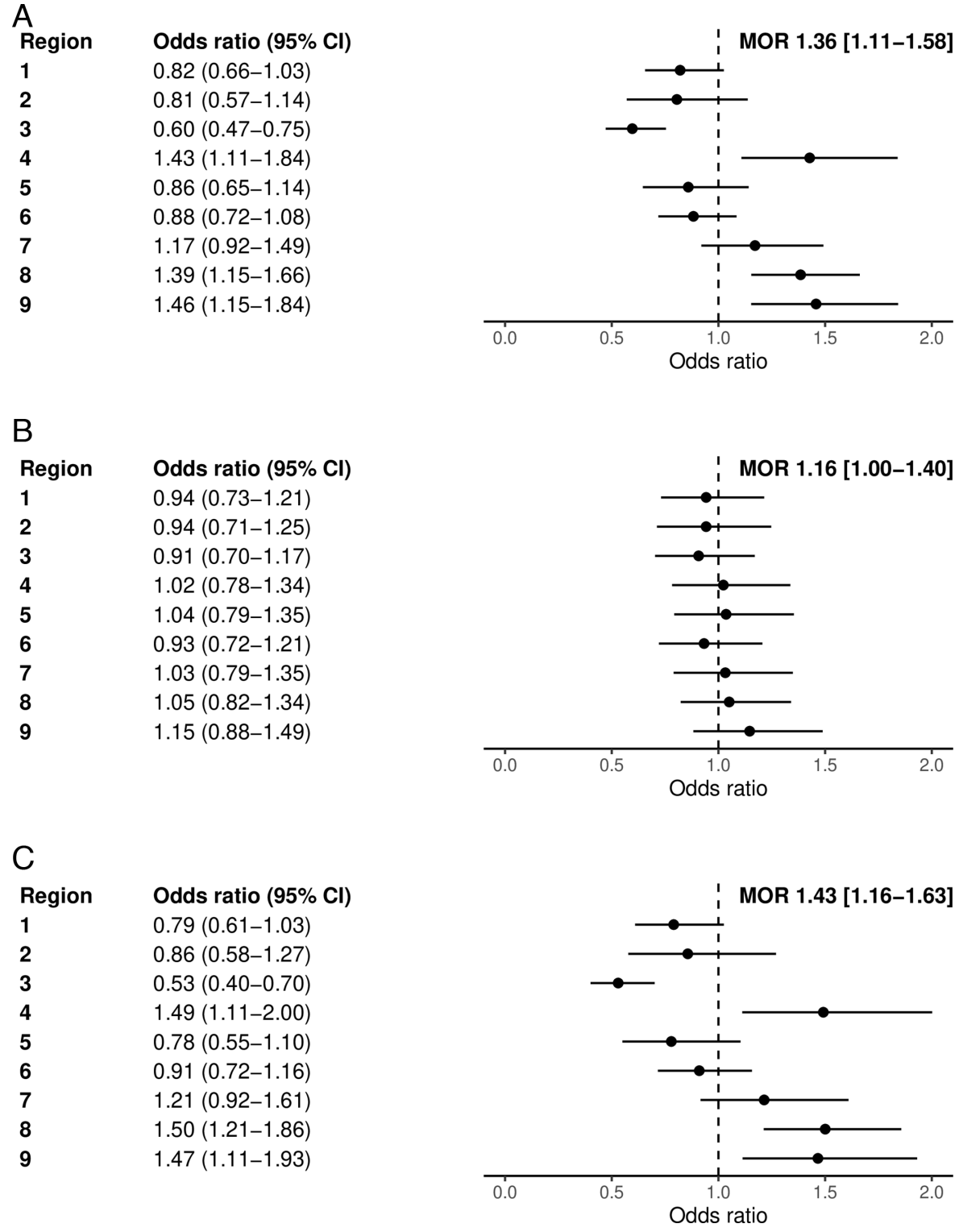

Figure 1 The between-region differences in the application of intensive chemotherapy in patients with AML in the Netherlands. This figure shows the forest plot reporting the random region effect (ORs and 95% CIs) on applying intensive chemotherapy in AML patients using random-effect logistic regression analysis. Casemix adjustment included age, sex, socioeconomic status, secondary AML and hyperleucocytosis. The median OR (MOR) reflects the between-centre variation. An MOR equal to one represents no variation, whereas a larger MOR represents more considerable variation. (A) total AML population; (B) AML patients ≤60 years; (C): AML patients >60 years. AML, acute myeloid leukaemia.

in OS. Prior population-based studies addressed practice variation in AML management; however, our study is the first to directly quantify this variation and its effect on OS.

Practice variation in the application of intensive chemotherapy

The Netherlands aims to provide its residents with equal

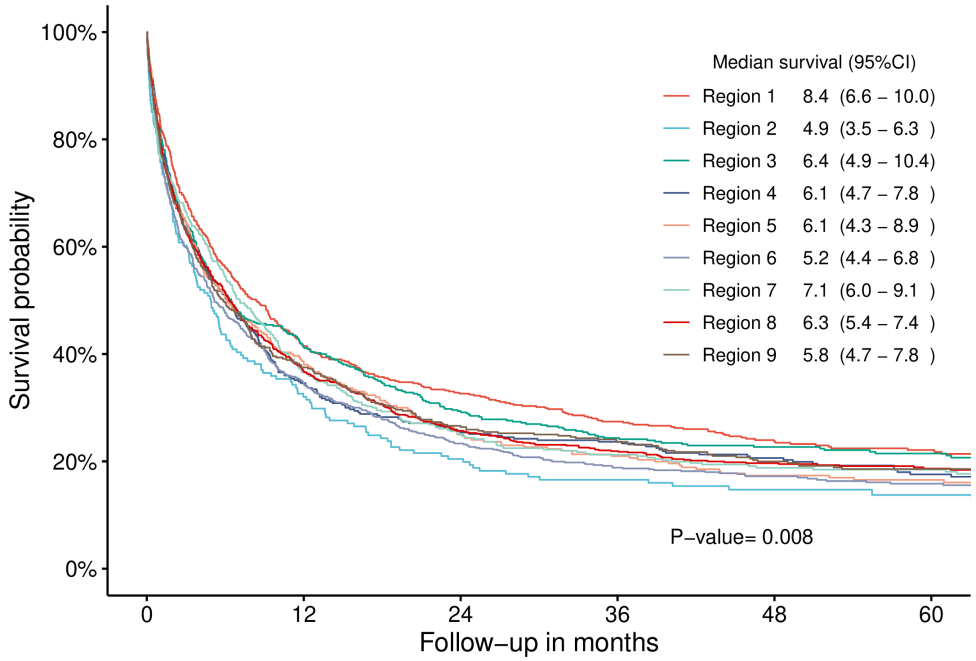

Figure 2 Overall survival of patients with AML in the Netherlands across the nine regional networks. This figure shows the Kaplan-Meier curves for all acute myeloid leukaemia patients in the Netherlands diagnosed between 2014 and 2018. The nine curves denote the nine different treatment regions in the Netherlands. The p value within this figure indicates the result of the log tank test. The table on the right side of the survival curve shows the median survival with 95% CIs per region. Of note, the number of patients at-risk was not shown to counteract potential traceability to a specific region. AML, acute myeloid leukaemia.

access to healthcare services, irrespective of their socioeconomic position and place of residence. Furthermore, it is well known that ICT followed by postremission therapy can secure long-term survival in patients with AML, even in carefully selected older patients.[32 33] Nevertheless, based on these two premises, we observed differences in ICT application between regional cancer networks, ranging from 36% to 57%. This phenomenon was also observed in Sweden—a country with a healthcare system similar to the Netherlands—with the most significant practice variation in ICT application among patients aged 70–79.[17 18 20]

In our study, the between-region variance in applying ICT might stem from different perspectives among haematologists towards applying ICT to particular patient subsets with AML.[9 17 18 34] Moreover, we show that patients with AML with the same baseline characteristics from a random region have a 36% higher chance of receiving ICT when they present to another random region. It is essential to recognise this practice variation and investigate how it arises from provider and patient-centric perspectives to overcome these regional disparities in the future. Of note, practice variation could not arise from treatment in a region different from the region of diagnosis, as patient referral between regions is very uncommon.

Patients with AML are generally eligible for intensive, potentially curative therapy based on age and physical and mental health status. Concerning the former, our study and other population-based studies show that AML patients managed with intensive therapy are younger than those managed with non-intensive approaches. As mentioned earlier, the most significant practice variation in ICT application in Sweden was observed among patients aged 70–79 years. This variation is unfortunate, although somewhat apprehensible, since practice shows that evaluating treatment eligibility in older patients lacks standardisation.[35] We reaffirmed this finding, as we observed that practice variation was most profound in patients aged >60 years. The reluctance towards administering ICT in older patients might be explained by the reduced tolerance to ICT among this population and the anticipated poor outcome with a lower OS and higher early death rates than younger patients.[9 10 35] After all, older patients with AML more frequently have adverse prognostic factors (eg, poor-risk cytogenetics, poor performance score and comorbidities) than their younger counterparts. Despite the overall anticipated poor outcome, older patients with AML managed with ICT generally have better long-term survival than those managed with non-intensive approaches.[26] Additionally, although clinicians perceive treatment with ICT as burdensome for patients, evidence shows that older patients receiving intensive or non-intensive chemotherapy have similar quality of life (QoL) and mood trajectories.[36] Also, compared with their younger counterparts, older patients tolerate ICT quite well from QoL and physical function perspectives.[37] Therefore, using a standardised and uniform treatment decision-making tool to aid haematologists in objectively estimating

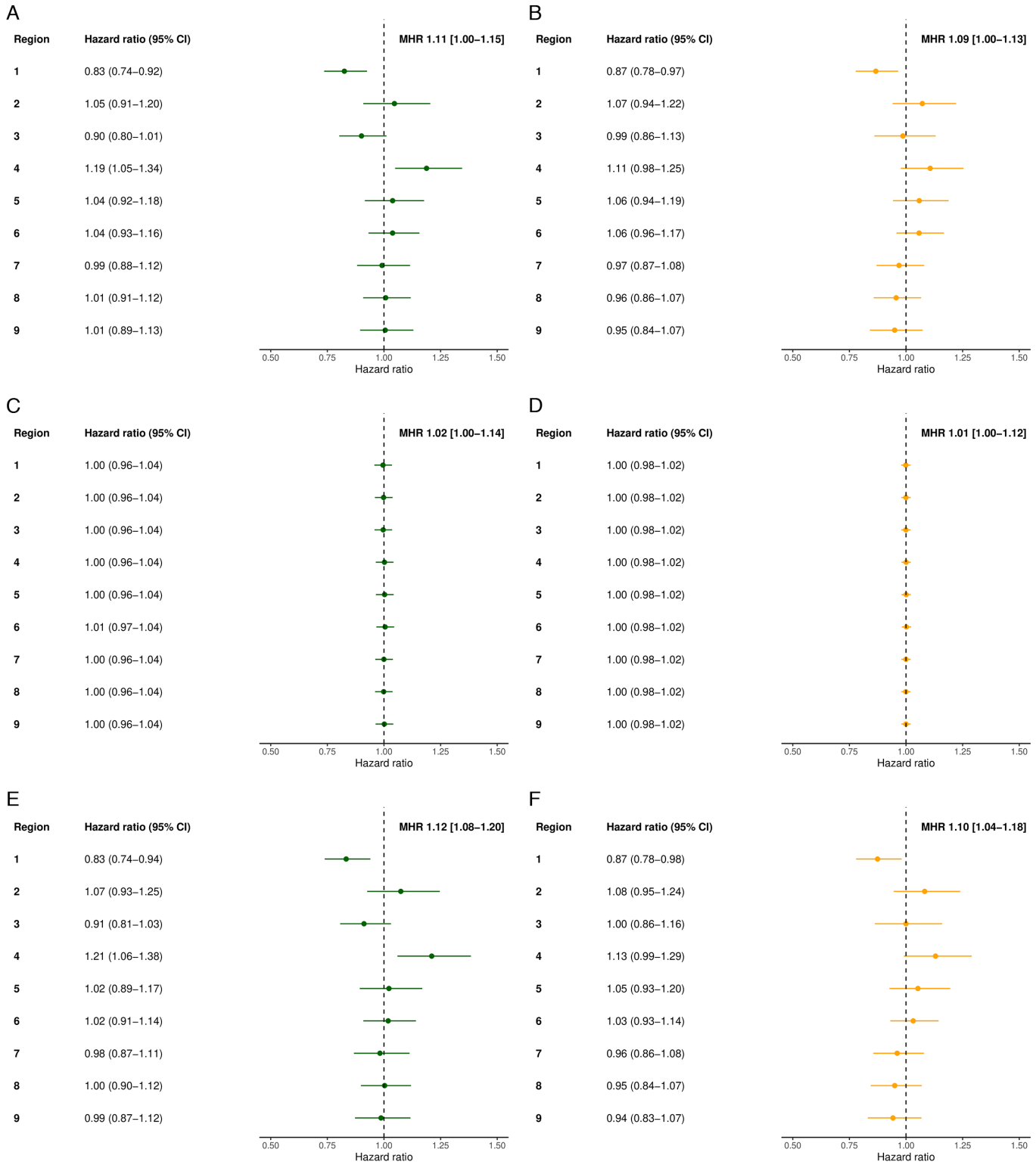

Figure 3 The between-region differences in overall survival of patients with AML in the Netherlands. This figure shows the forest plots reporting the random region effect (HRs and 95% CIs) on the survival of AML patients using random effect Cox proportional regression analysis. (A, C, E) The model with casemix correction and trial participation, namely age, sex, socioeconomic status, ELN 2010 classification, secondary AML and hyperleucocytosis. (A) Total AML population; (C) AML patients ≤60 years; (E) AML patients >60 years. (B, D, F) The adjustment for casemix variables and trial participation and additional adjustment for the chance of treatment with intensive chemotherapy per region. (B) Total AML population; (D) AML patients ≤60 years; (F) AML patients >60 years. The median HR (MHR) reflects the between-centre variation. An MHR equal to one represents no variation, whereas a larger MHR represents more considerable variation. AML, acute myeloid leukaemia.

the benefits and risks associated with ICT in older patients could standardise treatment choices between regions,[38 39] particularly in light of (1) recent advances with hypomethylating agents combined with venetoclax in managing older patients ineligible for ICT and (2) clinical trials investigating hypomethylating agents—with or without venetoclax—for managing older patients eligible for intensive treatment.[40]

Regional disparities in OS

Our study shows differences in OS across the regional cancer networks, which we could only partially link to the observed practice variation in applying ICT. Remarkably, variation in OS was observed in the total population. However, this variation was primarily driven by patients aged >60 years. Despite observing some practice variation in the application of ICT in patients aged ≤60 years, no variation in OS was observed in this age group. Although practice variation in the younger AML population was observed at a smaller scale, these findings could indicate that practice variation does not always lead to measurable outcome differences. Taken together with the relatively small proportion of survival differences influenced by ICT practice variation, these findings also reflect on which scale outcomes are modifiable by differences in patient management. As denoted previously, practice variation might arise from the unstandardised patient selection for ICT. Also, practice variation and the remaining unexplained regional difference of 9% in OS might be driven by differences in healthcare processes, which are factors that are generally hard to measure and not ascertained in cancer registries.[41 42]

Additionally, ICT administration is accompanied by several complications, such as infections, leucostasis and haemorrhages, associated with early treatment-related mortality. Managing these complications requires experienced healthcare teams and advanced resources to offset the toxicity associated with ICT.[42] Academic centres are generally assumed to have the highest level of knowledge and experience in AML management and are more likely to apply ICT than non-academic centres, especially in the older patient group, which may result in better patient outcomes.[43 44] Othus *et al* reported that the early death rates in patients with AML treated with ICT in an academic centre dramatically declined from the 1990s.[41] A study with data from the National Cancer Database—analysing the outcome of more than 60 000 AML patients who received ICT between 2003 and 2011 in the USA—reaffirmed that managing AML within an academic setting was associated with better survival outcomes.[45] These findings might hint that the level of experience with ICT and adverse event management might be associated with OS in AML. However, the underlying healthcare process measures that clarify the association between the level of experience and patient outcome remain unknown and point to a valuable direction for future research.[42 46 47]

Strengths and limitations of our study

The main strength of our study is the use of a nationwide, population-based cancer registry with detailed data on patient and AML characteristics. Population-based registries diminish the selection bias inherent in randomised controlled clinical trials and provide a unique opportunity to investigate geographical variation in the application of treatment and OS. Another strength of our study is using mixed effects modelling to analyse the regional networks. The multilevel structure of the data induces correlation among patients within the same region, and therefore, demands a multilevel approach to the analysis.[24] Additionally, there will always be some variation in survival between regions caused by chance. Disregarding this variation by chance may lead to an overinterpretation or underinterpretation of differences between regions, especially in smaller regions due to less available data. Random effect modelling accounts for the multilevel structure of the data and the variation by chance.[23 24]

Several limitations of our study should also be acknowledged. Although we performed rigorous adjustments for casemix and random variation, we cannot rule out residual and unmeasured confounders commonly encountered in observational studies that might have influenced our estimates. Due to potential unmeasured confounding, no causal inference can be drawn between the application of ICT and OS. Our study did not have complete information on performance status (PS) and comorbidity, which are factors associated with treatment allocation and OS. PS quantifies a patient's general well-being and aids in deciding whether a patient can tolerate ICT.[21 22] Although PS can be ascertained in the NCR, it is often not standardly ascertained in the medical records. Further, comorbidity is an independent prognostic factor influencing OS in patients with AML receiving ICT.[21 48] However, comorbidity is not standardly ascertained in the NCR. Nevertheless, SES was incorporated into our model, which is known to be a proxy for multimorbidity.[49] The variance between regions in applying ICT and OS could differ if adjustment for PS and combordity was possible. Also, genetic risk profiling during our study period was registered in the NCR based on the ELN 2010 risk stratification instead of the ELN 2017 and 2022 classification. The ELN 2017 and 2022 include more extensive and precise genotypes than the ELN 2010 risk classification.[7 14 50] These data are, however, ascertained for patients diagnosed as of 2021.

Handling practice variation

Regional disparities in the use of ICT and OS are observed in AML management in the Netherlands. Differences were most profound in elderly AML patients, implying initiatives for more uniform ICT eligibility criteria in this population are warranted. The first step in pursuing uniformity across regional networks might lie in creating transparency about treatment choices and patient outcomes within and between regions. The former is already established in the Netherlands through

yearly regional reports, wherein diagnostic and treatment decision-making and patient outcomes across hospitals within a regional network are evaluated by haematologists.[51] The latter is as yet not established. Based on the results of this study, the outcomes between the regions will be discussed yearly at the national level, where the regional networks can learn from each other to reduce undesired practice variation and assess which factors could be related to the unexplained regional difference in OS. Our study could serve as a benchmark to study whether these efforts, combined with emerging treatment approaches, will reduce regional variation in AML management and survival.

Author affiliations
[1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[2]Department of Research and Development, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands
[3]Department of Registration, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, The Netherlands
[4]Department of Internal Medicine, Reinier de Graaf Gasthuis, Delft, The Netherlands
[5]Department of Hematology, Leiden University Medical Center, Leiden, The Netherlands
[6]Department of Hematology, Haga Hospital, The Hague, The Netherlands
[7]Department of Hematology, Medisch Spectrum Twente, Enschede, The Netherlands
[8]Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands
[9]Department of Hematology, Utrecht University Medical Center, Utrecht, The Netherlands
[10]Department of Hematology, Radboud University Medical Center, Nijmegen, The Netherlands
[11]Department of Hematology, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, Netherlands
[12]Department of Hematology, Amsterdam UMC Location VUmc, Amsterdam, The Netherlands
[13]Department of Hematology, University Medical Center, Groningen, The Netherlands

X Avinash G Dinmohamed @ADinmohamed

Acknowledgements The authors would like to thank the registration clerks of the Netherlands Cancer Registry (NCR) for their dedicated data collection. The nationwide population-based NCR is maintained and hosted by the Netherlands Comprehensive Cancer Organisation (IKNL).

Contributors AGD designed the study; ZLRK analysed the data and is the guarantor of this study; NvL and DvK provided statistical consultation; 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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval According to the Central Committee on Research Involving Human Subjects (CCMO), this type of observational, non-interventional study does not require approval from an ethics committee in the Netherlands. The Privacy Review Board of the NCR approved using anonymous data for this study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The data that support the findings of this study are available via The Netherlands Comprehensive Cancer Organisation. These data are not publicly available, and restrictions apply to the availability of the data used for the current study. However, these data are available on reasonable request and with permission of The Netherlands Comprehensive Cancer Organisation.

ORCID iD
Z L Rana Kaplan http://orcid.org/0000-0003-1620-1811

REFERENCES

1 Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med* 2015;373:1136–52.
2 Derolf AR, Kristinsson SY, Andersson TM-L, *et al*. Improved patient survival for acute myeloid leukemia: a population-based study of 9729 patients diagnosed in Sweden between 1973 and 2005. *Blood* 2009;113:3666–72.
3 Deschler B, Lübbert M. Acute myeloid leukemia: epidemiology and etiology. *Cancer* 2006;107:2099–107.
4 Dinmohamed AG, Visser O, van Norden Y, *et al*. Treatment, trial participation and survival in adult acute myeloid leukemia: a population-based study in the Netherlands, 1989-2012. *Leukemia* 2016;30:24–31.
5 Arber DA, Orazi A, Hasserjian R, *et al*. The 2016 revision to the world health organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391–405.
6 Cancer Genome Atlas Research N, Ley TJ, Miller C, *et al*. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med* 2013;368:2059–74.
7 Döhner H, Estey EH, Amadori S, *et al*. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European leukemianet. *Blood* 2010;115:453–74.
8 Figueroa ME, Lugthart S, Li Y, *et al*. DNA methylation signatures identify biologically distinct subtypes in acute myeloid leukemia. *Cancer Cell* 2010;17:13–27.
9 Juliusson G, Antunovic P, Derolf A, *et al*. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish acute leukemia registry. *Blood* 2009;113:4179–87.
10 Juliusson G, Hagberg O, Lazarevic VL, *et al*. Improved survival of men 50 to 75 years old with acute myeloid leukemia over a 20-year period. *Blood* 2019;134:1558–61.
11 Kantarjian H, Kadia T, DiNardo C, *et al*. Acute myeloid leukemia: current progress and future directions. *Blood Cancer J* 2021;11:41.
12 Papaemmanuil E, Gerstung M, Bullinger L, *et al*. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med* 2016;374:2209–21.
13 Yates JW, Wallace HJ, Ellison RR, *et al*. Cytosine arabinoside (NSC-63878) and daunorubicin (NSC-83142) therapy in acute nonlymphocytic leukemia. *Cancer Chemother Rep* 1973;57:485–8.
14 Döhner H, Estey E, Grimwade D, *et al*. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017;129:424–47.
15 Heamato Oncology Foundation for Adults in the Netherlands. Hospital regions (NL). 2024 Available: https://hovon.nl/en/hospitals/per-region-nl
16 Kaplan ZLR, van Leeuwen N, Posthuma EFM, *et al*. 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. *Leukemia* 2022;36:596–8.
17 Juliusson G, Lazarevic V, Hörstedt A-S, *et al*. Acute myeloid leukemia in the real world: why population-based registries are needed. *Blood* 2012;119:3890–9.

18 Juliusson G, Billström R, Gruber A, *et al*. Attitude towards remission induction for elderly patients with acute myeloid leukemia influences survival. *Leukemia* 2006;20:42–7.
19 Schouten LJ, Höppener P, van den Brandt PA, *et al*. Completeness of cancer registration in Limburg, the Netherlands. *Int J Epidemiol* 1993;22:369–76.
20 van den Berg MJ, Kringos DS, Marks LK, *et al*. The Dutch health care performance report: seven years of health care performance assessment in the Netherlands. *Health Res Policy Syst* 2014;12:1.
21 Østgård LSG, Nørgaard JM, Sengeløv H, *et al*. Comorbidity and performance status in acute myeloid leukemia patients: a nation-wide population-based cohort study. *Leukemia* 2015;29:548–55.
22 Rao AV. Fitness in the elderly: how to make decisions regarding acute myeloid leukemia induction. *Hematology Am Soc Hematol Educ Program* 2016;2016:339–47.
23 Austin PC, Wagner P, Merlo J. The median hazard ratio: a useful measure of variance and general contextual effects in multilevel survival analysis. *Stat Med* 2017;36:928–38.
24 Merlo J, Chaix B, Ohlsson H, *et al*. A brief conceptual tutorial of multilevel analysis in social epidemiology: using measures of clustering in multilevel logistic regression to investigate contextual phenomena. *J Epidemiol Community Health* 2006;60:290–7.
25 Bewersdorf JP, Zeidan AM. Hyperleukocytosis and leukostasis in acute myeloid leukemia: can a better understanding of the underlying molecular pathophysiology lead to novel treatments *Cells* 2020;9:2310.
26 Jentzsch M, Grimm J, Bill M, *et al*. ELN risk stratification and outcomes in secondary and therapy-related AML patients consolidated with allogeneic stem cell transplantation. *Bone Marrow Transplant* 2021;56:936–45.
27 Mengis C, Aebi S, Tobler A, *et al*. Assessment of differences in patient populations selected for excluded from participation in clinical phase III acute myelogenous leukemia trials. *J Clin Oncol* 2003;21:3933–9.
28 Austin PC, Leckie G. Bootstrapped inference for variance parameters, measures of heterogeneity and random effects in multilevel logistic regression models. J Stat Comput Simul 2020;90:3175–99.
29 Team R. Rstudio: integrated development environment for R. RStudio, PBC; 2021.
30 Douglas Bates MM, Bolker B, Walker S, *et al*. Linear mixed-effects models using “Eigen” and S4: 1.1-28. 2022.
31 Therneau TM. Coxme: mixed effects Cox models: 2.2-16. 2020.
32 Estey E, Smith TL, Keating MJ, *et al*. Prediction of survival during induction therapy in patients with newly diagnosed acute myeloblastic leukemia. *Leukemia* 1989;3:257–63.
33 Walter RB, Othus M, Borthakur G, *et al*. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. *J Clin Oncol* 2011;29:4417–23.
34 Juliusson G, Karlsson K, Lazarevic VL, *et al*. Hematopoietic stem cell transplantation rates and long-term survival in acute myeloid and lymphoblastic leukemia: real-world population-based data from the Swedish acute leukemia registry 1997-2006. *Cancer* 2011;117:4238–46.
35 Kantarjian H, O’brien S, Cortes J, *et al*. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer* 2006;106:1090–8.
36 El-Jawahri A, Abel GA, Traeger L, *et al*. Quality of life and mood of older patients with acute myeloid leukemia (AML) receiving intensive and non-intensive chemotherapy. *Leukemia* 2019;33:2393–402.
37 Mohamedali H, Breunis H, Timilshina N, *et al*. Older age is associated with similar quality of life and physical function compared to younger age during intensive chemotherapy for acute myeloid leukemia. *Leuk Res* 2012;36:1241–8.
38 Krug U, Röllig C, Koschmieder A, *et al*. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. *Lancet* 2010;376:2000–8.
39 de Leeuw DC, Ossenkoppele GJ, Janssen JJWM. Older patients with acute myeloid leukemia deserve individualized treatment. *Curr Oncol Rep* 2022;24:1387–400.
40 Maiti A, Qiao W, Sasaki K, *et al*. Venetoclax with decitabine vs intensive chemotherapy in acute myeloid leukemia: a propensity score matched analysis stratified by risk of treatment-related mortality. *Am J Hematol* 2021;96:282–91.
41 Othus M, Kantarjian H, Petersdorf S, *et al*. Declining rates of treatment-related mortality in patients with newly diagnosed AML given ‘intense’ induction regimens: a report from SWOG and MD Anderson. *Leukemia* 2014;28:289–92.
42 Giri S, Pathak R, Aryal MR, *et al*. Impact of hospital volume on outcomes of patients undergoing chemotherapy for acute myeloid leukemia: a matched cohort study. *Blood* 2015;125:3359–60.
43 Kalin B, Pijnappel EN, van Gelder M, *et al*. Intensive treatment and trial participation in elderly acute myeloid leukemia patients: a population-based analysis in the Netherlands. *Cancer Epidemiol* 2018;57:90–6.
44 Ma E, Bonthapally V, Chawla A, *et al*. An evaluation of treatment patterns and outcomes in elderly patients newly diagnosed with acute myeloid leukemia: a retrospective analysis of electronic medical records from US community oncology practices. *Clin Lymphoma Myeloma Leuk* 2016;16:625–36.
45 Bhatt VR, Shostrom V, Giri S, *et al*. Early mortality and overall survival of acute myeloid leukemia based on facility type. *Am J Hematol* 2017;92:764–71.
46 Hahn AW, Jamy O, Nunnery S, *et al*. How center volumes affect early outcomes in acute myeloid leukemia. *Clin Lymphoma Myeloma Leuk* 2015;15:646–54.
47 Thompson MP, Waters TM, Kaplan EK, *et al*. Hospital volume and acute myeloid leukemia mortality in medicare beneficiaries aged 65 years and older. *Blood* 2016;128:872–4.
48 Etienne A, Esterni B, Charbonnier A, *et al*. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. *Cancer* 2007;109:1376–83.
49 Pathirana TI, Jackson CA. Socioeconomic status and multimorbidity: a systematic review and meta-analysis. *Aust N Z J Public Health* 2018;42:186–94.
50 Döhner H, Wei AH, Appelbaum FR, *et al*. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022;140:1345–77.
51 Korf-van Vliet CH, Cornelissen JJ, Blijlevens NMA, *et al*. Regiorapportages: wat, hoe en Waarom? *Nederlands Tijdschrift Voor Hematologie* 2018;15:229–32.