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MR. LASSE HJORT JAKOBSEN (Orcid ID : 0000-0001-6575-7686)

DR. ANDREAS KIESBYE ØVLISEN (Orcid ID : 0000-0002-4631-9936)

DR. TAREC CHRISTOFFER EL-GALALY (Orcid ID : 0000-0002-4406-380X)

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Temporal changes in survival among adult AML patients in the period 2000-2016: A Danish population-based study

Lasse Hjort Jakobsen[1,2], Anne Stidsholt Roug[1,2], Andreas Kiesbye Øvlisen[1,2], Claus Werenberg Marcher[3], Hans Beier Ommen[4], Kim Theilgaard-Mönch[5], Peter Møller[6], Claudia Schöllkopf[7], Daniel Kristensen[1], Therese Maria Henriette Naur[1], Martin Bøgsted[1,2], Tarec Christoffer El-Galaly[1,2], and Marianne Tang Severinsen[1,2]

1) Department of Hematology, Aalborg University Hospital, Aalborg, Denmark
2) Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
3) Department of Hematology, Odense University Hospital, Odense, Denmark
4) Department of Hematology, Aarhus University Hospital, Aarhus, Denmark
5) Department of Hematology and Finsen Laboratory, Rigshospitalet and Biotech Research and Innovation Centre, University of Copenhagen, Copenhagen, Denmark
6) Department of Hematology, Roskilde Sygehus, Roskilde, Denmark
7) Department of Hematology, Herlev Hospital, Herlev, Denmark

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orrespondence: Lasse Hjort Jakobsen, PhD

Department of Hematology

Aalborg University Hospital

Sdr. Skovvej 15, Aalborg DK-9000, Denmark

Email: lasse.j@rn.dk or lahja@dcm.aau.dk

Abstract

In this study, we quantify the development in overall survival (OS) during the period 2000-2016 among Danish acute myeloid leukemia (AML) patients. This population-based study, including 3,820 adult AML patients, demonstrates a significantly improved OS over time with two-year age-standardized OS increasing from 23% in 2002 to 31% in 2016. The improvement in OS was exclusively seen in AML patients ≥50 years of age with absolute improvements in two-year OS from 2002 to 2016 of ≥10% among patients aged 50-75 years and a small absolute increase among AML patients >75 years of age.

Short report

Acute myeloid leukemia (AML) patients have a high mortality in response to standard therapeutic regimens due to primary resistance, relapse, and treatment-related death. Despite substantial efforts into developing new drugs and treatment regimens, cytarabine and anthracycline remain the backbone of intensive AML therapy (Burnett *et al*, 2011). However, referral of more patients to curative intended chemotherapy and allogeneic stem-cell transplantation (ASCT), improved supportive care, and approval of a few new treatment regimens for elderly/unfit patients have led to improved overall survival (OS) of AML patients over the past two decades (Koreth *et al*, 2009; Juliusson *et al*, 2019; Dombret *et al*, 2015). In a recent Swedish AML registry study, a significant temporal OS improvement was observed among AML patients during the period 1997-2016, particularly among male patients aged 50-75 years (Juliusson *et al*, 2019). The aim of the present study was to investigate temporal survival trends among Danish AML patients.

In this population based study, we included adult (aged ≥18 years) AML patients (excluding acute promyelocytic leukemia) from the Danish National Acute Leukemia Registry (Østgård *et al*, 2016), who were diagnosed in the period 2000-2016. Treatments were categorized as either intensive (remission induction therapy defined as one or more courses of chemotherapy including standard to high dose cytarabine for a minimum of five days), non-intensive (low-dose cytarabine, azacytidine, or different experimental drugs added to a backbone of low-dose cytarabine or azacytidine), or palliative/no treatment according to the most intensive therapy administered within 30 days of diagnosis. OS was defined as the time from diagnosis until death from any cause, and post-transplant OS was computed for patients treated with ASCT in first complete remission (CR1). Patients still alive at the end of follow-up (August 2019) were censored. Temporal two-year OS estimates were obtained by flexible parametric survival models with diagnosis year as (continuous) dependent variable modelled with a time-varying coefficient (suppl. methods) (Royston & Parmar, 2002; Liu *et al*, 2018). To adjust for temporal changes in the age distribution among the AML population, we computed age-standardized survival curves (suppl. methods), which provide the projected OS that would have been observed if the age distribution remained unchanged in the period 2000-2016 (Lambert *et al*, 2015). To compute crude OS estimates, we also grouped patients according to diagnostic periods (i.e. 2000-2006, 2007-2011, 2012-2016) and diagnostic age (i.e. <50, 50-59, 60-75, >75 years) in concordance with a previous study (Juliusson *et al*, 2019). Log-

rank tests and Cox models were used to test for crude and adjusted differences between the diagnostic periods, respectively, while logistic regression models were used to test for differences in treatment intensity.

In total, 3,820 patients for whom treatment could be classified (22/3,842 were unclassifiable) were included in the study. The median age at diagnosis for the periods 2000-2006, 2007-2011, and 2012-2016 was 68, 70, and 71 years, and the proportion of therapy-related AML was 1.6%, 3.4%, and 4.9%, respectively (Table 1). For the entire population, the crude OS did not improve throughout the investigated period (P=0.321, Figure 1A), but OS significantly improved after adjusting for the increasing age distribution of the AML population over time (P<0.001, Figure 1A). The 2-year age-standardized OS was 22% (95% CI, 21-24%), 26% (95% CI, 24-28%), and 31% (95% CI, 28-35%) for patients diagnosed in 2002, 2010, and 2016, respectively. Further adjustment for AML subtype (de novo, secondary, or therapy-related) and performance score did not change this result (P<0.001, Table S1). Age-stratified analyses revealed temporal improvements in OS only among patients ≥50 years (<50, P=0.360; 50-59, P=0.014; 60-75, P=0.010; >75, P=0.023; Figure 1B). The 2-year OS for patients aged 50-59 years diagnosed in 2002 and 2016 was 39% (95% CI, 32-45%) and 55% (95% CI, 44-65%), respectively. For patients aged 60-75 years, the 2-year OS increased from 20% (95% CI, 17-23%) in 2002 to 30% (95% CI, 25-35%) in 2016. Relative survival analyses confirmed the improved OS of AML patients over time (Figure S1). Throughout the study period, no significant differences were observed between male and female patients in terms of OS (P=0.083) and OS improvement over time (P = 0.785, Table S2). Furthermore, patients with an intermediate cytogenetic risk profile (Grimwade *et al*, 2010) had significantly improved OS after adjusting for age (favorable, P=0.504; intermediate, P<0.001; unfavorable, P=0.242, Table S3, Figure S2).

In 2000-2006, 2007-2011, and 2012-2016, intensive therapy was administered to 53%, 49%, and 44% of AML patients, respectively (Table 1). The use of non-intensive chemotherapy as first-line therapy increased from 2000-2006 (3%) to 2012-2016 (14%, P<0.001), particularly among patients aged >75 years (2000-2006, 4%; 2012-2016, 21%, Table 1). Among patients treated with intensive chemotherapy (n=1,867), the proportion reaching CR1 was 71%, 75%, and 76% in 2000-2006, 2007-2011, and 2012-2016, respectively. Consistently, OS among intensively treated AML patients

significantly improved during the study period (P=0.001) with a 2-year OS of 41% (95% CI, 38-45%) and 56% (95% CI, 50-62%) for patients diagnosed in 2002 and 2016, respectively. The improvement in 2-year OS remained significant after adjusting for age (P<0.001, Table S4). However, the OS increase was exclusively seen in patients aged ≥50 years (<50, P=0.208; 50-59, P=0.031; 60-75, P=0.001; >75, P =0.017, Figure S3). Among intensively treated patients aged 50-59 years, the 2-year OS was 42% [95% CI, 35-49%] in 2002 and 57% [95% CI, 45-67%] in 2016, whereas 60-75-year-old patients had a 2-year OS of 26% [95% CI, 22-31%] in 2002 and 47% [95% CI, 39-55%] in 2016 (Figure S4). No OS improvement was observed among patients treated with non-intensive or palliative/no treatment (Table S5). The proportion of patients in CR1 after intensive chemotherapy who were referred to ASCT significantly increased (P<0.001) from 8% in 2000-2006 to 28% in 2012-2016 (Table 1). The increase was particularly pronounced among 50-59-year-olds (from 10% in 2000-2006 to 36% in 2012-2016) and 60-75-year-olds (from 3% in 2000-2006 to 25% in 2012-2016). Notably, the median age of patients receiving ASCT increased from 46 years (range 19-64) in 2000-2006 to 59 years (range 18-73) in 2012-2016. Two-year age-standardized post-transplant OS increased from 58% (95% CI, 34-68%) in 2007 to 79% (95% CI, 67-88%) in 2016 (Figure S5), although the increase in the period 2007-2016 was not statistically significant (P=0.190).

Overall, the present study of Danish AML patients including age-stratified analyses and analyses adjusting for a changing age distribution over time, revealed a significantly improved OS among AML patients during the period 2000-2016. In 2001, the WHO-defined 30% blast threshold for distinguishing AML from MDS was reduced to 20%, which might bias our results, as some of the included patients diagnosed after 2001 would have been classified as MDS previously (Vardiman *et al*, 2002). However, the vast majority of patients included in the study were diagnosed after 2001, and a sensitivity analysis restricted to AML patients with ≥30% blasts showed a similar OS improvement over time (Figure S6 and S7). Consistent with a recent Swedish AML registry study (Juliusson *et al*, 2019), we report a significant OS improvement in patients 50-75 years of age, with an absolute improvement in 2-year OS of ≥10% from 2002 to 2016. However, we did not find any differences between men and women in terms of crude OS or temporal OS improvements. The latter may relate to the inclusion of patients diagnosed as early as 1997-1999 in the Swedish study - a period that generally exhibits larger mortality differences between men and women in western

countries (Rosella *et al*, 2016). Additionally, OS did not improve for patients <50 years, which indicate a lack of major improvements to the clinical management of this subgroup.

Intriguingly, we observed a significant OS improvement among patients treated with intensive chemotherapy (Table S5), which in part may be attributed to 1) the intensified focus on prompt risk-stratification using cytogenetics (Fey *et al*, 2013) and 2) the increased rate of ASCT for patients in CR1. The latter might relate to improved risk-stratification based on novel risk factors (Estey, 2013), improved availability of donors from expanding donor registries, and increased ASCT eligibility after implementation of reduced-intensity conditioning regimens. However, only 46, 65, and 114 patients were treated with ASCT in the periods 2000-2006, 2007-2011, and 2012-2016, respectively, which constitutes a minority of all AML patients.

Treatment of patients aged <60 years has not changed substantially since 2000 with most patients allocated to intensive therapy, although a slight increase in the proportion of intensively treated patients was seen among 50-59-year-olds (Table 1). More patients aged 60-75 years received non-intensive therapies, but the majority still receive intensive chemotherapy. In contrast, very few patients >75 years were allocated to intensive therapy, but these patients were more frequently allocated to non-intensive therapy during the study period (Table 1). This is likely explained by a trend toward improved health, indicated by decreasing mortality risks (University of California Berkeley & Max Planck Institute for Demographic Research), in the elderly Danish general population, an increased propensity to apply medical interventions to frail and elderly patients, and perhaps also a request for active treatment among elderly patients (Juliusson & Swedish AML Group, 2011). The main therapeutic change for elderly AML patients since 2000 has been the introduction of azacytidine, which has been routinely used since 2009 in Denmark (Dombret *et al*, 2015). In addition to the introduction of azacytidine a number of new treatment options have been evaluated in combination with low-dose cytarabine or azacytidine in clinical trials, but have not yet led to new non-intensive standard treatments. With new promising treatment approaches available (such as venetoclax and hypomethylating agents), improved outcomes among elderly real-world patients may be observed in the future. Our study also demonstrated a decreasing risk of early (within 28 days of diagnosis) death (age-adjusted odds ratio, 2000-2006 vs 2012-2016, 0.79 [95% CI, 0.64-0.98], P=0.029). The reason for this is not clear, but improved supportive care including prophylactic platelet transfusions, prophylactic anti-fungal and anti-bacterial treatment in

combination with a broader spectrum of systemic anti-fungal treatments available upon hospital admission with neutropenic infections may be an explanation.

In conclusion, our population-based registry study demonstrates a significant temporal OS improvement among AML patients in Denmark since 2000. The OS improvement was particularly pronounced in the age group 50-75 years, where ASCT in CR1 and non-palliative therapy were more frequently allocated during the period 2000-2016. However, our study also highlights the need for novel therapeutic options for patients aged >75 years, which constituted 36% of all Danish AML patients diagnosed in 2012-2016.

Conflict of interest

The authors declare no competing financial interests

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LHJ, ASR, TCEG, and MTS initiated and designed the study. LHJ and MTS acquired data. LHJ and MB did the statistical analysis. All authors interpreted the data, drafted and reviewed the manuscript, and approved the final manuscript.

References

Burnett, A., Wetzler, M. & Löwenberg, B. (2011) Therapeutic advances in acute myeloid leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, **29,** 487–94 Available at: http://www.ncbi.nlm.nih.gov/pubmed/21220605 [Accessed March 18, 2020].

Dombret, H., Seymour, J.F., Butrym, A., Wierzbowska, A., Selleslag, D., Jang, J.H., Kumar, R., Cavenagh, J., Schuh, A.C., Candoni, A., Récher, C., Sandhu, I., Del Castillo, T.B., Al-Ali, H.K., Martinelli, G., Falantes, J., Noppeney, R., Stone, R.M., Minden, M.D., McIntyre, H., et al (2015) International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood*, **126,** 291–299.

Estey, E.H. (2013) Acute myeloid leukemia: 2013 update on risk-stratification and management. *American*

Journal of Hematology, **88,** 318–327 Available at: http://doi.wiley.com/10.1002/ajh.23404 [Accessed March 10, 2020].

Fey, M.F., Buske, C. & on behalf of the ESMO Guidelines Working Group (2013) Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, **24,** vi138–vi143.

Grimwade, D., Hills, R.K., Moorman, A. V., Walker, H., Chatters, S., Goldstone, A.H., Wheatley, K., Harrison, C.J. & Burnett, A.K. (2010) Refinement of cytogenetic classification in acute myeloid leukemia: Determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*, **116,** 354–365.

Juliusson, G., Hagberg, O., Lazarevic, V.L., Ölander, E., Antunovic, P., Cammenga, J., Wennström, L., Möllgård, L., Brune, M., Jädersten, M., Deneberg, S., Lehmann, S., Derolf, Å.R. & Höglund, M. (2019) Improved survival of men 50 to 75 years old with acute myeloid leukemia over a 20-year period. *Blood*, **134,** 1558–1561.

Juliusson, G. & Swedish AML Group, for the S.A. (2011) Most 70- to 79-year-old patients with acute myeloid leukemia do benefit from intensive treatment. *Blood*, **117,** 3473–4.

Koreth, J., Schlenk, R., Kopecky, K.J., Honda, S., Sierra, J., Djulbegovic, B.J., Wadleigh, M., DeAngelo, D.J., Stone, R.M., Sakamaki, H., Appelbaum, F.R., Döhner, H., Antin, J.H., Soiffer, R.J. & Cutler, C. (2009) Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia in First Complete Remission. *JAMA*, **301,** 2349.

Lambert, P.C., Dickman, P.W. & Rutherford, M.J. (2015) Comparison of different approaches to estimating age standardized net survival. *BMC medical research methodology*, **15,** 64.

Liu, X.-R., Pawitan, Y. & Clements, M. (2018) Parametric and penalized generalized survival models. *Statistical Methods in Medical Research*, **27,** 1531–1546.

Østgård, L.S.G., Nørgaard, J.M., Raaschou-Jensen, K.K., Pedersen, R.S., Rønnov-Jessen, D., Pedersen, P.T., Dufva, I.H., Marcher, C.W., Nielsen, O.J., Severinsen, M.T. & Friis, L.S. (2016) The Danish national acute leukemia registry. *Clinical Epidemiology*, **8,** 553–560.

Rosella, L.C., Calzavara, A., Frank, J.W., Fitzpatrick, T., Donnelly, P.D. & Henry, D. (2016) Narrowing mortality gap between men and women over two decades: A registry-based study in Ontario, Canada. *BMJ Open*, **6,**.

Royston, P. & Parmar, M.K.B. (2002) Flexible parametric proportional-hazards and proportional-odds

models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Statistics in Medicine*, **21,** 2175–2197.

University of California Berkeley, (USA) & Max Planck Institute for Demographic Research, (Germany) Human Mortality Database. Available at: https://www.mortality.org/hmd/DNK/STATS/bltper_1x1.txt [Accessed September 8, 2020].

Vardiman, J.W., Harris, N.L. & Brunning, R.D. (2002) The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood*, **100,** 2292–2302.

Figures and Tables

Table 1: Demographical, treatment, treatment response, and mortality information on adult Danish AML patients diagnosed between 2000 and 2016 stratified by diagnostic period (2000-2006, 2007-2011, and 2012-2016).

	2000-2006	**2007-2011**	**2012-2016**	**Total**
n	1454	1129	1237	3820
Median age, years(range)	68(18-95)	70(18-98)	71(18-99)	70(18-99)
Male sex, n(%)	801(55.1)	614(54.4)	671(54.2)	2086(54.6)
Performance score 2-4, n(%)	512(35.7)	300(26.6)	337(27.2)	1149(30.2)
AML subtype, n(%)				
- De novo AML	1078(74.1)	804(71.2)	878(71.0)	2760(72.3)
- Secondary AML	353(24.3)	287(25.4)	298(24.1)	938(24.6)
- Therapy-related AML	23(1.6)	38(3.4)	61(4.9)	122(3.2)
Platelets 10(9)/L, mean(Q1-Q3)	79(25-101)	87(28-97)	85(30-106)	83(28-102)
WBC 10(9)/L, mean(Q1-Q3)	38(3-49)	37(2-46)	30(2-38)	35(2-44)
BM blast percent, mean(Q1-Q3)	50(29-75)	51(30-74)	51(30-72)	51(30-73)
PB blast percent, mean(Q1-Q3)	35(5-60)	33(5-59)	30(3-50)	33(5-57)
Cytogenetics performed, n(%)	1016(69.9)	901(79.8)	948(76.6)	2865(75.0)
Cytogenetic risk group, n(%)				
- Favorable	47(4.6)	31(3.4)	65(6.9)	143(5.0)
- Intermediate	766(75.4)	630(69.9)	643(67.8)	2039(71.2)
- Unfavorable	203(20.0)	240(26.6)	240(25.3)	683(23.8)

Intensive treatment within 30 days, n(%)	772(53.1)	552(48.9)	543(43.9)	1867(48.9)
Treatment - 18-49 years, n(%)				
- Intensive	232(92.8)	134(93.7)	118(90.8)	484(92.5)
- Non-intensive	0(0.0)	2(1.4)	4(3.1)	6(1.1)
- Palliative/no treatment	18(7.2)	7(4.9)	8(6.2)	33(6.3)
Treatment - 50-59 years, n(%)				
- Intensive	188(84.3)	136(87.7)	131(92.3)	455(87.5)
- Non-intensive	2(0.9)	2(1.3)	1(0.7)	5(1.0)
- Palliative/no treatment	33(14.8)	17(11.0)	10(7.0)	60(11.5)
Treatment - 60-75 years, n(%)				
- Intensive	328(56.4)	270(58.7)	273(52.5)	871(55.8)
- Non-intensive	28(4.8)	69(15.0)	76(14.6)	173(11.1)
- Palliative/no treatment	226(38.8)	121(26.3)	171(32.9)	518(33.2)
Treatment - >75 years, n(%)				
- Intensive	24(6.0)	12(3.2)	21(4.7)	57(4.7)
- Non-intensive	14(3.5)	51(13.7)	93(20.9)	158(13.0)
- Palliative/no treatment	361(90.5)	308(83.0)	331(74.4)	1000(82.3)
CR among intensive, n(%)	545(70.6)	413(74.8)	412(75.9)	1370(73.4)
ASCT among CR after intensive, n(%)	45(8.3)	65(15.7)	114(27.9)	224(16.4)
Mortality %(95% CI)				
- 28 days	17.4(19.3-15.4)	19.8(22-17.4)	17.1(19.1-14.9)	18(19.2-16.8)
- 56 days	28.4(30.7-26)	28.3(30.9-25.7)	26.6(29-24.1)	27.8(29.2-26.4)
- 2 years	74.2(76.4-71.9)	76.4(78.7-73.7)	74.9(77.2-72.4)	75.1(76.4-73.7)
Two-year mortality (intensive therapy)	58.3(61.6-54.7)	57.6(61.5-53.3)	51.4(55.4-47)	56.1(58.3-53.8)
Two-year mortality (non-intensive therapy)	77.3(86.8-60.8)	91.1(95-84.4)	88.5(92.4-82.6)	88(91-84)

Figure 1: A) Two-year crude and age-standardized overall survival according to the year of diagnosis for adult Danish AML patients. B) Age-stratified two-year overall survival for AML patients according to year of diagnosis. The shaded areas indicate pointwise 95% confidence intervals.