


# The prognostic effect of smoking status on intensively treated acute myeloid leukaemia – A Danish nationwide cohort study

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Received 4 January 2020; revised 21 March 2020; accepted for publication 23 March 2020

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## Introduction

Acute myeloid leukaemia (AML) is an aggressive haematological malignancy arising from clonal expansion of pluripotent haematopoietic stem cells or common progenitor cells, resulting in bone marrow failure and subsequent risk of life-threatening bleeding and infections. Factors affecting the prognosis of AML have been intensively studied over the past decades and can be subdivided into those which are patient-related (e.g. age, performance status and comorbidity) or disease-related (e.g. molecular genetics and cytogenetic alterations, laboratory findings at diagnosis, prior haematological disease or cytotoxic treatment for cancer).<sup>1,2</sup> The patient-related factors predict risk of therapy-related death, and the disease- or leukaemia-related factors predict response to chemotherapy and remission durability.<sup>1,2</sup>

The risk of AML among smokers has been an area of interest, with evidence suggesting that previous or an active

## Summary

With rising life expectancy, the importance of patient-related prognostic factors and how to integrate such data into clinical decision-making becomes increasingly important. The aim of this study was to evaluate the prognostic impact of smoking status in patients with acute myeloid leukaemia (AML) treated with intensive chemotherapy. We conducted a nationwide cohort study based on data obtained from the Danish National Leukaemia Registry (DNLR). The study comprised Danish patients aged 18–75 years, diagnosed with AML between 1 January 2000 and 31 December 2012. Medical records were reviewed and data on smoking status were collected. A total of 1040 patients (median age 59 years) were included, and 602 patients (58.9%) were categorised as ever-smokers and the remaining as never-smokers. Kaplan–Meier survival estimates revealed that ever-smokers had a significant shorter median overall survival (OS) at 17.2 months [95% CI (14.9;19.1)] compared to never-smokers at 24.5 months (95% CI [19.2;30.7]). Multivariate analysis revealed smoking status as a significant prognostic factor for inferior OS with a hazard ratio (HR) of 1.22 [95% CI (1.04;1.44)]. In conclusion, smoking status was found to be associated with inferior OS in intensively treated AML patients.

**Keywords:** acute myeloid leukaemia, AML, prognosis, tobacco-smoking, lifestyle factors, population.

tobacco-smoking history is associated with up to 40% higher incidence of AML.<sup>3</sup> Tobacco smoking has also been correlated to worse outcomes following haematopoietic stem cell transplantation (HSCT).<sup>4,5</sup> Tobacco-smoking is carcinogenic with a causal role in the development of several types of cancer, as well as being one of the strongest risk factors for cardiovascular and pulmonary diseases. The latter two can have detrimental effects on chemotherapy tolerance and poorer outcomes among smokers have been observed in several cancers,<sup>6</sup> including ovarian cancer,<sup>7</sup> head and neck cancer,<sup>8,9</sup> lung cancer,<sup>10</sup> renal cell carcinoma,<sup>11</sup> colorectal cancer<sup>12</sup> and non-Hodgkin lymphoma.<sup>13</sup>

The influence of lifestyle and socioeconomic factors on the prognosis in AML are either poorly studied or show a minimal effect with a few exceptions.<sup>14,15</sup> With ageing populations in the Western world and a growing armamentarium of active therapies against AML, it is imperative that we understand the impact of comorbidities and lifestyle factors

on treatment outcomes. For example, a higher risk of early treatment-related mortality (TRM) may lead physicians to refrain from intensive therapies and consider those which are novel and less intensive. However, knowledge on how to integrate factors like lifestyle and comorbidity in clinical decision-making remains limited.

The aim of this study was to evaluate the prognostic impact of smoking status on overall survival (OS) of patients with AML treated with intensive chemotherapy regimens in Denmark between 2000 and 2012.

## Materials and methods

### Patients

The Danish population (5.8 million people) has free access to medical care provided by the tax-supported public health-care system. Intensive treatment of AML is fully centralised to tertiary haematology clinics at university hospitals. Danish residents are assigned a unique civil registration number (CPR-number) at birth or immigration. The CPR registry covers information on name and residential address in addition to vital status for the entire Danish population. The Danish National Leukaemia Registry (DNLR)<sup>16</sup> was established in 2000 by the Danish Acute Leukaemia Group (ALG) and includes detailed data on all adult acute leukaemia patients treated in Denmark. DNLR is described in detail elsewhere.<sup>16</sup> A validation study from 2013 found that coverage was comprehensive, with 99% of AML patients diagnosed in Denmark included in the DNLR.<sup>17</sup>

In this nationwide Danish cohort study, the DNLR was surveyed for patients diagnosed with AML at age 18–75 years in the time period of 1 January 2000 to 31 December 2012 and who had been treated with intensive chemotherapy. Intensive chemotherapy was defined as treatments aimed at inducing complete remission (CR). More precisely, the treatments had to include a minimum of one course of chemotherapy, containing a standard to high dose of cytarabine ( $\geq 200$  mg/m<sup>2</sup>/day) for at least five days, in combination with an anthracycline (daunorubicin or idarubicin) or anthracycline-related compound (mitoxantrone). Patients with acute promyelocytic leukaemia were excluded.

### Exposure and outcome

Medical records from the time of diagnosis for the AML patients fulfilling the inclusion criteria were retrieved, and information on lifestyle factors, including comorbidities, alcohol consumption and smoking habits were collected. Information regarding smoking habits were given as never, former and current, based on the clinical notes from the time of diagnosis. Information on comorbidities, including diabetes mellitus, chronic obstructive pulmonary disease, ischaemic heart disease, rheumatological disease, hypertension and hypercholesterolaemia were also collected directly

from clinical notes. Data on exposure were merged with the prospectively collected baseline clinicopathological features, as well as the treatment details and outcome data from the DNLR, using the CPR-number as link.

### Statistical analysis

Patients were followed from the date of AML diagnosis until either death, emigration or end of follow-up (24 April 2015). Smoking status was dichotomised into never- and ever-smoking, with the latter including both former and current smokers. Descriptive statistics were summarised and categorical variables were presented as percentage, and continuous variables as median and range for non-normally distributed, and mean and range for normally distributed. Variables were compared to explore univariate associations between smoking status as the dependent variable and the variable of interest. To assess differences, the chi-squared test was used for categorical variables and the Wilcoxon rank-sum test for continuous variables.

Crude survival curves were calculated using the Kaplan–Meier method and the log-rank (Mantel–Cox) test was used for statistical testing of differences in OS. The independent association between covariates and OS was examined in multivariate Cox proportional hazard regression analysis, including age, gender, BMI, comorbidities, WHO performance status, AML presentation and smoking status. All statistical analyses were made using R version 3.6.0 (R Core Team, 2019), and a *P*-value < 0.05 was considered as statistically significant. The study was approved by the Danish Data Protection Agency (jr. nr. 2008-58-0028).

## Results

### Patient characteristics

A total of 1489 patients aged 18–75 years were diagnosed with AML and received intensive chemotherapy between 1 January 2000 and 31 December 2012. However, medical records only included information on smoking status for 1040 of the patients (69.8%). Table I summarises the baseline characteristics of the patients; median age was 59 years and male to female ratio was 1.25. The median follow-up time was 3.5 years. Of the 1040 patients, 80.4% had *de novo* AML, whereas 16.1% and 3.6% had secondary AML (sAML) and therapy-related AML (tAML), respectively. A total of 602 patients were ever-smokers (57.9%), of whom 36.2% were categorised as current smokers and 21.7% as former smokers. The remaining 438 patients (42.1%) had no history of smoking and formed the never-smoker group. Of the never-smoker group, 47.9% were female patients and 52.1% were male patients, whereas of the ever-smoker group, 39.0% were female patients and 61.0% were male patients. Never-smokers were more likely to present as sAML, compared to ever-smokers (19.2% and 13.8% respectively; *P* = 0.02).

When investigating comorbidity and WHO performance status, the ever-smoker group tended to have a higher WHO-performance status ( $P = 0.069$ ). In addition, ever-smokers had significantly more comorbidities compared to never-smokers ( $P = 0.006$ ), including 13.1% having  $\geq 2$  comorbidities, compared to 7.5% in the never-smoker group.

#### Overall survival and smoking status

Table II shows the OS for all AML patients included in the study, as well as OS by smoking status. The median OS was 18.7 months [95% CI (17.2;21.3)] for the whole cohort. Female patients had a significantly longer median OS of 22.5 months [95% CI (17.8;28.9)] as compared to male patients [17.5 months 95% CI (15.3;19.7),  $P = 0.002$ ].

When stratifying for smoking status, ever-smokers had a significantly shorter median OS of 17.2 months [95% CI (14.9;19.1)] compared to never-smokers, who had a median of 24.5 months [95% CI (19.2;30.7),  $P = 0.001$ ] (Fig 1). When stratifying for gender and smoking status, female never-smokers had a longer median OS compared to male never-smokers ( $P = 0.013$ ); however, for ever-smokers no differences in median OS was observed between females and males ( $P = 0.200$ ). While no difference in median OS was

found between male patients according to smoking status ( $P = 0.178$ ), female ever-smokers had a significantly shorter median OS of 17.4 months [95% CI (14.2;25.1)] as compared to the 28.4 months for female never-smokers [95% CI (20.8;58.4),  $P = 0.008$ ] (Fig 2). Patients aged  $\geq 60$  years remained associated with inferior survival in both ever-smoker and never-smoker groups. When comparing OS by age ( $\geq 60$  or  $< 60$  years) in the never- and ever-smokers, OS was significantly lower in the ever-smokers compared to the never-smokers ( $P = 0.035$  and  $0.027$ , respectively) (Fig 2).

#### Multivariate analysis

Multivariate analysis adjusting for age, gender, BMI, comorbidities, WHO performance status (WHO-PS), AML presentation and smoking status as covariates are shown in Table III. Ever-smoker status was associated with a hazard ratio (HR) of 1.22 [95% CI (1.04;1.44)] for an event (death) compared to that of never-smokers ( $P = 0.01$ ). Being aged  $\geq 60$  years was associated with a HR of 1.84 [95% CI (1.56;2.016),  $P < 0.001$ ]. Performance status was associated with inferior survival with a HR of 1.24 [95% CI (1.04;1.48),  $P = 0.016$ ] for WHO-PS = 1 and HR 1.76 [95% CI (1.41;2.20),  $P < 0.001$ ] for WHO-PS  $\geq 2$ . Additionally,

**Table I.** Comparison of selected baseline characteristics of the study cohort and stratification by smoking status.

Characteristics	Total (n = 1040)	Never-smokers (n = 438)	Ever-smokers (n = 602)	P-value
Gender				<0.001
Male, n (%)	577 (55.5)	210 (47.9)	367 (61.0)	
Female, n (%)	463 (44.5)	228 (52.1)	235 (39.0)	
Age, median, years (range)	59 (18-75)	58 (18-75)	59 (18-75)	
$\geq 60$ y, n (%)	484 (46.5)	197 (45.0)	287 (47.7)	0.425
Comorbidity, n (%)				0.006
0	680 (65.4)	306 (69.9)	374 (62.1)	
1	207 (19.9)	82 (18.7)	125 (20.8)	
$\geq 2$	112 (10.8)	33 (7.5)	79 (13.1)	
ND	41 (3.9)	17 (3.9)	24 (4.0)	
WHO PS, n (%)				0.069
0	348 (33.3)	160 (36.5)	188 (31.2)	
1	501 (48.2)	211 (48.2)	290 (48.2)	
$\geq 2$	188 (18.1)	67 (15.3)	121 (20.1)	
BMI, mean (range)	25.99 (15.6 - 60.6)	26.21 (15.6 - 51.5)	25.83 (16.8 - 60.6)	0.215
Response to first treatment				0.990
CR achieved, n (%)	625 (60.1)	265 (60.5)	360 (59.8)	
CR not achieved, n (%)	228 (21.9)	96 (21.9)	132 (21.9)	
CR ND, n (%)	187 (18.0)	77 (17.6)	100 (18.3)	
HSCT, n (%)	114 (11.0)	56 (12.8)	58 (9.6)	0.132
BMB, median, % (range)	56 (0-100)	53 (0-100)	60 (0-100)	0.065
AML presentation, n (%)				0.015
dn-AML	836 (80.4)	344 (78.5)	492 (81.7)	
sAML	167 (16.1)	84 (19.2)	83 (13.8)	
tAML	37 (3.6)	10 (2.3)	27 (4.5)	

HSCT, haematopoietic stem cell transplantation; BMB, bone marrow blasts; CR, complete remission; AML, acute myeloid leukaemia; dn-AML, *de novo* AML; sAML, secondary AML; tAML, therapy-related AML; BMI, Body Mass Index; WHO-PS, World Health Organisation performance score; P-value, probability value comparing ever-smokers and never-smokers.

Table II. Median overall survival (mOS) in months for selected characteristics, estimated with Kaplan–Meier survival, analysis stratified by smoking status (*n* = 1040).

Characteristics	Total				Never-smoker				Ever-smoker				Ever vs. never smokers		
	<i>N</i>	<i>n</i> <sup>c</sup>	mOS	95% CI	<i>P</i>	<i>n</i>	<i>n</i> <sup>c</sup>	mOS	95% CI	<i>P</i>	<i>n</i>	<i>n</i> <sup>c</sup>	mOS	95% CI	<i>P</i>
Total	1040	304	18.7	[17.2;21.3]	NA	438	154	17.2	[14.9;19.1]	NA	602	150	24.5	[19.2;30.7]	NA
Sex					<b>0.002</b>					0.200					<b>0.013</b>
Male	577	146	17.5	[15.3;19.7]		210	63	17.2	[14.4;19.1]		367	83	19.5	[14.9;29]	0.178
Female	463	758	22.5	[17.8;28.9]		228	91	17.4	[14.2;25.1]		235	67	28.4	[20.8;58.4]	<b>0.008</b>
Age					<b>&lt; 0.001</b>					<b>&lt; 0.001</b>					<b>&lt; 0.001</b>
< 60 y	556	228	33.1	[26.3;54.2]		241	112	26.3	[20.5;39.7]		315	116	62.9	[32.1;NR]	<b>0.027</b>
≥ 60 y	484	76	12.2	[9.9;14.8]		197	42	11.2	[9.1;14.4]		287	34	14.4	[8.9;17.4]	<b>0.035</b>
Comorbidity					<b>&lt; 0.001</b>					<b>&lt; 0.001</b>					<b>0.0213</b>
0	680	225	23.8	[20.2;29.2]		306	117	21.1	[17.4;28.2]		374	108	28.4	[21.1;40.8]	<b>0.039</b>
1	207	49	14.7	[11.9;18.3]		82	26	12.3	[9.4;15.3]		125	23	21.9	[14.4;45.6]	<b>0.022</b>
≥ 2	112	20	10.7	[7.7;17.4]		33	8	10.6	[7.7;18]		79	12	12.2	[5.4;22.5]	0.582
WHO-PS					<b>&lt; 0.001</b>					<b>&lt; 0.001</b>					<b>&lt; 0.001</b>
0	348	132	29.1	[23.1;39.2]		160	66	28.2	[22.5;43]		188	66	32.5	[20.8;93.6]	0.431
1	501	138	18.7	[16.9;22.3]		211	73	16.4	[12.6;18.7]		290	65	25.7	[20.4;40.8]	<b>0.002</b>
≥ 2	188	34	9.7	[7.1;12.9]		67	15	9.8	[7.2;14.4]		121	19	7.5	[4.7;16.1]	0.807
BMI					0.406					0.279					0.646
< 18.5	23	9	31.7	[17.4;NR]		10	4	31.7	[15.3;NR]		13	5	38.9	[14.6;NR]	0.988
18.5-24.9	434	130	19.8	[16.9;25.1]		174	68	17.2	[13.9;21.9]		260	62	27.0	[20.6;48.9]	<b>0.004</b>
25-29.9	377	103	18.0	[16.1;21.3]		167	53	17.4	[14.2;20.8]		210	50	22.5	[16.6;37.6]	<b>0.095</b>
≥ 30	162	54	20.0	[13.5;30.9]		72	25	19.7	[12.4;36.7]		90	29	20.1	[10.8;80.7]	0.923
AML presentation					<b>&lt; 0.001</b>					<b>&lt; 0.001</b>					<b>0.003</b>
dn-AML	836	273	21.3	[18.8;26.3]		344	133	18.8	[17.2;22.5]		492	140	29.2	[22.4;42.5]	<b>0.006</b>
sAML	167	23	9.2	[7.1;15.1]		84	17	8.2	[4.7;12.1]		83	6	15.3	[7.3;23.1]	<b>0.010</b>
tAML	37	8	12.4	[5.8;31.4]		10	4	12.4	[8.3;14.4]		27	4	15.4	[2.0;NR]	0.318

mOS, median overall survival in months; AML, acute myeloid leukaemia; dn-AML, *de novo* AML; sAML, secondary AML; tAML, therapy-related AML; BMI, Body Mass Index; WHO-PS, World Health Organisation performance score; *n*<sup>c</sup>, number of censored individuals in each stratum; CI, confidence interval; NR, not reached; NA, not applicable. *P*-values from log-rank test, bold indicates statistical significance.

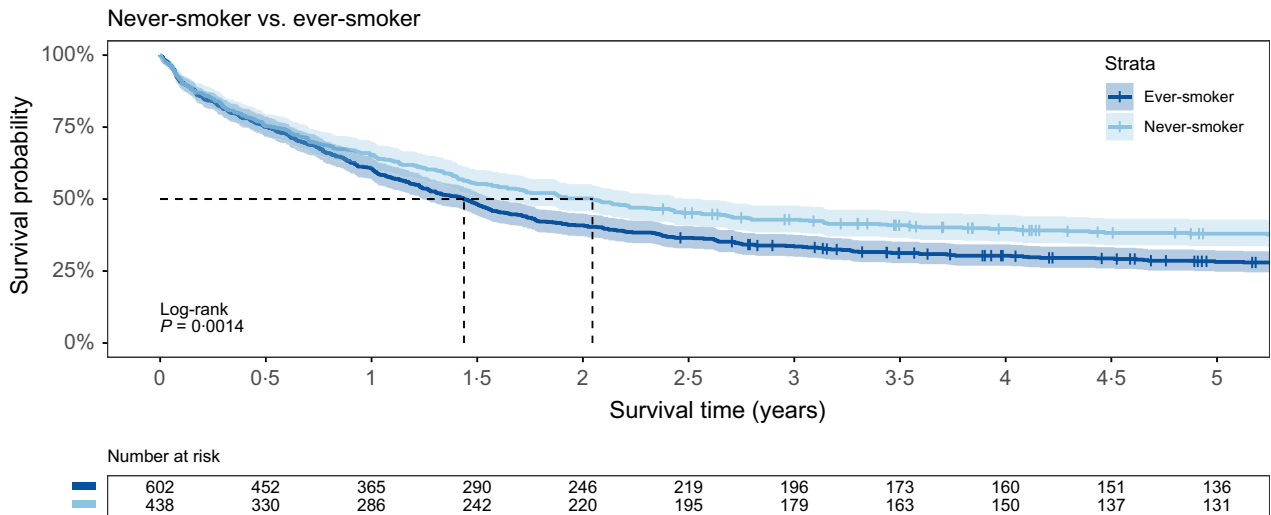


Fig 1. Crude survival and 95% CI for 1080 patients with acute myeloid leukaemia (AML) by smoking status for all patients. Survival time is displayed as time after diagnosis.  $P$ -value from log-rank test. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

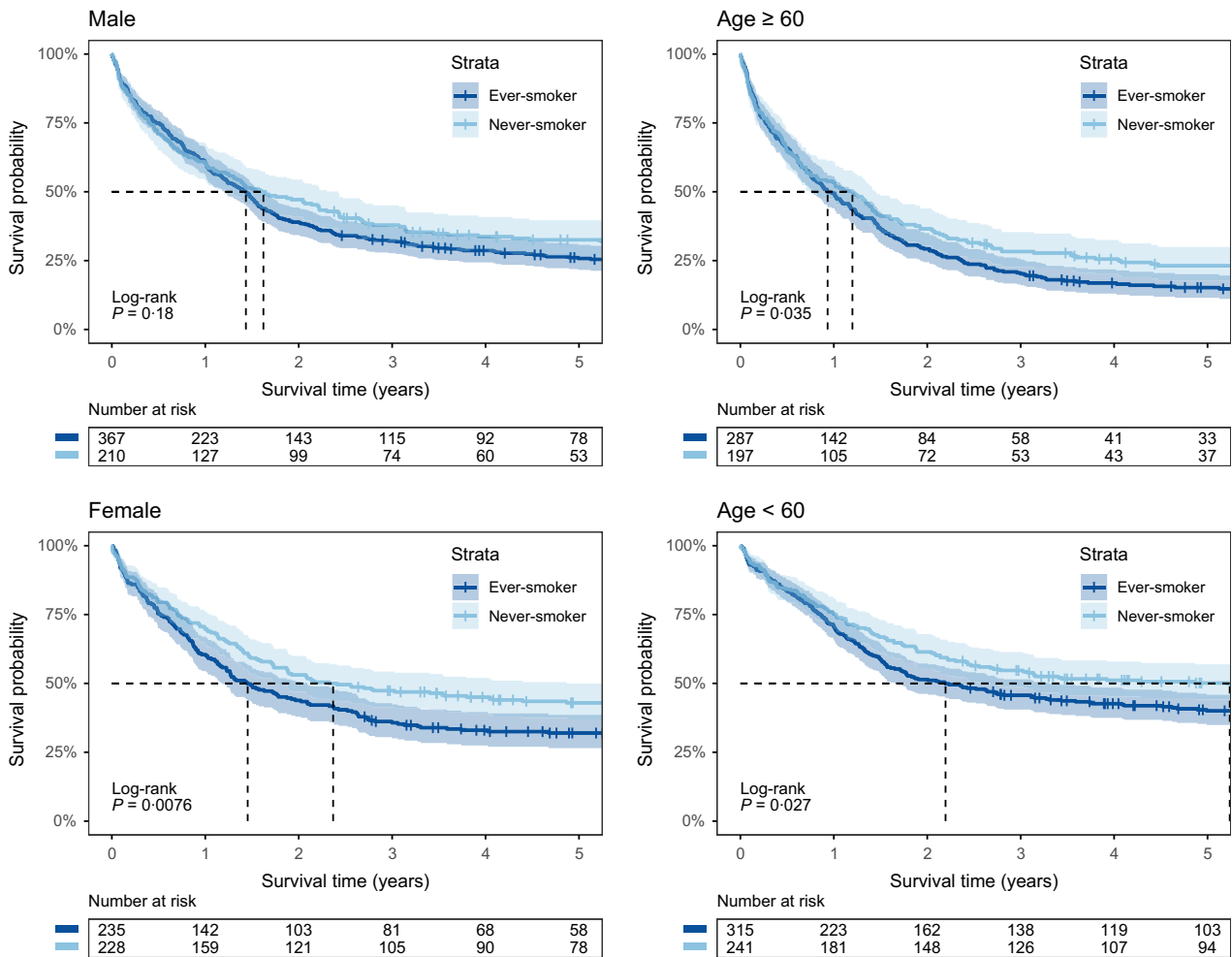


Fig 2. Crude survival and 95% CI for 1080 patients with acute myeloid leukaemia (AML) by smoking status for (upper left) male, (bottom left) female, (upper right) with age <60 years and (bottom right) with age ≥ 60 years. Survival time is displayed as time after diagnosis.  $P$ -values from log-rank tests. [Colour figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

sAML was associated with a worse outcome [HR 1.58, 95% CI (1.26;1.90),  $P < 0.001$ ] whereas tAML was not. Gender, BMI and comorbidity were not associated with inferior OS.

Since we missed information for a minor part of the cohort ( $n = 41$  for comorbidities and  $n = 3$  for performance status) we did an imputation of the missing values using predictive mean matching and a random forest method and the estimates were not altered significantly (data not shown).

## Discussion

In the past decades, knowledge of leukaemia-related factors as predictive of prognosis has expanded substantially.<sup>2</sup> Patient-related factors, such as age and performance status, are important factors when evaluating eligibility to receive intensive chemotherapy.<sup>18,19</sup> In this large nationwide study, we have shown that previous and current tobacco usage significantly decreases the OS of intensively treated patients with AML.

To the best of our knowledge, this is the largest nationwide study conducted on real-world patients with a complete

follow-up. This set-up allows for a true population-based design with a limited bias. A major strength of this study is that information on variables was collected to ensure quality and is thus free of a hypothesis-limiting information bias. Information on smoking status was collected at the time of referral and collected retrospectively for this study, eliminating recall bias. This study is however not free of bias, as we were not able to gather information on smoking for approximately 30% of the included study population. Missing information was mainly due to loss of medical records during transition to electronic patient systems. Some of the retrieved medical records did however not include information on smoking history.

To date, a limited number of studies have investigated the association between smoking status and outcomes in AML.<sup>20-22</sup> A retrospective single-centre study by Chelghoum *et al.* comprised of 643 patients with newly diagnosed AML in the time period of 1984 to 1998 also found inferior OS for smokers. However, in multivariate analysis, only karyotype and age remained of prognostic significance for progression-free survival (PFS) and OS.<sup>20</sup> In addition, they demonstrated that a dose-response relationship with a more intensive or longer smoking history of smoking is associated with a shorter PFS and OS and, importantly, smokers were at a higher risk of severe pulmonary infections during post-chemotherapy myelosuppression. As in our study, no difference in response to treatment was observed, measured as CR achievement. However, the information regarding smoking history was obtained retrospectively through family members of the patients, potentially causing recall-bias and potentially confounding the results of the study. Similarly, in this period the different treatment strategies differed, resulting in a more heterogeneously treated population. Finally, the study was only able to recruit 75% of patients due to loss of follow-up, making selection bias likely.

The most recent study by Varadarajan *et al.* addressed the prognostic impact of smoking in a single-centre study comprised of 280 newly diagnosed AML patients between 1990 and 2008.<sup>21</sup> All patients received similar intensive induction therapy, whereas consolidation therapy varied over time. In line with our study, they found that former and current smokers had an adverse prognosis. When adjusting for white blood cell count, gender, age, karyotype and AML presentation, smoking remained an independent prognostic factor with a HR of 1.64 [95% CI (1.21,2.21)]. The estimate presented by Varadarajan *et al.* is comparable with that of a similar study on smoking habit and outcome following HSCT,<sup>5</sup> which reported a HR for OS of 1.17 [95% CI (0.72,1.91)] and 1.75 [95% CI (1.00;3.06)] for former and current smoking patients after HSCT, respectively. However, none of these studies included comorbidity and WHO performance status as a covariant in the analysis, which could account for the rather pronounced effect of smoking on OS, since our data demonstrate ever-smokers to have significantly more comorbidities compared to

**Table III.** Multivariate analysis for OS by selected characteristic (Cox Proportional Hazard modelling,  $n = 1040$ ).

Characteristics	<i>n</i>	Hazard ratio (HR)	95% CI	<i>P</i>
<b>Smoking</b>				
Never	438	1.00	(reference)	
Ever	602	1.22	1.04-1.44	0.01
<b>Gender</b>				
Male	577	1.00	(reference)	
Female	463	0.89	0.76-1.05	0.159
<b>Age</b>				
< 60 y	556	1.00	(reference)	
≥ 60 y	484	1.84	1.56-2.16	<0.001
<b>Comorbidity</b>				
0	680	1.00	(reference)	
1	207	1.13	0.92-1.37	0.242
≥ 2	112	1.15	1.02-1.67	0.034
<b>WHO PS</b>				
0	348	1.00	(reference)	
1	501	1.24	1.04-1.48	0.016
≥ 2	188	1.76	1.41-2.20	< 0.001
<b>BMI</b>				
18.5-24.9	260	1.00	(reference)	
< 18.5	13	0.94	0.54-1.64	0.821
25-29.9	210	0.99	0.84-1.18	0.934
≥ 30	90	0.85	0.67-1.07	0.161
<b>AML presentation</b>				
dn-AML	836	1.00	(reference)	
sAML	167	1.58	1.26-1.90	< 0.001
tAML	37	1.39	0.94-2.06	0.099

AML, acute myeloid leukaemia; dn-AML, *de novo* AML; sAML, secondary AML; tAML, therapy-related AML; BMI, Body Mass Index; WHO-PS, World Health Organisation performance score; CI; confidence interval.

never-smokers. In our study, we were able to adjust for these potentially confounding factors with a very small number of missing values. We acknowledge that smoking status may be related to other impactful covariates not captured in our study. Intriguingly, alcohol consumption did not affect survival in any analysis (data not shown).

Another interesting finding in our study is the inferior median OS observed for men as compared to women for the total cohort as well as for the non-smoker subset. However, no difference was observed between ever-smoking males and females. Also, when comparing median OS in the smoking strata, female ever-smokers had a significantly shorter median OS as compared to never-smokers, whereas this was not observed for men. This could indicate that females are more susceptible to the chemical compounds of tobacco. Previous studies have indicated that female smokers have a faster annual decline rate in forced expiratory volume in one second (FEV<sub>1</sub>) compared to males.<sup>23,24</sup> However, whether females are more susceptible to the carcinogenic compounds of tobacco remains to be further investigated.

A limitation of our study is the lack of discrimination between leukaemia-related deaths and all-cause mortality. Hence, it remains unknown if the increased mortality in the ever-smoker group is due to leukaemia-related deaths. Previous studies have shown conflicting reports on the cause of death. Chelghoum *et al.* reports an increased prevalence of invasive pulmonary infections in the smoker group, whereas Varadarajan *et al.* did not find an increased risk of infection among smoking patients.<sup>20,21</sup> In general, the effect of smoking habits on invasive pulmonary infections in immunocompromised patients seems uncertain.<sup>25</sup>

Another point of criticism of this study is the failure of quantifying the intensity, duration and cessation of smoking (e.g., expressed as pack-years). This was largely due to inconsistent information in medical records. Data on smoking habits were retracted from the medical record taken at the very first admission to the haematology department by the physician taking care of the patient. Since the medical records are based on patient-reporting, information bias is possible. Patients have a tendency to underreport smoking habits and smokers may have been categorised as non-smokers – we may thereby inadvertently have underestimated the effects of smoking. We also pooled former and current smokers into one stratum, and were therefore not able to scrutinise the effect of former smoking versus current smoking. Pooling former and current smokers in an ‘ever-smokers’ group may thus underestimate the actual prognostic effects of active tobacco-smoking. Finally, data on laboratory values, cytogenetics and on mutational status were not available. Our study is not able to point out the exact mechanism or effect of tobacco-smoking on outcome parameters. Previous studies have investigated the association between tobacco-smoking

and cytogenetic findings in AML, summarised in Ref.[26]. Smoking has been associated with abnormalities of chromosome 8 [especially trisomy 8 and t(8,21)] and chromosome 7 [del(7) or del(7q)]. However, the two previous studies investigating the prognostic association of smoking did not find any differences in the cytogenetic risk category between smoking and non-smoking strata [19,20]. A recent presentation by Alfayez *et al.* also found smoking to be associated with inferior OS in univariate analysis, but not in multivariate.<sup>27</sup> They also found smoking to be associated with poor European Leukemia Net (ELN) risk, complex karyotype and *GATA2* mutation when controlling for age. This unpublished work indicates the possibility that the inferior OS associated with smoking could be explained by altered biology, rather than with the comorbidity associated with smoking.<sup>27</sup> Since the abovementioned studies, including our own, are correlational of nature, they do not imply a causal relationship between smoking status and inferior OS in AML patients. To shed light on this matter, further investigations are needed to elucidate whether smoking alters the underlying biology, including the mutational profile of AML.

In conclusion, our present study confirms smoking status as an important patient-related prognostic factor for outcome in a Danish cohort of AML patients, intensively treated between 2000 and 2012. This association was independent of gender, performance status, comorbidities, age, AML-presentation and BMI. Due to the observational and hypothesis-generating character of this study, it remains uncertain whether tobacco-smoking affects OS in patients with AML through leukaemia-related (e.g., somatic mutations) or patient-related (e.g., pulmonary morbidity) factors. We suggest that future studies on this subject should aim to include socio-economic and leukaemia-related prognostic factors to study the exact mechanism of inferior survival in previous and current smokers with AML.

## Acknowledgements

DK received research support from the Health Research Foundation of North Denmark Region. MTS received research support from the Danish Cancer Society (DCS) for data collection. TCEG received research support from DCS. A profound gratitude to everyone who has participated in forming and gathering data for DNLR.

## Author contributions

DK, ASR, TCKK and MTS designed the research. DK, ASR, TCKK, TCEG, JMN, CWM, CS, KTM and MTS collected data. DK, LBN, ASR and MTS analysed the data. DK, ASR and MTS wrote the manuscript. All authors interpreted data and took part in critical revision of the manuscript. All authors approved the final manuscript.

## Finding information

This work is supported by the Health Research Foundation of North Denmark Region and the Danish Cancer Society.

## Conflicts of interest

TCEG: Employment by Roche Ltd, Basel.

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