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Impact of Allogeneic Stem Cell Transplantation in First Complete Remission in Acute Myeloid Leukemia: A National Population-Based Cohort Study

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A B S T R A C T

To examine the outcomes of allogeneic stem cell transplantation (HSCT) in first complete remission (CR1) compared with chemotherapy alone in a population-based setting, we identified a cohort of patients with acute myeloid leukemia (AML) aged 15 to 70 years diagnosed between 2000 and 2014 in Denmark. Using the Danish National Acute Leukemia Registry, we compared relapse risk, relapse-free survival (RFS), and overall survival (OS) between patients with unfavorable cytogenetic features receiving postremission therapy with conventional chemotherapy only versus those undergoing HSCT in CR1. To minimize immortal time bias, we performed Cox proportional hazards regression, included date of allogeneic HSCT as a time-dependent covariate, and stratified the results by age (<60 or ≥60 years) and cytogenetic risk group. Overall, 1031 patients achieved a CR1. Of these, 196 patients (19%) underwent HSCT. HSCT was associated with a lower relapse rate (24% versus 49%) despite a similar median time to relapse (287 days versus 265 days). In all subgroups, the risk of relapse was lower and both RFS and OS were superior in recipients of HSCT (OS, adjusted mortality ratios: all patients, .54 [95% confidence interval (CI), .42-.71]; patients age <60 years, .58 [95% CI, .42-.81]; patients age ≥60 years, .42 [95% CI, .26-.69]; patients with intermediate-risk cytogenetics, .63 [95% CI, .43-.87]; patients with adverse-risk cytogenetics, .40 [95% CI, .24-.67]). In conclusion, in this population-based nationwide cohort study, HSCT was associated with improved survival in both younger and older patients and in patients with both intermediate and adverse cytogenetic risk.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HSCT) is a potentially curative treatment strategy for patients with acute myeloid leukemia (AML) due to the antileukemic effects of cytotoxic conditioning regimens and to the immunologic graft-versus-leukemia effect mediated by donor T cells [1,2]. Until recently, cytogenetic risk classification was the most important criterion when selecting postremission risk-adapted therapy [3], including HSCT in first complete remission (CR1). Most patients achieving CR1 have intermediate-risk cytogenetics, but to date, no truly randomized study has been completed in these patients. Several studies have investigated the role of HSCT using genetic assignment substituting for the lack of randomized trials on the basis of the availability of a matched related donor (MRD); however, these studies were not powered to examine survival within cytogenetic subgroups. Three meta-analyses combining these studies reported superior survival in the transplant groups with intermediate cytogenetic risk only [4], with adverse

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cytogenetic risk only [5], and with both intermediate and adverse cytogenetic risks [6]. In those studies, most patients underwent transplantation in the 1990s, and extrapolation to current treatment practice is hampered by the restricted use of matched unrelated donors (MUDs), the younger age of subjects included in previous comparisons, the limited number of reduced-intensity conditioning (RIC) regimens, and higher transplantation-related morbidity [7].

More recently, authors have compared HSCT including both RIC regimens and MUDs with chemotherapy only treatment in selected populations of varying ages using different methodological approaches [8-12],; however, none of these studies has convincingly demonstrated an overall survival benefit within cytogenetic subgroups after taking differences in characteristics between groups into consideration.

Although conventional chemotherapy has not changed substantially over the last 2 decades, the field of allogeneic transplantation has greatly expanded. The introduction of RIC and nonmyeloablative (NMA) regimens and improved supportive care has decreased transplantation-related morbidity, which may translate into more significant clinical improvement than previously reported in patients with AML. To further investigate which patients are likely to benefit from HSCT in CR1, we conducted a comparative effectiveness study of the 2 postremission treatment options, HSCT and chemotherapy only, evaluating relapse risk, relapse-free survival (RFS), and overall survival (OS) in Danish patients using the Danish National Acute Leukemia Registry (DNLR).

METHODS

We conducted a population-based nationwide cohort study of 3486 patients with AML age ≥15 years registered in the DNLR between 2000 and 2014 [13]. The registry collects clinical data prospectively and covers 99.6% of all patients with AML diagnosed in Denmark. Danish citizens (5.7 million people) are entitled to free access to medical care provided by the public tax-supported health care system, and no cancer treatment is provided outside of these public centers [13,14]. During the study period, patients with AML were treated with intensive therapy at 5 centers, and all HSCTs were performed at 2 centers: Aarhus University Hospital and Rigshospitalet. Tissue typing was recommended at the time of diagnosis for all patients without contraindications for HSCT, and a donor search was initiated when cytogenetic results were available, at the discretion of the treating physician [15].

We included patients age ≤70 years who achieved CR after 1 or 2 cycles of remission- induction chemotherapy. Patients with favorable cytogenetic risk features were excluded, because HSCT was not routinely recommended for these patients (Figure 1A).

Clinical Data

We obtained baseline demographic data, laboratory test results, and information on chemotherapy and treatment response (morphological CR) [16] from the DNLR. Cytogenetic results were grouped according to the Medical Research Council's 2010 revised criteria [17]. We obtained information on non-AML-related comorbidities before the diagnosis of AML from the Danish National Registry of Patients according to a modified version of the Charlson Comorbidity Index [18,19]. Information on type of AML was grouped according to World Health Organization criteria into secondary AML (s-AML; including previous myelodysplastic syndrome or chronic myelomonocytic leukemia, myeloproliferative neoplasm, or other), and therapy-related AML (t-AML) [20]. As a surrogate for complications during remission-induction therapy, we calculated the cumulative length of hospital stay between the date of AML diagnosis (day 0) and day 100.

Therapy Including HSCT

Intensive chemotherapy was defined as selection for 2 courses of remission-induction therapy including cytarabine (≥100-400 mg/m^2/day) [21] in combination with an anthracycline or anthracycline-like compound. Postremission therapy consisted of 1 or 2 courses of consolidation therapy (eg,amsacrine/cytarabine/etoposide, mitoxantrone/cytarabine high-dose cytarabine).

A national board generates consensus recommendations for allo-HSCT in AML in Denmark [15]. The recommendation is to perform HSCT in CR1 following 1 or 2 courses of consolidation therapy in patients with an adverse-risk karyotype and those with a normal karyotype and the presence of an *FLT3-ITD*$^+$/*NPM1*$^-$ mutation (since 2010). In intermediate-risk patients before 2010 and in patients without an *FLT3-ITD*$^+$/*NPM1*$^-$ mutation after 2010, HSCT was done at the discretion of the treating physician or according to clinical trials. The intensity of the conditioning regimen was based on current guidelines (age <50 years, myeloablative conditioning [MAC]; age 50-70 years, NMA), but the final decision was left to the attending physician.

Information on transplantation-related factors was obtained from local transplantation registries and included disease state at time of transplantation (CR1, CR2, not in CR), conditioning regimen (MAC/NMA), graft type (peripheral blood stem cells or bone marrow), and donor source (MRD, MUD, or umbilical cord blood). Detailed descriptions of the use of immunosuppressive therapy are available elsewhere [22].

Outcome

We obtained information on all-cause mortality and emigration through linkage to the Civil Registration System [23]. The date of confirmed relapse and detailed information on cause of death were obtained from the DNLR and local transplantation registries. Relapse was defined as measurement of >5% blasts in the bone marrow or the development of extramedullary myeloid lesions in a patient with previously documented CR. If the cause of death was registered as "progressive disease" or "relapse" and a date of relapse was missing, medical records were reviewed. RFS was defined as the time from the date of CR1 to the date of first relapse or death in CR1.

Statistical Analyses

Descriptive results

We stratified descriptive data by group (HSCT in CR1 or chemotherapy-only) and computed the median time to HSCT from both diagnosis and from CR1 overall, by donor type, and by conditioning regimen. Patients were followed from CR1 until death, emigration, or end of follow-up (February 18, 2016).

Comparative effectiveness of HSCT versus intensive therapy only; relapse risk, RFS, and OS using time of HSCT as a time-dependent exposure. We computed crude and adjusted mortality ratios comparing patients who underwent HSCT with those who received chemotherapy only using a Cox proportional hazards regression model, considering time of allo-HSCT as a time-dependent exposure. In essence, this approach assigns person-time (follow-up) for individuals before HSCT to the chemotherapy-only group. We estimated the RFS (hazard ratio [HR]) as a composite endpoint (relapse or death in CR1). Log-log plots were used to graphically verify that the proportional hazards assumption was not violated. We computed the risk of relapse using a Cox proportional hazards regression model, accounting for competing risk by censoring at death in CR1.

We present crude results and confounder-adjusted results (adjusted for sex, age, propensity score [PS], s-AML/t-AML, WBC, cytogenetic risk group, cumulative length of hospital stay within the first 100 days, and year of transplantation). All results were further presented overall and stratified by age (<60 or ≥60 years) and cytogenetic risk group (intermediate or adverse risk).

Sensitivity analysis: relapse risk, cumulative incidence of relapse, RFS, and OS using a landmark approach. We conducted landmark analyses to graphically compare relapse risk and survival and to assess the robustness of the time-dependent covariate approach. We started follow-up at days 200 (primary) and 365 (secondary) from diagnosis, to evaluate whether choice of landmark had an impact on interpretation of the landmark analyses. Patients in whom death, end of follow-up, or relapse occurred before the landmark were excluded. Patients undergoing HSCT before the landmark were categorized in the HSCT group, whereas those undergoing HSCT after the landmark were included in the chemotherapy-only group (Figure 1). This approach avoids immortal-time bias by synchronizing the start of follow-up for both treatment groups [24]. We computed the cumulative risk of relapse (using Fine and Gray methods) and created Kaplan-Meier plots overall and by subgroups. Subgroups were compared using the log-rank test.

To minimize confounding when comparing the effectiveness of HSCT with intensive chemotherapy only, we computed a PS for each individual, which predicted the probability of undergoing HSCT in CR1 conditional on the individual's observed baseline factors using multivariable logistic regression [25-27].

The PS model included factors associated with referral to HSCT in CR1 and outcome, or to outcome alone, including age (<30, 30-39, 40-49, 50-59, 60-70 years), sex, WBC at diagnosis, World Health Organization performance status, cytogenetic risk group (imputing missing as the intermediate risk group), type of AML, comorbidity at time of AML diagnosis, and cumulative length of hospital stay over days 0 to 100.

We balanced these factors across the treatment groups using standardized mortality ratio (SMR) weighting [28], and evaluated the covariate balance

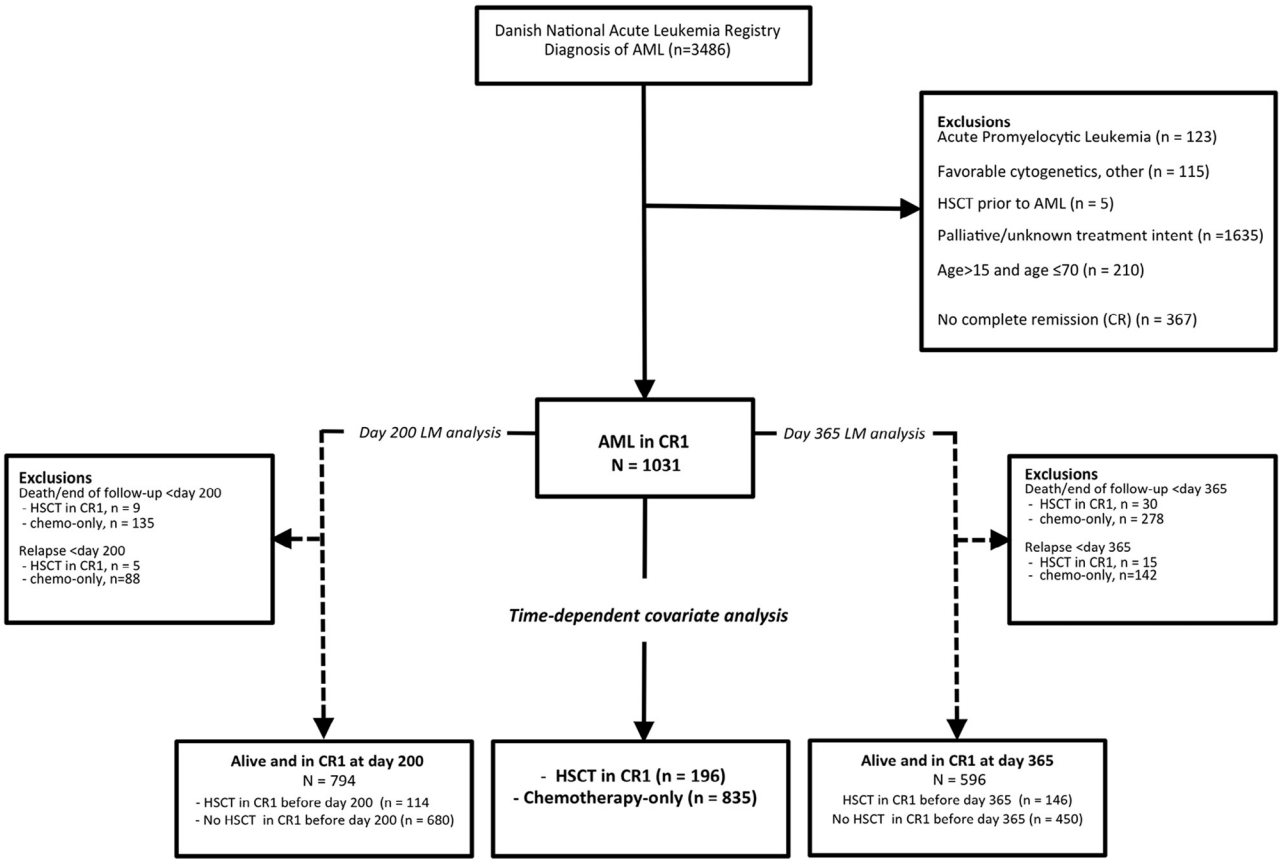

Figure 1. Study cohort inclusion and exclusion diagram. The flow chart shows the selection process for the main analysis using time-dependent covariates and for the secondary landmark analyses using the day 200 and day 365 landmarks.
LM, landmark.

using standardized absolute mean difference, with a value <.1 considered to indicate adequate balance [29,30].

We then calculated crude and adjusted (via SMR weighting) HRs for OS, RFS, and relapse risk, comparing patients who underwent HSCT and those receiving chemotherapy only using a Cox proportional hazards regression model.

The study protocol was approved by the Danish Data Protection Agency (j.nr. 2012-41-0878) and the National Board of Health (j.nr.3-3013-158). All analyses were performed using the Stata 13.0 package (StataCorp, College Station, TX).

RESULTS

Patient and Treatment Characteristics

The final study population comprised 1031 patients. Selection of the study population is shown in Figure 1. A total of 196 patients (19.0%) underwent transplantation in CR1.The proportion of patients who underwent transplantation increased during the study period (2000-2004, 10.9%; 2005-2009, 20.0%; 2010-2014, 26.6%). The median patient age was 56 years (range, 16-70 years), and 52.8% were men. The characteristics of all patients and of the matched cohort by treatment status are presented in Table 1. The HSCT recipients were generally younger, had less comorbidity, and had better performance status at diagnosis. However, more HSCT recipients had s-AML and adverse cytogenetics or abnormal karyotype.

The total follow-up time in the cohort was 4202 person-years, with a median duration of 2.2 years. During this time, 654 patients (63.4%) died (571 in the chemotherapy-only group and 83 in the HSCT group). The time from diagnosis to CR1 did not differ between the HSCT and chemotherapy-only groups (39 days; interquartile range [IQR], 33-67 days versus 37 days; IQR, 32-51 days). All chemotherapy-only patients received at least 1 cycle of induction chemotherapy, 89% received 2 cycles, 70% received 1 consolidation regimen, and 40% received 2 or more consolidation regimens. The corresponding proportions in the HSCT group were 100%, 91%, 74%, and 24%. The remission-induction regimens used differed between the 2 groups. HSCT recipients more often received remission-induction therapy with daunorubicin and cytarabine with or without etoposide (DA/ADE; 71%), idarubicin and cytarabine (16%), or FLAG-based regimens (6%). In contrast, the chemotherapy-only cohort received DA/ADE (42%), idarubicin and cytarabine (30%), and mitoxantrone-based regimens (18%).

Conditioning Regimens in HSCT Recipients

Transplantation-related information for the 196 patients who underwent transplantation in CR1 is provided in Table 1. The median time from diagnosis to HSCT was 182 days (IQR, 152-216 days), and the median time from CR1 to HSCT was 128 days (IQR, 97-169 days), including 143 days (IQR, 120-203 days) in MUD recipients, 112 days (IQR, 79-134 days) in MRD recipients, 119 days (IQR, 76-162 days) in patients receiving MAC, and 133 days (IQR, 106-170 days) in those receiving NMA conditioning. In patients age <60 years, 48.5% received a MAC regimen, and all patients age ≥60 years received NMA conditioning. A graft from a related donor was

Table 1
Patient and Transplantation-Related Characteristics According to Treatment in All Patients and by Age

Characteristic	Entire Cohort (n = 1031)	
	HSCT in CR1 (n = 196; 19.0%)	Chemotherapy-Only (n = 835; 81.0%)
Patient characteristics		
Male sex, n (%)	107 (54.6)	437 (52.3)
Age, yr, median (range)	53 (17-70)	57 (15-70)
Comorbidities, n* (%)		
0	151 (85.3)	587 (75.1)
1	21 (11.9)	145 (18.5)
≥2*	5 (2.8)	50 (6.4)
WHO performance status, n (%)		
0	90 (45.9)	314 (37.6)
1	83 (42.4)	393 (47.1)
≥2	23 (11.7)	128 (15.3)
t-AML, n (%)	6 (3.1)	50 (6.0)
s-AML, n (%)	35 (17.9)	85 (10.2)
Disease characteristics		
Time to treatment initiation, d, median (IQR)	4 (1-7)	3 (1-7)
Cumulative length of hospital stay (days 1-100), n (%)		
0-29 d	45 (25.4)	184 (24.0)
30-60 d	92 (52.0)	403 (52.5)
≥60 d	40 (22.6)	181 (23.6)
Blast count in marrow, %, median (IQR)	52 (32-80)	56 (33-80)
Blast count blood, %, median (IQR)	17 (1-56)	25 (5-61)
WBC, $\times 10^9$/L, median (IQR)	6 (2-36)	10 (2-31)
Platelet count, $\times 10^9$/L, median (IQR)	71 (37-119)	58 (31-107)
Cytogenetics risk group, MRC 2010, n, (%)		
Intermediate risk	116 (73.0)	619 (83.8)
Adverse risk	43 (27.0)	120 (16.3)
Missing	22 (11.2)	96 (11.4)
Cytogenetics, karyotype, n (%)		
Normal	93 (52.8)	449 (60.6)
Abnormal	83 (47.2)	292 (39.4)
Transplantation-related characteristics		
Conditioning regimen, n (%)		
MAC	70 (35.7)	
NMA	126 (64.3)	
Donor source, n (%)		
MRD	91 (46.4)	
MUD	99 (50.1)	
Umbilical cord blood	6 (3.1)	
HLA match, n (%)		
10/10 or 10/9	183 (93.4)	
HLA-identical match		
1 antigen mismatch	7 (3.6)	
Umbilical cord blood	6 (3.1)	
Time from diagnosis to HSCT in CR1, d, median (range)	182 (152-216)	
Time from CR to transplantation in CR1, d, median (range)	128 (98-168)	

WHO indicates World Health Organization; MRC, Medical Research Council.
* According to the modified Charlson Comorbidity Index, which includes non-leukemia-related comorbidity.

more common in younger patients than in older patients (56% versus 25%). In total, 97% of the patients received a 10/10 or 9/10 HLA-matched graft. MAC regimens consisted of cyclophosphamide 120 mg/kg and total body irradiation (TBI) 12.5 Gy (in 90% of the patients), busulfan 12.8 mg/kg and cyclophosphamide 120 mg/kg (in 9%), or fludarabine 150 mg/m^2 and treosulfane 42 g/m^2 (in 1%). NMA conditioning regimens included fludarabine 90 mg/m^2 and TBI 2 Gy (in 92%); fludarabine 160 mg/m^2, cyclophosphamide 50 mg/kg, and TBI 2 Gy (4.8%); and fludarabine 90 mg/m^2 and TBI 4 Gy (in 2.4%) or TBI 3 Gy (in 1%). No survival difference was seen between MAC and NMA conditioning groups (age <60 years; $P = .20$) or between MUD and MRD groups ($P = .70$, log-rank test).

Risk of Relapse and RFS Overall and by Age and Cytogenetic Risk Group

Relapse occurred in 47 patients (24.0%) in the HSCT group, compared with 411 patients (49.2%) in the chemotherapy-only group, but these was no between-group difference in the median time from CR1 to relapse (265 days [IQR, 157-466 days] in the chemotherapy-only group versus 287 days [IQR, 216-591 days] in the HSCT group). When censoring patients at death in CR, the crude and adjusted risks of relapse were higher in the chemotherapy-only group (adjusted HR [aHR], .37; 95% CI, .26-.53). This effect was comparable across age and cytogenetic risk groups (Table 2).

The median RFS was 293 days (IQR, 142-910 days) in the chemotherapy-only group and 1068 days (IQR, 397-2698 days) in the HSCT group. The crude and adjusted results of the regression analysis for RFS are shown in Table 2. Both crude and adjusted estimates of RFS overall and within age and cytogenetic subgroups were superior in the HSCT cohort compared with the chemotherapy-only cohort. The effect of HSCT on RFS tended to be greater in older patients compared with younger patients (aHR, .38 [95% CI, .23-.62] versus .52 [95% CI, .38-.71]), whereas a similar effect was seen in adverse-risk and intermediate-risk patients (aHR, .44 [95% CI, .26-.75] versus .52 [95% CI, .38-.71]).

Adjusted survival overall and within subgroups

The median OS was 476 days (IQR, 167-1589 days) in the chemotherapy-only group and 1173 days (IQR, 474-2859 days) in the HSCT group. The results of the overall crude and adjusted survival analyses are shown in Figure 2. Overall and within all subgroups, the HSCT group had superior survival (aHR: overall, .54 [95% CI, .42-.71]; younger patients, .58 [95% CI, .42-.81]; older patients, .42 [95% CI, = .26-.69]; intermediate-risk patients, .63 [95% CI, .43-.87]; adverse-risk patients, .40 [95% CI, .24-.67]) compared with the chemotherapy-only group.

Within s-AML categories, s-AML patients with previous myelodysplastic syndrome or chronic myelomonocytic leukemia had superior outcomes after allo-HSCT compared with after chemotherapy only (aHR, .35; 95% CI, .14-.92). In contrast, allo-HSCT recipients with t-AML or s-AML and previous myeloproliferative neoplasm had outcomes comparable to the chemotherapy-only group (aHR, .80 [95% CI, .10-3.88] versus 1.09 [95% CI, .30-4.02]).

Relapse Risk, RFS, and OS Using a Landmark Approach

To allow for a visual comparison between the HSCT and chemotherapy-only groups and consideration of competing risks, we reanalyzed the data using a landmark approach, starting follow-up at day 200 (n = 794, including 114 allo-HSCT recipients in CR1) and at day 365 (n = 596, including 146 allo-HSCT recipients in CR1). Confounders were well balanced using PS weighting (Supplementary Figure S1).

Table 2
Crude HRs and aHRs Comparing HSCT versus Chemotherapy-Only and the Risk of Relapse and RFS Analyses Considering Transplantation as a Time-Dependent Covariate

	Relapse Risk*		RFS†	
	Crude HR (95% CI)	aHR‡ (95% CI)	Crude HR (95% CI)	aHR‡ (95% CI)
Overall				
HSCT in CR1	.45 (.33-.61)	.37 (.26-.53)	.54 (.43-.68)	.48 (.37-.62)
Chemotherapy-only	1	1	1	1
Stratified by age				
<60 yr				
HSCT in CR1	.45 (.31-.65)	.39 (.25-.59)	.58 (.44-.77)	.52 (.38-.71)
Chemotherapy-only	1	1	1	1
≥60 yr				
HSCT in CR1	.45 (.27-.78)	.34 (.18-.65)	.49 (.33-.74)	.38 (.23-.62)
Chemotherapy-only	1	1	1	1
Stratified by cytogenetics				
Intermediate risk				
HSCT in CR1	.35 (.23-.54)	.35 (.23-.55)	.50 (.38-.68)	.52 (.38-.70)
Chemotherapy-only	1	1	1	1
Adverse risk				
HSCT in CR1	.64 (.36-1.11)	.46 (.24-.87)	.52 (.33-.82)	.44 (.26-.75)
Chemotherapy-only	1	1	1	1

* Patients are censored at death in CR.
† Relapse and death in CR served as a composite endpoint.
‡ Adjusted for age, sex, WHO performance status, type of AML (de novo, s-AML, or t-AML), WBC, cytogenetic risk group, comorbidity, cumulative length of hospital stay in days 0-100, and year of diagnosis.

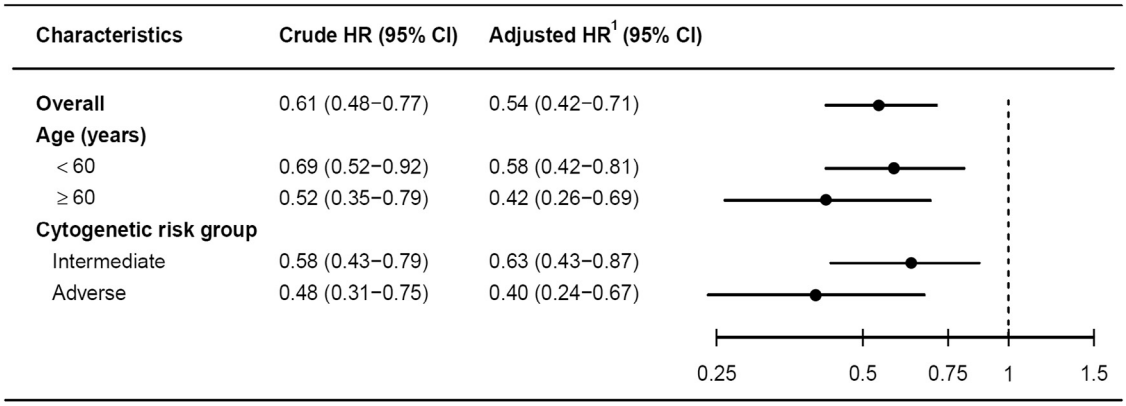

Figure 2. Forest plot of the crude HRs and aHRs comparing HSCT versus chemotherapy only and OS after CR by subgroup, considering transplantation as a time-dependent covariate.
*Adjusted for age, sex, World Health Organization performance status, type of AML (de novo, s-AML, or t-AML), WBC, cytogenetic risk group, comorbidities, cumulative length of hospital stay between day 0 and day 100, and year of diagnosis.

The cumulative incidences of relapse overall and within subgroups for the day 365 landmark cohort are shown in Figure 3. At 1 year from CR1, the risk of relapse remained lower in patients undergoing transplantation before day 365. Crude survival was superior overall and within subgroups in HSCT recipients undergoing transplantation within 1 year from diagnosis (Figure 4). The cumulative incidence of relapse and crude OS for the day 200 landmark are shown in Supplementary Figures S2 and S3.

Using day 180 (or median time to HSCT) as a landmark resulted in estimates comparable to those of the day 200 landmark analyses (results not shown).

Our use of the landmark approach did not change the interpretation of the primary results using the time-dependent covariate analysis with follow-up starting at CR1. However, owing to smaller cohorts, shorter follow-up time, the start of follow-up several months after an eventual HSCT was performed, and the inclusion of true HSCTs in the unexposed group, especially in the day 200 landmark analysis, the estimates differed among the 3 approaches and were less precise in the landmark analyses, especially for the small subgroup of adverse-risk patients who were alive and relapse-free after the landmark. Relapse risk, RFS, OS, and crude and SMR-weighted results for both landmarks are presented in Supplementary Tables S2–S4.

DISCUSSION

In this large and contemporary population-based study of patients with AML, we found that postremission therapy with HSCT in CR1 was superior to consolidation chemotherapy in otherwise comparable patients. HSCT was associated with improved relapse rate, RFS, and OS both overall and within subgroups of patients stratified by age or cytogenetic risk group. Interestingly, time to relapse was not different in the 2 groups.

To our knowledge, this is the first population-based study directly comparing patients with AML treated with conventional chemotherapy only with those receiving additional

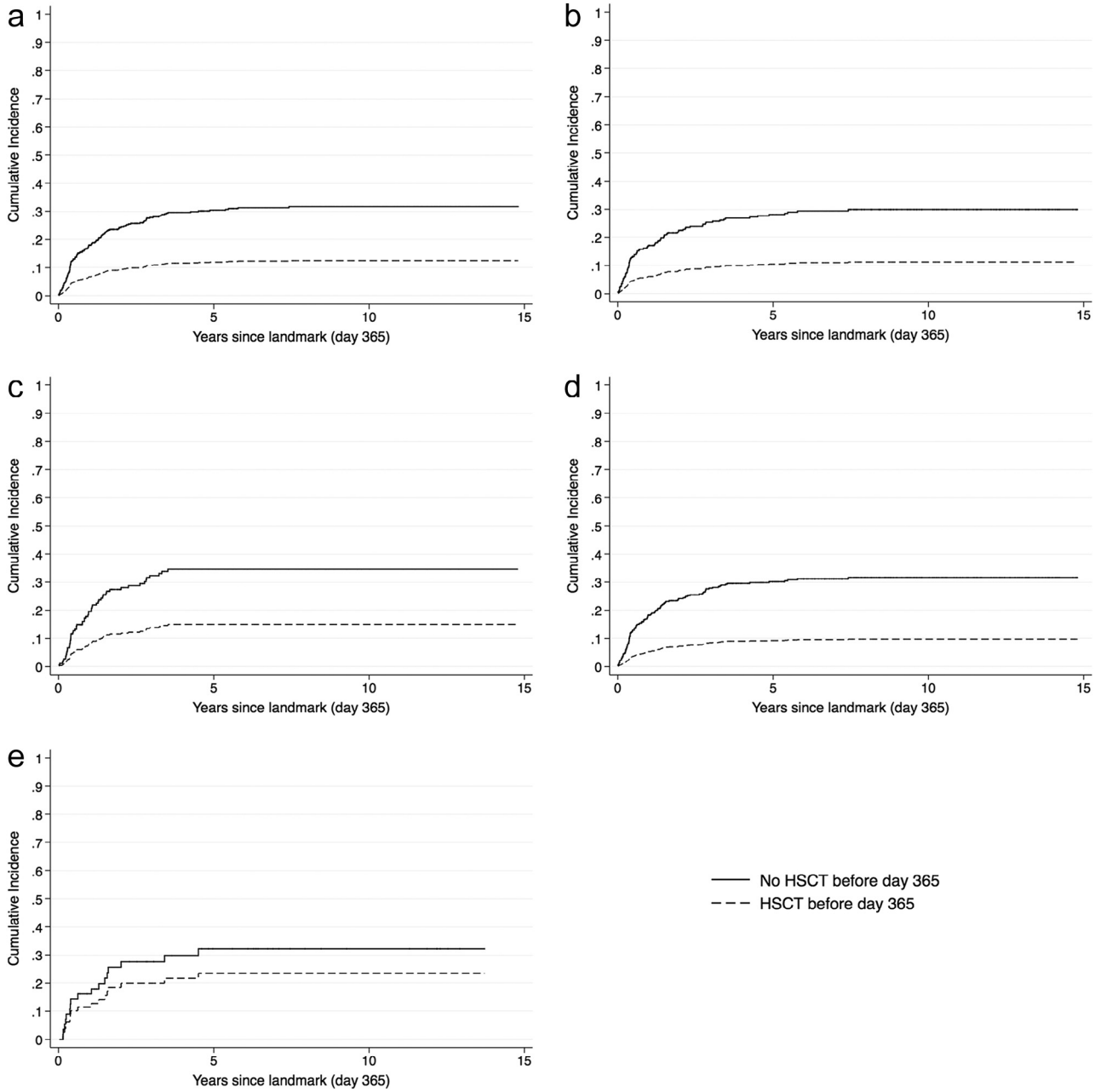

Figure 3. Crude cumulative incidence of relapse, using death as a competing risk and day 365 as a landmark, overall (A), in patients age <60 years (B), in patients age ≥60 years (C), in patients with intermediate-risk cytogenetics (D), and in patients with adverse-risk cytogenetics (E).

consolidation with HSCT within cytogenetic risk groups. The population-based design with a large number of patients and long follow-up allowed for sufficient statistical power to evaluate the effect of HSCT within age and cytogenetic risk groups using advanced statistical methods to control for measured confounding. The accuracy and completeness of our data have been confirmed as high through various validation processes [31,32], and the transplantation-related data were validated using medical records, thereby minimizing misclassification bias. In addition, complete follow-up data were available. Finally, the inclusion of patients treated within the last 15 years ensured generalizability to current treatment strategies and outcomes.

We found a survival benefit of HSCT as a postremission treatment strategy across age and cytogenetic risk groups. In general, previous studies of mainly younger patients failed to show an overall survival benefit from HSCT, with inconsistent findings regarding the effect within cytogenetic risk groups [4-6,10,32-34]. These differences are likely explained by improved supportive care and transplantation effectiveness over time, heterogeneity of treatment regimens and patient characteristics, as well as the use of donor versus no-donor comparisons in earlier studies. The donor versus no-donor approach is likely to underestimate the antileukemic effect of HSCT, given that only 50% to 75% of patients actually receive the assigned treatment.

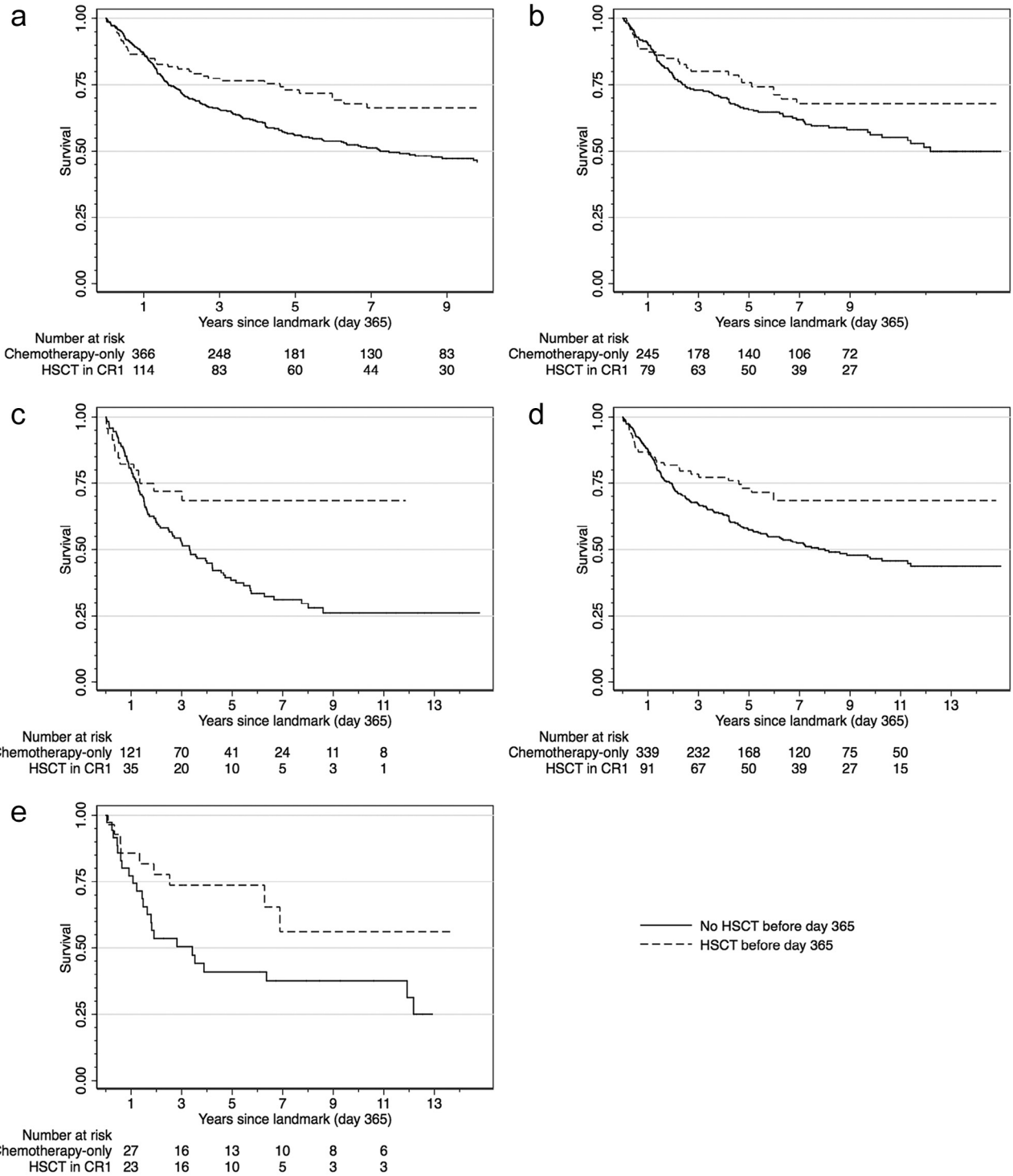

Figure 4. Crude survival in patients with AML by treatment for the day 365 landmark analysis. Kaplan-Meier plots show crude survival for the study population overall (A), in patients age <60 years, (B), in patients age ≥60 years (C), in patients with intermediate-risk cytogenetics (D), and in patients with adverse-risk cytogenetics (E). Superior survival is seen overall and within the subgroups.

In the light of the increasing use of MUDs, other methodological approaches are now used to compare survival between patients receiving MAC or NMA HSCT to those receiving consolidation only [8,9,12,35,36]. However, the conclusions from these reports are limited by various methodological limitations. Juliusson et al. [35] reported that a higher HSCT rate in patients age <60 years in a population-based setting was associated with overall superior long-term survival, and Kurosawa et al. [8] reported superior survival in patients with intermediate and adverse cytogenetic risk undergoing NMA-conditioned HSCT compared with those receiving chemotherapy only. However, in both of those studies, only crude results were reported, and thus confounding by indication could be present. In another

study, postremission use of NMA HSCT was associated with a survival benefit in older patients, but these results were not controlled for clinical confounders such as comorbidities, and the series included a large proportion of chemotherapy-only patients who did not receive any consolidation chemotherapy, which might have biased results toward a superior outcome in the HSCT recipients [36]. Recently, Russell et al. [12] reported superior survival overall and within intermediate and adverse cytogenetic risk group in younger HSCT patients compared to chemotherapy-only, however, this analysis was restricted only to patients receiving an allograft from a MRD.

Other studies have shown that RIC/NMA-based transplantation conditioning regimens are well tolerated in older patients, and that the effect is not age-dependent [37,38]. In our study, patients age ≥60 years achieved a similar reduction in RFS as younger patients, despite the use of MAC regimens in ~50% of patients age <60 years. Our results confirm that the use of NMA conditioning expands the application of HSCT in patients with AML of advanced age or with comorbidities, who are not otherwise candidates for MAC HSCT [39].

We also found the relative reduction in relapse risk and RFS within the intermediate risk group to be comparable to that seen in adverse risk patients.

The European Leukemia Networking party has suggested that HSCT should be performed in patients when the procedure is expected to improve RFS by 10% or more, based on pretransplantation assessments of relapse risk and NRM [39]. In our study, we observed a >10% difference not only in RFS, but also in OS, between HSCT and chemotherapy-only patients for all subgroups. Nonetheless, relapse remains a major problem after HSCT, and therapeutic strategies for post-HSCT relapse of AML are much needed. In the present study, one-fourth of the HSCT recipients experienced relapse, in agreement with results from large clinical trials reporting relapse rates ranging from 24% to 37% [40]. Novel targeting agents or adjuvant post-transplantation treatments, such as low-dose demethylating agents (eg, azacytidine) have been suggested to increase the graft-versus-leukemia effect. FLT3 inhibitor therapy post-transplantation is currently undergoing prospective evaluation in clinical trials, with the aim of reducing the risk of relapse [41-43].

The patients in the chemotherapy-only group received more cycles of chemotherapy than those in the HSCT group, and although the remission-induction regimens differed slightly between the 2 groups, DA/ADE, FLAG, and idarubicin-based induction chemotherapy have shown similar outcomes [44-46]. It was not possible to include different transplantation approaches, such as donor source or the level of HLA matching, in the analysis; however, given that 94% of patients undergoing transplantation in CR1 had a 9/10 or 10/10 HLA match, and that there was no survival difference between MUD and MRD graft recipients, these factors were less likely to have affected the results. This is supported by previous studies showing comparable survival in HSCT recipients with MUD and MRD grafts [11,46] as well as similar relapse risk and survival in HSCT recipients conditioned with NMA and those conditioned with MAC [22,47].

In recent years, molecular data have refined the prognostication of the large intermediate-risk group, adding the recommendation for HSCT in patients with a normal karyotype with an *FLT3-ITD*$^{+}$/*NPM1*$^{-}$ mutation in 2010. We did not have molecular information, including minimal residual disease, for all patients, and thus we could not take this into consideration in our analyses and address whether—based on molecular alterations—chemotherapy only would have been at least equal to HSCT within a subgroup of intermediate-risk patients.

The time from CR1 to HSCT in our series did not differ from that reported by Mohty et al. [10] and Farag et al. [48], but was shorter than reported in another recent study (172 days [11] versus 128 days), owing primarily to a shorter time to HSCT in recipients of MUD grafts in our study. This indicates early tissue typing and an efficient search for unrelated donors through national and international registries. Although, it is recommended that HSCT should be performed as early as possible after induction chemotherapy to prevent unnecessary treatment-related morbidity, which could preclude patients from proceeding to HSCT, the observed time to transplantation shows that consolidation chemotherapy can be avoided in only a very few patients. Improvements in supportive care after transplantation and the use of new conditioning regimens have led to improved outcomes over time [7].

Our study has some limitations. The patients were not randomized to allo-HSCT, which introduced confounding by indication, because some chemotherapy-only patients might have been scheduled for allo-HSCT but could have experienced relapse or death before undergoing transplantation. To avoid immortal-time bias, we primarily used time of transplantation as a time-dependent covariate, in which allo-HSCT recipients contribute follow-up time to the chemotherapy-only group until the day of transplantation in CR1. Second, we used a landmark approach, in which immortal-time bias is avoided by synchronizing the start of follow-up for all individuals in the 2 treatment groups. The landmark approach restricts the analytic cohort by excluding patients who experience early outcomes, who do not have the opportunity to undergo allo-HSCT (and thus are not truly exchangeable with those who actually undergo allo-HSCT). Inclusion of these individuals would artificially exaggerate the beneficial effects of allo-HSCT compared with the chemotherapy-only approach. Moreover, the use of an active comparator (ie, chemotherapy-only) and PS weighting helped reduce confounding by measured indication and frailty [24]. However, because the landmark approach prevented us from comparing outcomes before day 200/day 365 and this approach would (depending on choice of landmark) misclassify a proportion of allo-HSCT recipients as chemotherapy-only patients, we used time-dependent covariate analyses as our main analytic approach. Nonetheless, we found that the 2 different approaches generated comparable results for RFS and OS in all subgroups, strengthening our study conclusions. We lacked information on reasons why chemotherapy-only patients did not receive HSCT; however, the wide extent of clinical information used in this study including, comorbidities, performance status, and time spent in the hospital, in combination with the use of PS weighting, allowed us to compare the 2 treatment approaches. Even still, however, residual confounding might have affected the results toward a superior survival in HSCT recipients.

In conclusion, our results indicate that the antileukemic effect of HSCT can improve RFS and OS in a large fraction of both younger and older patients with intermediate and adverse cytogenetic risk features. The field of HSCT is constantly developing, and a continued effort should be made to conduct clinical prospective trials comparing HSCT and nonallogeneic treatments.

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SUPPLEMENTARY DATA

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