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Allotransplants for Patients 65 Years or Older with High-Risk Acute Myeloid Leukemia

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A B S T R A C T

The outcome of persons > 65 years with acute myeloid leukemia (AML) is poor. A transplant from an HLA-identical sibling or an HLA-matched unrelated donor can cure some of these patients but is associated with a substantial transplant-related mortality and a high relapse risk. We analyzed 185 subjects > 65 years with high-risk AML receiving conventional (n = 42) or reduced-intensity (n = 143) pretransplant conditioning and a transplant from an HLA-identical sibling (n = 66) or a 10/10 loci HLA-matched unrelated donor (n = 119). Two-year survival was 37%. Subjects with serious adverse events during before chemotherapy for their leukemia had a poor outcome after stem cell transplantation. Patients who had active leukemia or measurable residual disease (MRD) before transplantation had a worse outcome. Delayed hematologic recovery after induction or consolidation chemotherapy, high-risk AML genetics, donor–recipient HLA-DRβ3/4/5-DP mismatches, and history of cardiovascular disease were also correlated with survival in multivariate analyses. The 57 MRD-negative patients with few other adverse prognostic factors had an excellent outcome (2-year overall survival, 76%), whereas the 58 patients with detectable leukemia and more than 1 other additional factor fared poorly (2-year overall survival, 8%). These data indicate it is possible to identify persons > 65 years with high-risk AML likely to benefit from an allotransplant. Validation of this prediction is needed.

INTRODUCTION

More than one-half of persons with acute myeloid leukemia (AML) are older than 65 years [1]. Their prognosis is poor, with 2-year survival of about 20% [2–5] and <10% 5-year survival based on data from Surveillance, Epidemiology, and End Results. Moreover, about 50% are never treated [6]. AML in these persons is intrinsically less sensitive to chemotherapy and is often associated with unfavorable risk features such as complex cytogenetics [7–10]. Moreover, older persons may be frail or have comorbidities that limit therapy options. Outcomes are significantly worse in persons with high-risk features such as measurable residual disease (MRD) after therapy, prior myelodysplastic syndrome, therapy-related leukemia, high-risk cytogenetics, and advanced leukemia, with 2-year survivals of 3% to 15% [3,11–17].

Allotransplants are increasingly used in persons > 65 years with AML [18]. Transplants are attractive in high-risk AML because they offer the possibility of cure [19–23]. However, they are also associated with considerable morbidity and mortality in this age cohort. For these reasons it is important to identify persons most likely to benefit. We analyzed transplant outcomes in 185 subjects older than 65 years with high-risk AML to identify prognostic and predictive variables correlated with these outcomes.

METHODS

Patient and Transplant Characteristics

Between 2010 and 2015, 213 consecutive AML patients older than 65 years underwent stem cell transplantation (SCT) at our institution; 28 (13.1%) patients had missing key data (see below) and were excluded from the analysis. The remaining 185 patients are the subjects of this study. The median follow-up of surviving patients was 35 months (range, 8 to 72). Table 1 shows the patient and transplant characteristics.

All patients received a transplant from either an HLA-identical sibling or a voluntary unrelated donor matched at high resolution level at HLA-A, -B, -C, -DRβ1, and -DQ loci (10/10 match). Patients and donors were also typed at the HLA-DRβ3/4/5 and HLA-DP loci and further classified as 10-14/14 patient–donor match. HLA-DP mismatches were defined as permissive or nonpermissive as described elsewhere, and only nonpermissive HLA-DP mismatches were considered in our analysis [24].

We used several different conditioning regimens based on 1 of 3 schemes: (1) myeloablative conditioning (MAC) with fludarabine and 130 mg/m^2 i.v. busulfan for 4 days or its equivalent pharmacokinetic-guided dose

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[25] (Bu-Flu-MAC), (2) reduced-intensity conditioning (RIC) with fludarabine and 100 mg/m^2 i.v. busulfan for 4 days or its equivalent pharmacokinetic-guided dose (Bu-Flu-RIC), or (3) RIC with fludarabine in combination with 100 to 140 mg/m^2 melphalan (Flu-Mel-RIC). Graft-versus-host disease (GVHD) prophylaxis consisted of tacrolimus and methotrexate. Rabbit antithymocyte globulin was added to the GVHD prophylaxis regimen in recipients of an unrelated donor transplant.

MRD was assessed before transplant by 8-color flow cytometry in bone marrow samples as described elsewhere. A minimum of 200,000 live events was acquired to achieve a potential sensitivity of at least 10^{-4} [26-28]. AML cytogenetic and molecular risk were defined using the 2017 European LeukemiaNet genetic risk stratification [10]. Complete remission (CR) and CR with incomplete hematologic recovery (CRi) were defined using standard criteria [10]. Delayed hematologic recovery was defined as failure to recover the absolute neutrophil count to $\geq .5 \times 10^9$ cells/L by day +28 after chemotherapy. This study was performed in accord with the Declaration of Helsinki after informed consent and was approved by the local institutional review board.

Patients with No Available MRD Assessment or Molecular Risk Group Characterization

Samples for MRD assessment or molecular risk group characterization were not available in 28 patients. For those patients overall survival (OS; $P = .85$), treatment-related mortality (TRM; $P = .71$), cumulative incidence of relapse (CIR; $P = .90$), cytogenetic risk group ($P = .61$), and remission status ($P = .78$) were similar to the 185 patients included in the study.

Statistical Methods

The probability of OS was calculated by the Kaplan-Meier method. The probabilities of disease relapse and TRM were calculated using the cumulative incidence procedure, where disease relapse or death in remission were the events of interest and death and disease relapse were the competitors. Variables found to be significant at the $P < .15$ level in the univariate analysis (Table 1) were included in the multivariate analysis, where OS was examined with a Cox regression model and relapse and TRM by Fine-Gray regression analysis. Tests for interactions were carried out and were negative except in the following cases: (1) multivariate analysis for OS, in which the variables major medical complication (MMC) and detectable leukemia and the variables conditioning regimen and detectable leukemia had significant interactions; (2) multivariate analysis for TRM, in which the variables MMCs and detectable leukemia had significant interactions; and (3) multivariate analysis for relapse, in which the variables genetic risk and detectable leukemia had significant interactions. In these cases we have presented the various hazard ratios (HRs) for the individual variables. The proportional hazards assumption was confirmed by adding a time-dependent covariate for each covariate.

Categorical data were compared with Fisher's exact test,and quantitative data with the Mann-Whitney or the Kruskal-Wallis test. HRs are reported with 95% confidence intervals (CIs). All *P*-values are 2-sided.

RESULTS

Patient Risk Factors and Outcomes

One hundred seventy-eight patients (96.2%) had at least 1 (median, 3) high-risk AML features other than age, such as at least in second CR (CR2), high genetic risk, detectable MRD, secondary leukemia, primary refractory disease, or active disease (Table 1). The remaining 7 patients (3.8%) had gene mutations associated with poor outcome but not included in the European LeukemiaNet high-risk definition (data not shown).

The 2- and 5-year probabilities of OS were 37.3% (95% CI, 30.4 to 44.8) and 28.2% (95% CI, 18.5 to 31.0), respectively. Table 2 shows the adjusted HRs for the various outcomes according to key patient and transplant characteristics. Patients receiving a graft from a fully matched sibling or from a 10/10 HLA-matched unrelated donor had similar outcome. However, when we took into account mismatches at HLA-DRβ3/4/5 and HLA-DP loci, recipients of a graft from an unrelated donor with more than 1 mismatch had a significantly lower OS and higher TRM than those receiving a graft from a 13-14/14 HLA-matched unrelated donor or a fully HLA matched sibling.

We also examined the prognostic value of other variables that are often considered when planning for a transplant, such as patient cytomegalovirus serostatus, donor–patient sex mismatch, donor–patient ABO group mismatch, or stem cell source. None of these variables had a significant impact on outcome (Table 2).

MRD Status before Transplantation Is the Chief Predictor of Leukemia Relapse

The 2-year cumulative incidence of relapse (CIR) was 41.0% (95% CI, 33.8 to 48.1). Patients who relapsed had a dismal outcome, with a postrelapse median survival of 2.2 months (95% CI, 1.6 to 2.8). Interestingly, patients receiving a transplant in first CR (CR1) or in at least CR2 had a very similar outcome, as did patients transplanted in CR or CRi (Table 1). The 64 patients in CR/CRi who were MRD-negative at the time of SCT had a significantly lower 2-year CIR and a higher 2-year OS than the 82 patients who were in remission but were MRD-positive and the 39 patients who had morphologic evidence of leukemia before transplant, namely 17.6% versus 55.6% versus 48.7% ($P < .0001$) and 69.4% versus 21.4% versus 19.9% ($P < .0001$), respectively (Table 1). Remarkably, MRD-positive patients in CR/CRi and patients with active leukemia at transplantation had nearly identical outcomes (Figure 1); for this reason we grouped them for the rest of the analysis (referred as patients with detectable leukemia).

We performed multivariate analysis for 2-year CIR, including the variables in Table 1 as described in Methods. Having detectable leukemia at the time of SCT (HR, 14.482; 95% CI, 3.413 to 61.445; $P < .0001$), receiving fewer than 3 cycles of chemotherapy before SCT (HR, 1.779; 95% CI, 1.119 to 2.830; $P = .01$), and high-risk genetics [10] were independent predictors of relapse. Interestingly, high-risk genetics only had a deleterious effect on outcomes for MRD-negative patients (HR, 9.384; 95% CI, 2.019 to 43.605; $P = .004$) but did not affect the outcome of patients with detectable leukemia (HR, 1.144; 95% CI, .694 to 1.875; $P = .61$). Remarkably, the 2-year CIR for the 38 MRD-negative patients without genetic high-risk features was 5.2% (95% CI, .9 to 10.5).

Dose Intensity of the Conditioning Regimen Does Not Affect the Risk of Relapse after Transplantation and MRD-Negative Patients May Benefit from Melphalan-Based Regimens

The proportion of patients receiving MAC was similar among MRD-negative patients (MAC, n = 15; 23.4%) and patients with detectable disease (MAC, n = 27; 22.3%; $P = .86$). However, patients with hematopoietic cell transplant-specific comorbidity index (HCI-CI) $\geq$ 3 or a Karnofsky performance status $\leq$ 80 were less likely to receive MAC than RIC (odds ratio, .648 [$P = .02$] and .261 [$P = .009$], respectively). Seventy-six patients received Flu-Mel-RIC, 67 Bu-Flu-RIC, and 42 Bu-Flu-MAC. The proportion of MRD-negative patients was similar among the 3 groups ($P = 1.0$).

Patients who received RIC or MAC had similar OS, TRM, and CIR, irrespective of their MRD status and other prognostic factors (Table 2). However, MRD-negative patients who received Flu-Mel-RIC had a superior OS than patients who received Bu-Flu-RIC transplantation (adjusted HR, 1 versus 5.284; $P = .02$) and patients who received Bu-Flu-MAC (HR, 1 versus 5.093; $P = .04$). This difference in OS is explained by a significantly lower relapse rate in MRD-negative patients receiving Flu-Mel-RIC compared with patients receiving Bu-Flu-RIC (adjusted HR, 1 versus 4.845; $P = .03$) and a significantly lower TRM in patients receiving Flu-Mel-RIC compared with patients receiving Bu-Flu-MAC (adjusted HR, 5.079; $P = .01$). The 121 patients undergoing transplantation with detectable leukemia had similar survival irrespective of the conditioning regimen (Table 3).

Table 1
Two- and 5-Year Probabilities of OS and 2-Year Cumulative Incidence of TRM and Relapse according to Patient, Leukemia, and SCT Characteristics and HCT-CI and Individual Comorbidities with $P < .15$ for at Least 1 Outcome

	No. of Patients (%)	5-Year OS (95% CI)	2-Year OS (95% CI)	2-Year TRM (95% CI)	2-Year CIR (95% CI)
Age*		P = .13	P = .15	P = .18	P = .99
65-70 yr	137 (74.1)	31.5 (23.6-40.6)	40.4 (32.4-49.0)	21.6 (15.1-29.0)	41.5 (33.1-49.7)
>70 yr	48 (25.9)	17.1 (7.1-35.8)	28.5 (17.2-43.3)	33.2 (19.9-47.2)	39.6 (25.9-53.0)
Sex		P = .90	P = .76	P = .38	P = .84
Male	120 (64.9)	28.1 (20.1- 7.8)	36.0 (27.6-5.4)	27.0 (19.2-35.4)	40.4 (31.5-49.1)
Female	65 (35.1)	27.9 (16.7-42.8)	39.8 (28.4-52.4)	20.1 (11.4-30.5)	42.1 (29.9-53.8)
Remission status†		P = .009	P = .02	P = .46	P = .76
CR1	85 (45.9)	32.3 (22.3-44.2)	39.7 (29.3-51.1)	24.0 (15.2-33.9)	41.3 (30.5-51.7)
CR1i	31(16.8)	34.1 (19.1-53.1)	42.9 (26.8-60.7)	16.1 (5.9-30.9)	38.7 (22.0-55.1)
≥CR2	23(12.4)	47.8 (29.2-67.0)	47.8 (28.5-67.8)	18.2 (5.7-36.3)	36.3 (17.4-55.7)
≥CR2i	7 (3.8)	42.9 (15.9-75.0)	42.9 (15.9-75.0)	28.6 (4.1-61.1)	28.5 (4.1-61.1)
No CR (active leukemia)	39 (21.1)	8.5 (2.6-24.5)	19.9 (10.2-35.1)	33.7 (19.5-48.5)	48.7 (32.4-63.1)
Remission status		P = .70	P = .90	P = 1.00	P = .66
CR	108 (74.0)	35.9 (26.5-46.5)	42.3 (33.0-52.2)	22.5 (14.9-31.0)	40.0 (30.5-49.3)
CRi	38 (26.0)	28.9 (15.5-47.5)	41.7 (27.2-57.8)	20.5 (9.6-34.2)	35.9 (21.4-50.6)
Remission status†		P = .94	P = .86	P = .73	P = .60
CR1/CR1i	116 (79.5)	32.8 (24.1-42.9)	40.6 (31.7-50.2)	21.8 (14.6-30.0)	40.5 (31.4-49.4)
≥CR2/CR2i	30 (20.5)	35.0 (16.4-59.6)	46.7 (30.3-63.9)	23.3 (10.3-39.4)	33.3 (17.5-50.0)
Remission status†		P = .0003	P = .001	P = .10	P = .20
CR/CRi	146 (78.9)	34.1 (25.9-43.3)	42.1 (34.0-50.6)	22.0 (15.5-29.2)	39.9 (30.9-46.8)
No CR	39 (21.1)	8.5 (2.6-24.5)	19.9 (10.2-35.1)	33.7 (19.5-48.5)	48.7 (32.4-63.1)
MRD		P < .0001	P < .0001	P = .07	P < .0001
CR/CRi MRD−	64 (34.6)	67.0 (54.1-77.7)	69.4 (57.0-79.5)	14.5 (7.1-24.4)	17.6 (9.3-28.0)
CR/CRi MRD+	82 (44.3)	8.4 (3.3-19.6)	21.4 (13.5-32.1)	32.9 (18.5-42.2)	55.6 (44.0-65.6)
No CR/CRi	39 (21.1)	8.5 (2.6-24.5)	19.9 (10.2-35.1)	33.7 (19.5-48.5)	48.7 (32.5-63.1)
Remission status/MRD		P < .0001	P < .0001	P = .03	P < .0001
MRD -negative	64 (34.6)	67.0 (54.1-77.7)	69.4 (57.0-79.5)	14.5 (7.1-24.4)	17.6 (9.3-28.0)
Detectable leukemia (MRD-positive, no CR/CRi	121 (64.4)	8.5 (4.1-16.9)	21.1 (14.5-29.7)	29.7 (21.7-38.1)	53.4 (44.0-62.0)
European LeukemiaNet 2017 genetic risk group ‡		P = .002	P = .002	P = .26	P = .03
Good + intermediate	93 (50.3)	36.9 (26.5-48.7)	47.8 (37.7-58.1)	20.8 (13.2-29.6	33.6 (24.2-43.3)
Adverse	92 (49.7)	19.1 (11.5-30.1)	26.7 (18.3-37.2)	28.2 (19.2-37.9)	48.6 (37.9-58.5)
Secondary leukemia		P = .28	P = .41	P = .12	P = .87
No	110 (59.5)	31.3 (22.0-42.4)	38.7 (29.7-48.6)	21.1 (13.8-29.4)	42.0 (32.5-51.2)
Yes	75 (40.5)	24.0 (15.1-35.9)	35.1 (25.1-46.6)	29.7 (19.7-40.2)	40.0 (28.9-50.8)
Primary refractory disease		P = .05	P = .11	P = .04	P = .86
No	120 (64.9)	33.7 (24.9-43.8)	42.2 (33.4-51.5)	19.6 (12.9-27.2)	41.0 (32.1-49.6)
Yes	65 (35.1)	18.8 (10.3-31.9)	28.6 (18.6-41.2)	33.5 (22.2-45.3)	41.3 (29.0-53.1)
Delayed hematologic recovery		P = .04	P = .06	P = .04	P = .64
No	135 (73.0)	32.2 (24.0-41.7)	41.3 (33.1-50.1)	21.0-14.4 (28.4)	42.1 (33.6-50.4)
Yes	50 (27.0)	18.2 (8.9-33.6)	27.4 (16.9-41.2)	34.1 (21.4-47.2)	38.1 (24.9-51.3)
Use of intensive chemotherapy during the last line of treatment§		P = .67	P = .31	P = .01	P = .07
No	102 (55.1)	26.3 (17.8-37.0)	39.7 (30.5-49.7)	17.1 (10.4-25.1)	47.4 (37.4-56.8)
Yes	83 (44.9)	32.5 (22.7-44.1)	34.4 (24.6-45.7)	33.7 (23.5-44.2)	33.2 (23.2-43.6)
No. of cycles of chemotherapy ¶ during the last line of therapy		P = .11	P = .25	P = .55	P = .036
1-2	75 (40.5)	19.8 (11.0-3.0)	31.9 (22.3-43.4)	21.9 (13.2-31.9)	49.6 (37.8-60.3)
>2	110 (59.5)	33.6 (24.5-44.1)	41.3 (32.2-51.1)	26.3(18.3-35.0)	35.2 (26.3-44.3)
Karnofsky performance status‖		P = .61	P = .70	P = .87	P = .65
100%	38 (21.1)	38.4 (24.0-55.2)	42.4 (27.7-58.6)	24.7 (12.2-39.5)	34.6 (20.0-49.7)
90%	93 (51.7)	26.0 (16.5-38.4)	35.3 (25.8-46.1)	23.5 (15.2-32.7)	42.9 (32.5- 52.9)
≤80%	49 (27.22)	28.8 (17.7-43.2)	40.3 (27.6-54.4)	26.8 (15.3-39.6)	38.9 (25.4-52.2)
HCT-CI		P = .36	P = .40	P = .61	P = .72
0	30 (16.2)	37.8 (19.5-60.3)	51.9 (34.4-69.0)	17.6 (5.2-35.7)	46.2 (26.6-63.6)
1-2	58 (31.4)	35.0 (23.5-48.6)	35.0 (23.5-48.6)	24.2 (14.2-35.9)	36.9 (24.5-49.3)
≥3	97 (52.4)	23.2 (15.3-33.5)	34.5 (25.5-44.8)	26.3 (18.1-35.2)	42.0 (32.2-51.4)
HCT-CI diabetes comorbidity		P = .35	P = .42	P = .06	P = .53
No	152 (82.2)	30.1 (22.6-38.8)	38.6 (31.0-46.8)	21.7 (15.5-28.7)	42.0 (34.0-49.7)
Yes	33 (17.8)	19.4 (7.9-40.3)	32.3 (18.7-49.7)	36.9 (20.9-53.0)	36.6 (20.7-52.7)
HCT-CI cardiovascular comorbidity **		P = .02	P = .02	P = .007	P = .36
No	141 (76.2)	31.5 (23.5-40.8)	40.9 (32.8-49.5)	19.8 (13.6-26.9)	43.1 (34.7-51.2)
Yes	44 (23.8)	18.7 (9.1-34.5)	26.2 (15.3-41.1)	39.3 (24.9-53.5)	34.4 (20.8-48.4)
HCT-CI pulmonary comorbidity		P = .93	P = .98	P = .09	P = .16
No	107 (57.8)	29.9 (20.9-40.8)	35.5 (26.5-45.7)	20.6 (13.3-29.0)	47.7 (37.8-56.9)
Moderate	56 (30.3)	27.5 (17.1-41.1)	38.6 (26.8-51.9)	25.4 (14.8-37.3)	35.9 (23.6-48.3)
Severe	22 (11.9)	26.0 (10.9-50.4)	40.4 (22.7-61.0)	41.5 (21.1-60.8)	22.7 (8.3-41.4)
DLCOcSB before SCT, % predicted		P = .62	P = .52	P = .06	P = .39
>80%	132(71.3)	26.3 (17.8-37.0)	37.9 (29.3-47.4)	18.5 (11.9-26.2)	47.1 (37.7-55.8)
66-80%	34 (18.4)	27.8 (15.2-45.2)	35.3 (21.5-52.1)	32.6 (17.6-48.0)	32.3 (17.6-48.0)
≤65%	19 (10.3)	28.9 (12.9-52.6)	36.1 (18.5-58.4)	37.7 (16.8-58.7)	31.5 (12.9-52.2)
FEV_1 before SCT, % predicted		P = .74	P = .96	P = .22	P = .34
>80%	145 (78.4)	31.1 (23.3-40.3)	37.5 (29.6-46.2)	21.0 (14.6-28.2)	44.3 (35.9-52.4)

(*continued*)

Table 1 (*Continued*)

	No. of Patients (%)	5-Year OS (95% CI)	2-Year OS (95% CI)	2-Year TRM (95% CI)	2-Year CIR (95% CI)
66-80%	30 (16.2)	20.3 (9.1-39.3)	36.7 (21.9-54.5)	30.0 (15.0-46.5)	36.6 (20.1-53.4)
≤65%	10 (5.4)	20.0 (4.2-58.8)	40.0 (16.8-68.7)	40.0 (12.3-67.0)	20.0 (3.1-47.5)
Creatinine clearance before SCT, mL/min		$P = .39$	$P = .38$	$P = .42$	$P = .03$
≥90	79 (42.7)	19.3 (10.8-32.0)	32.9 (22.9-44.7)	20.3 (12.0-30.2)	50.2 (38.5-60.8)
60-89	81 (43.8)	30.4 (20.1-43.1)	36.2 (26.2-47.6)	27.9 (18.5-38.1)	38.9 (28.2-49.4)
<60	25 (13.5)	40.8 (26.7-68.0)	51.9 (36.3-76.8)	28.0 (12.4-46.0)	20.0 (7.3-37.2)
MMCs during the last line of treatment		$P < .0001$	$P < .0001$	$P < .0001$	$P = .82$
No	149 (80.5)	35.0 (26.6-44.4)	44.6 (36.6-52.9)	16.8 (11.2-23.5)	41.4 (33.4-49.3)
Yes	36 (19.5)	2.8 (.5-13.9)	8.3 (2.9-21.8)	55.6 (38.0-69.9)	38.9 (23.3-54.3)
Time from diagnosis to SCT		$P = .40$	$P = .68$	$P = .04$	$P = .29$
≤12 mo	114 (61.6)	30.3 (21.5-40.8)	36.8 (28.0-46.5)	20.7 (13.5-28.9)	43.9 (34.5-52.9)
>12 mo	71 (38.4)	25.5 (15.8-38.4)	38.1 (27.5- 50.0)	31.4 (21.0-42.4)	35.8 (24.8-46.9)
Donor type		$P = .91$	$P = .82$	$P = .40$	$P = .54$
Matched sibling	66 (35.7)	28.1 (17.9-1.2)	38.6 (27.5-51.1)	19.1 (10.5-29.6)	44.3 (32.1-55.8)
10/10 unrelated donor	119 (64.3)	28.8 (19.8-39.8)	36.4 (27.7-46.1)	27.3 (19.2-36.0)	40.0 (30.7-49.2)
Graft Source		$P = .98$	$P = .97$	$P = .051$	$P = .03$
Bone marrow	70 (37.8)	27.3 (15.6-43.2)	39.4 (28.4-51.6)	32.2 (21.5-43.4)	30.6 (20.1-41.7)
Peripheral blood	115 (62.2)	28.0 (20.0-37.7)	36.4 (28.0-45.7)	19.7 (12.9-27.5)	47.4 (38.0-56.3)
CD34 graft content[††]		$P = .91$	$P = .80$	$P = .88$	$P = .96$
$<4 \times 10^6$/kg	86 (46.7)	30.9 (21.0-42.9)	37.6 (27.8-48.5)	23.8 (15.3-33.3)	39.6 (29.3-49.7)
$\geq 4 \times 10^6$/kg	98 (53.3)	26.1 (17.3-37.3)	37.5 (28.2-47.8)	25.3 (17.0-34.3)	41.6 (31.6-51.3)
Donor age[‡‡]		$P = .27$	$P = .38$	$P = .78$	$P = .11$
<40 yr	91 (50.8)	36.6 (26.5-48.0)	41.5 (31.5-52.2)	25.3 (16.7-34.7)	35.6 (25.7-45.6)
≥40 yr	88 (49.2)	20.9 (12.8-32.2)	31.0 (21.7-42.1)	25.0 (16.1-34.9)	46.8 (35.7-57.1)
Donor–recipient ABO match		$P = .50$	$P = .36$	$P = .71$	$P = .99$
No	97 (52.4)	30.5 (21.7-41.00	33.4 (24.3-43.9)	26.1 (17.6-35.4)	40.1 (30.3-49.8)
Minor	32 (17.3)	34.0 (19.3-52.6)	38.9 (23.8-56.4)	19.1 (7.7-34.3)	44.5 (26.9-60.7)
Major	56 (30.3)	21.7 (11.7-36.6)	41.2 (28.9-54.7)	25.7 (15.0-37.8)	41.6 (28.5-54.1)
Donor–recipient sex match		$P = .95$	$P = .81$	$P = .92$	$P = .51$
Male–female	45 (24.4)	28.8 (17.1-44.3)	32.4 (20.4-47.2)	24.7 (13.3-38.0)	40.5 (32.1-48.7)
Other	140 (75.6)	26.9 (19.1-36.5)	38.2 (30.2-46.9)	24.7 (17.7-32.3)	44.8 (29.9-58.5)
Donor–recipient cytomegalovirus status[§§]		$P = .91$	$P = .75$	$P = .87$	$P = .92$
Recipient–/donor–	15 (8.2)	8.6 (1.6-35.7)	25.7 (9.4-53.7)	31.1 (9.5-56.1)	42.2 (17.0-65.7)
Recipient+/donor–	84 (45.9)	31.9 (21.7-44.2)	37.1 (27.2-48.3)	21.6 (13.5-31.0)	42.6 (31.7-53.0)
Recipient–/donor+	10 (5.5)	15.0 (2.1-59.7)	60.0 (31.3-83.2)	20.0 (3.1-47.5)	30.0 (7.1-57.8)
Recipient+/donor+	74 (40.4)	29.4 (19.7-41.5)	35.3 (25.2-47.0)	27.5 (17.8-38.1)	42.0 (30.6-52.9)
Conditioning regimen		$P = .09$	$P = .17$	$P = .14$	$P = .004$
Flu-Mel-RIC	76 (41.1)	35.3 (25.0-47.2)	44.3 (33.7-55.5)	27.9 (18.3-38.3)	30.3 (20.4-40.8)
Bu-Flu-RIC	67 (36.2)	19.4 (10.9-32.1)	28.6 (18.9-40.7)	19.5 (11.0-29.7)	55.4 (42.8-66.5)
Bu-Flu-MAC	42 (22.7)	23.7 (8.8-50.0)	35.6 (20.7-54.0)	27.8 (14.0-43.6)	38.1 (22.7-53.3)

DLCOcSB indicates diffusing capacity of the lung for carbon dioxide corrected by hemoglobin concentration; FEV_1, forced expiratory volume in 1 second.

* The median age was 68.0 (range, 65.0-79.8).

† Twenty patients were in CR2, 6 in CR2i, 3 in CR3, and 1 in CR3i.

‡ Ten patients belong to the low-risk category.

§ A typical example of intensive therapy is a 3+7 induction regimen followed by consolidation with high-dose cytarabine. Repeated courses of decitabine would be a representative example of nonintense therapy [3].

¶ The median number of cycles during the last line of therapy was 3 (range, 1-14).

‖ Missing data in 5 patients.

** Only 5 patients had a left ventricular ejection fraction ≤ 50%.

†† The median CD34 dose was 4.19×10^6 cell/kg (range, 1.3-13.4). Data missing in 1 patient.

‡‡ Six patients had missing data. The median donor age was 39 years (range, 18-78). Recipients of unrelated donor had significantly younger donors than patients who received an SCT from a family member, namely 30 years (range, 18-55) vs. 64.5 year (range, 35-78; $P < .001$). Donor age had no significant impact on the 2-year probability of survival when patients where stratified according to the stem transplant source (full matched sibling or 10/10 unrelated donor). The 31 patients who received a fully matched sibling transplant from a donor younger than 65 years had equivalent 2-year OS than the 30 patients who received a transplant form an older donor: 29.79% (95% CI, 15.4-49.4) vs. 42.4% (95% CI, 25.3-61.5; $P = .54$). Similarly, there was no difference in the 2-year OS between the 57 and the 51 patients who received an SCT from a 10/10 unrelated donor younger or older than 30 years, respectively: 44.2% (95% CI, 42.6-45.8) vs. 30.3% (95% CI, 19.2-44.3; $P = .46$).

§§ Data missing in 2 patients.

Patients Conditioned with Mel-Flu-RIC Are More Likely to Have Full Donor Chimerism by Day +30 after Transplantation and This Is Associated with Better Outcome

On day +30 after transplantation 176 patients (95.1%) were alive and in CR. Of these patients 78 (46.4%) had full donor chimerism, 90 (53.6%) had mixed chimerism, and no data were available for the remaining 8 patients. Patients who received a Flu-Mel-RIC transplant were more likely to achieve a full donor chimerism by day +30 than patients receiving a Bu-FLU-RIC or a Bu-Flu-MAC transplant. Namely, 51 of 71 patients (71.8%) receiving Mel-Flu-RIC had full donor chimerism at day +30, whereas only 17 of 58 patients (29.3%) receiving a Bu-Flu-RIC transplant or 10 of 39 patients (18.1%) receiving a Bu-Flu-MAC transplant had full donor chimerism at that time point ($P < .00001$).

We performed a day +30 landmark analysis where patients who were alive and in remission were classified according to their MRD status before transplantation and their day +30 chimerism post-SCT. Sixty patients were MRD-negative before transplantation, of whom 26 (43.3%) achieved full donor chimerism on day +30 after SCT. These 26 patients had a superior 2-year OS (adjusted HR, .244; 95% CI, .073 to .822; $P = .02$) and a lower 2-year CIR (adjusted HR, .146; 95% CI, .036 to .596; $P = .007$) than the remaining 34 patients (56.7%) with mixed

Table 2
Adjusted Probabilities of 2-Year OS, 2-Year Cumulative Incidence of TRM, and 2-Year CIR according to Age, HCT-CI, Performance Status, and Transplant Characteristics

	No. of Patients (%)	OS HR (95% CI)	TRM HR (95% CI)	Relapse HR (95% CI)
Patient age, yr		*P* = .94	*P* = .68	*P* = .83
Quartile 1, 65-66.5	46 (24.9)	1	1	1
Quartile 2, 65.5-68	50 (27.0)	1.063 (.623-1.815)	.960 (.405-2.277)	1.124 (.572-2.213)
Quartile 3, 68-70	41 (22.2)	1.015 (.579-1.777)	.523 (.190-1.440)	1.451 (.763-2.763)
Quartile 4, >70	48 (25.9)	1.162 (.695-1.943)	1.227 (.554-2.719)	.958 (.489-1.786)
Karnofsky performance status*		*P* = .81	*P* = .77	*P* = .69
100%	38 (21.1)	1	1	1
90%	93 (51.7)	.973 (.580-1.6347)	.783(.358-1.711)	1.311 (.700-2.452)
≤80%	49 (27.22)	.851 (.476-1.520)	.925 (.385-2.219)	1.033 (.508-2.100)
HCT-CI		*P* = .35	*P* = .22	*P* = .77
0	30 (16.2)	1	1	1
1-2	58 (31.4)	1.600 (.838-3.056)	1.804 (.613-.316)	.904 (.431-1.894)
≥3	97 (52.4)	1.470 (.804-2.687)	1.830 (.639-5.244)	.910 (.486-1.497)
Donor		*P* = .97	*P*= 0.31	*P* = .28
Fully matched sibling	66 (35.7)	1	1	1
10/10 unrelated donor	119 (64.3)	.993 (.666-1.482)	1.426 (.721-2.819)	.764 (.470-1.242)
Donor		*P* = .02	*P* = .02	*P*= 0.41
Fully matched sibling	66 (35.7)	1	1	1
10/14, 11/14 or 12/14 unrelated donor	32 (17.3)	1.887 (1.057-3.370)	2.831 (1.220-6.568)	.817 (.352-1.899)
13/14 or 14/14 unrelated donor	87 (47.0)	.849 (.555-1.300)	1.140 (.550-2.367)	.752 (.454-1.245)
Conditioning intensity		*P* = .53	*P* = .91	*P* = .53
RIC	143 (77.3)	1	1	1
MAC	42 (22.7)	.854 (.525-1.389)	1.047 (.484-2.266)	.829 (.460-1.497)
Graft source		*P* = .58	*P* = .17	*P* = .20
Bone marrow	70 (37.8)	1	1	1
Peripheral blood	115 (62.2)	.875 (.547-1.398)	.547 (.232-1.287)	1.459 (.818-2.601)
Donor–recipient ABO match		*P* = .38	*P* = .43	*P* = .86
No	97 (52.4)	1	1	1
Minor	32 (17.3)	.776 (.456-1.318)	.662 (.268-1.637)	1.075 (.609-1.898)
Major	56 (30.3)	.675 (.333-1.454)	.834 (.433-1.605)	.976 (.561-1.699)
Donor–recipient sex match		*P* = .98	*P* = .94	*P* = .74
Other	140 (75.6)	1	1	1
Male–female	45 (24.4)	1.006 (.658-1.539)	0.976 (.508-1.875)	1.099 (.629-1.918)
Recipient cytomegalovirus status†		*P* = .26	*P* = .85	*P* = .48
Recipient–	25 (13.7)	1	1	1
Recipient+	158 (85.4)	1.398 (.783-2.495)	1.090 (.458-2.591)	1.276 (.649-2.509)

HRs were adjusted for age, degree of HLA-match, regimen conditioning intensity, HCT-CI, genetic risk group, MRD, and remission status (CR/CRi vs. no-CR).
* Missing data in 5 patients.
† Missing data in 2 patients.

chimerism. There was no statistically significant difference in TRM between the 2 groups (adjusted HR, .489; 95% CI, .097 to 2.456; *P* = .38). Similarly, of the 108 patients with detectable leukemia before transplantation, 52 (48.1%) achieved full donor chimerism at day +30 post-SCT. However, although these patients had statistically significantly lower CIR (adjusted HR, .542; 95% CI, .322 to .914; *P* = .02) compared with the 56 patients (51.9%) with mixed chimerism, there was no impact on OS (HR, .489; 95% CI, .855 to .549; *P* = .49) or TRM (adjusted HR, 1.499; 95% CI, .722 to 3.115; *P* = .28).

TRM in Geriatric AML Patients Undergoing SCT Is Not Predicted by Conventional Comorbidity Tools

The 100-day and 2-year TRM were 10.8% (95% CI, 6.9 to 15.8) and 24.5% (18.5 to 31.0), respectively. The 2-year cumulative incidence of grades II to IV and III to IV acute GVHD and chronic GVHD were 36.2% (95% CI, 29.3 to 43.1), 11.3% (95% CI, 8.3 to 16.4), and 22.2% (95% CI, 16.4 to 28.6), respectively. The median HCT-CI [29] score was 3 (range, 0 to 10). The HCT-CI was not a statistically significant predictor for outcome (Figure 2, Table 2) and failed to identify patients with a high risk for TRM using these treatment regimens (C-statistic, .53 [the C-statistic value of .5 indicates the model is no better than a random prediction, whereas a value of 1 indicates a totally accurate model]).

Patients Who Recover from an MMC Occurring during Leukemia Therapy Have a Dismal Outcome after Transplantation

Thirty-six patients (19.5%) had major medical complications (MMCs) during the line of induction or consolidation chemotherapy preceding the transplant. MMC was defined as a medical event requiring admission to the intensive care unit for ventilatory or inotropic support or a medical event that prolonged patient hospitalization for more than 2 weeks. The most common complications were pneumonia (n = 11), sepsis (n = 9), coronary events (n = 6), and congestive cardiac failure (n = 5). The median time from the onset of the event to transplant was 81 days (range, 34 to 255). All 36 patients were deemed as fully recovered before transplantation. These patients had a higher day +100 mortality (30.6% versus 6.0%, $P < .0001$), 2-year TRM (55.6% versus 16.8%, $P < .0001$), and lower 2-year OS (8.3% versus 44.6%, $P < .0001$) than the remaining 149 patients. Interestingly, because these 36 patients had recovered from their complication before transplantation, they had a similar HCT-CI, Karnofsky score, and organ function as the rest of the patients, making their identification only possible by taking a careful clinical history (Table 4).

We performed multivariate analysis for 2-year TRM. History of delayed hematologic recovery during induction or consolidation chemotherapy before transplantation (HR, 2.012; 95% CI, 1.076 to 3.765; *P* = .03); donor–recipient HLA matching

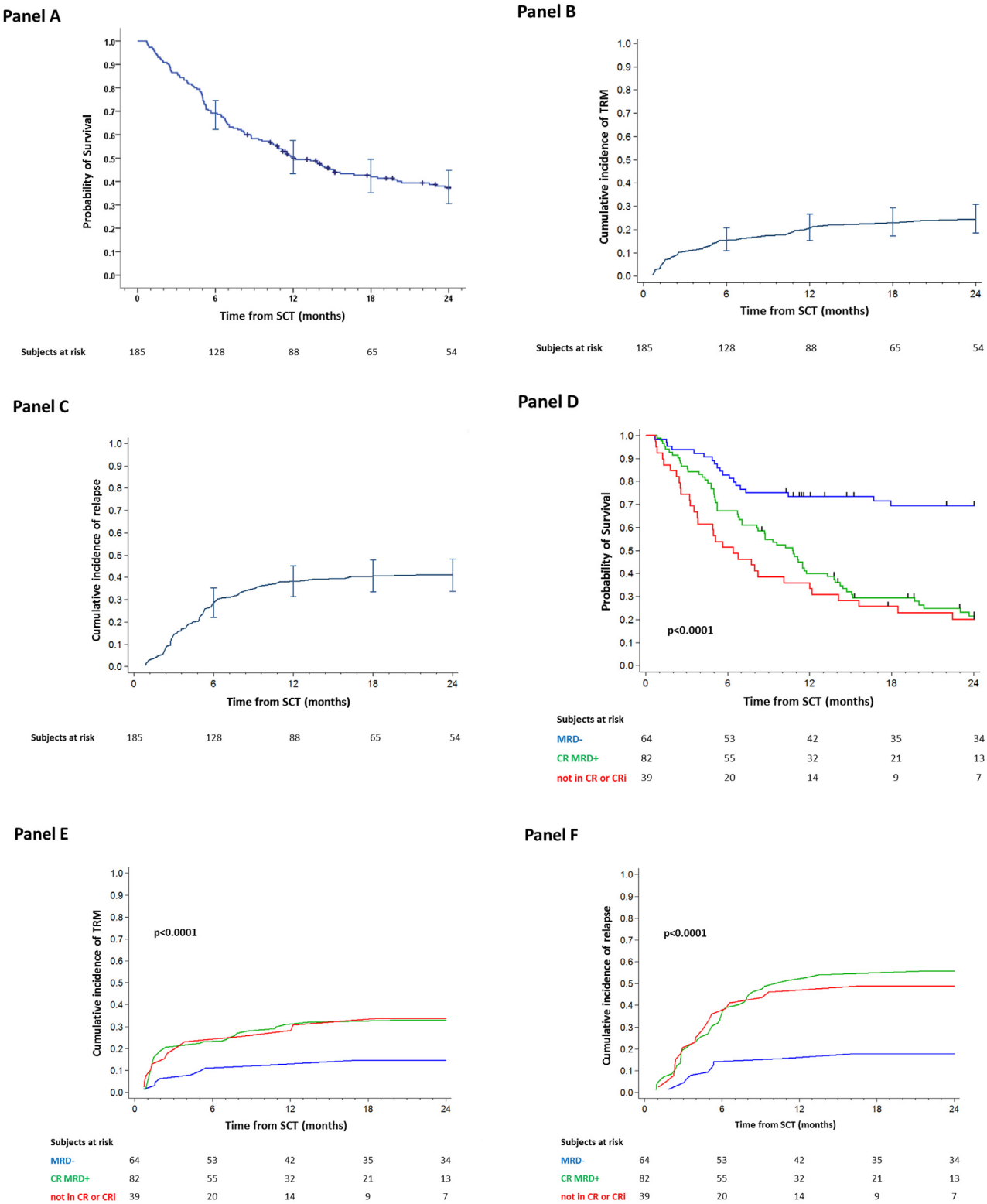


Figure 1. Two-year probability of OS and 2-year TRM and CIR in the whole cohort and according to the remission status of the patient before transplantation. (A) The 2-year probability of survival. (B and C) The 2-year TRM and 2-year CIR, respectively. The 64 MRD-negative patients had superior probability of survival (D) and a lower cumulative incidence of TRM (E) and relapse (F) than the 82 patients in remission but with evidence of MRD or the 39 patients who were not in morphologic remission (active leukemia) at the time of transplantation. MRD-positive patients and patients with active leukemia had very similar outcomes, namely 2-year CIR (adjusted HR, 1 versus 0.897; 95% CI, 424 to 1.899; $P = .77$), TRM (adjusted HR, 1 versus 1.115; 95% CI, .506 to 2.459; $P = .78$), and OS (adjusted HR, 1 versus 1.033; 95% CI, .794 to 1.987; $P = .76$). HRs were adjusted for age, degree of HLA match, regimen conditioning intensity, HCT-CI, and leukemia genetic risk group. Vertical ticks indicate censored survival times, whereas vertical bars indicate the 95% CIs.

Table 3
Two-Year Probabilities of OS, TRM, and CIR and Adjusted Probabilities of OS, TRM, and Relapse according to MRD Status and Conditioning Regimen

		2-Year OS		2-Year TRM		2-Year CIR	
	No. of Patients (%)	Probability (%)	Adjusted HR (95% CI)	Probability (%)	Adjusted HR (95% CI)	Probability (%)	Adjusted HR (95% CI)
MRD-negative		$P = .02$	$P = .01$	$P = .26$	$P = .09$	$P = .12$	$P = .10$
Flu-Mel-RIC	26 (40.6)	88.5	1	3.8	1	7.7	1
Bu-Flu-RIC	23 (35.9)	50.7	5.284 (1.313-21.257)*	22.1	2.164 (.678-9.304)	30.7	4.845 (1.192-19.688)‡
Bu-Flu-MAC	15 (23.4)	66.0	5.093 (1.171-10.810)†	20.7	5.079 (1.77-11.643)§	13.3	1.277 (.161-10.089)
Detectable leukemia		$P = .35$	$P = .74$	$P = .06$	$P = .34$	$P = .01$	$P = .06$
Flu-Mel-RIC	50 (41.3)	21.4	1	30.4	1	42.0	1
Bu-Flu-RIC	44 (36.4)	17.3	.980 (.621-1.546)	18.1	.463 (.213-1.006)	68.6	2.362 (1.36-4.087)
Bu-Flu-MAC	27 (22.3)	23.2	1.309 (.747-5.431)	29.7	1.215 (.513-4.439)	50.3	1.261 (.634-2.505)

HRs for each outcome were adjusted by the variables identified as independent predictors for the specific outcome in the corresponding multivariate analysis (see text).

* The *P* value of the comparison Flu-Mel-RIC vs. Bu-Flu-RIC was .02.

† The *P* value of the comparison Flu-Mel-RIC vs. Bu-Flu-MAC was .04.

‡ The *P* value of the comparison Flu-Mel-RIC vs. Bu-Flu-RIC was .03.

§ The *P* value of the comparison Flu-Mel-RIC vs. Bu-Flu-MAC was .01.

< 13/14 (HR, 2.686; 95% CI, 1.326 to 5.441; $P = .006$); having detectable leukemia at the time of transplantation (HR, 3.281; 95% CI, 1.165 to 9.240; $P = .02$); history of cardiovascular disease, defined per the HCT-CI (HR, 2.022; 95% CI, 1.065 to 3.84; $P = .03$); and MMC were the only independent predictors for TRM. The effect of MMC was significantly more pronounced in MRD-negative patients (HR, 19.404; 95% CI, 5.972 to 63.044; $P < .0001$) than in patients with detectable leukemia (HR, 2.671; 95% CI, 1.390 to 6.334; $P = .005$).

MRD Status in Combination with Other Risk Factors Identify Those Patients Destined to Fare Poorly

We performed multivariate analysis for 2-year OS including the variables shown in Table 1, and found history of lack of hematologic recovery during induction or consolidation chemotherapy before transplantation (HR, 1.543; 95% CI, 1.027 to 2.318; $P = .04$), high-risk genetics (HR, 1.752; 95% CI, 1.172 to 2.619; $P = .006$), donor–recipient HLA matching < 13/14 (HR, 2.228; 95% CI, 1.374 to 3.614; $P = .001$), and history of cardiovascular disease (HR, 1.700; 95% CI, 1.102 to 2.623; $P = .02$) were independent predictors for OS. Conditioning regimen, detectable leukemia at the time of SCT, and MMC were also independent predictors for OS. MRD-negative patients fared better, but the beneficial effect of MRD-negativity was greater in patients conditioned with Mel-Flu-RIC (HR, .082; 95% CI, .025 to .271; $P < .0001$) than in patients who received busulfan-based regimens (HR, .403; 95% CI, .203 to .799; $P = .009$). Similarly, the deleterious effect of MMC was more pronounced in MRD-negative patients (HR, 8.355; 95% CI, 2.990 to 23.347; $P < .0001$) than in patients with detectable leukemia (HR, 1.708; 95% CI, 1.047 to 2.788; $P = .03$).

Table 4
Comparison of HCT-CI, Karnofsky Score, Left Ventricular Ejection Fraction, Creatinine Clearance, and Pulmonary Function Test between the 36 Patients Who Had MMCs (see text) and the Remaining 149 Patients

	Patients with Complications	Remaining Patients	*P*
HCT-CI	4 (0-10)	3 (0-10)	.21
Karnofsky score, %	90 (70-100)	90 (70-100)	.19
LVEF, %	58 (33-68)	58 (43-82)	.29
Creatinine clearance, mL/min	73.5 (34-175)	87.1 (30-179)	.10
FEV_1, % predicted	85 (62-113)	96 (45-112)	.002
DLCOcSB, % predicted	71.0 (53-127)	89.0 (50-139)	.10

Values are median (range).

We sought to identify those patients who may clearly benefit from a SCT and those in whom a transplant may be counterproductive. To that end we classified patients according to MRD status before transplantation and the presence or absence of the other prognostic factors identified in the multivariate analysis in the 3 groups (Figure 3). The *high-risk group* (n = 58, 31.4%) included patients who had detectable leukemia and more than 1 additional adverse prognostic factors (or an MMC). These patients had an appalling outcome, with a 2-year OS of only 7.7% (95% CI, 3.1 to 17.8). The *low-risk group* (n = 57, 30.8%) included MRD-negative patients with ≤3 other prognostic factors (and no MMC). This group had an excellent outcome, with a 2-year OS of 76.2% (95% CI, 63.3 to 85.6). Finally, the *intermediate-risk group* (n = 70, 37.8%) consisted of the remaining patients, namely MRD-negative patients with multiple adverse factors or patients with detectable leukemia (or MMC) with ≤1 adverse factors. The 2-year OS for this group was 32.2% (95% CI, 22.1 to 44.3; $P < .00001$).

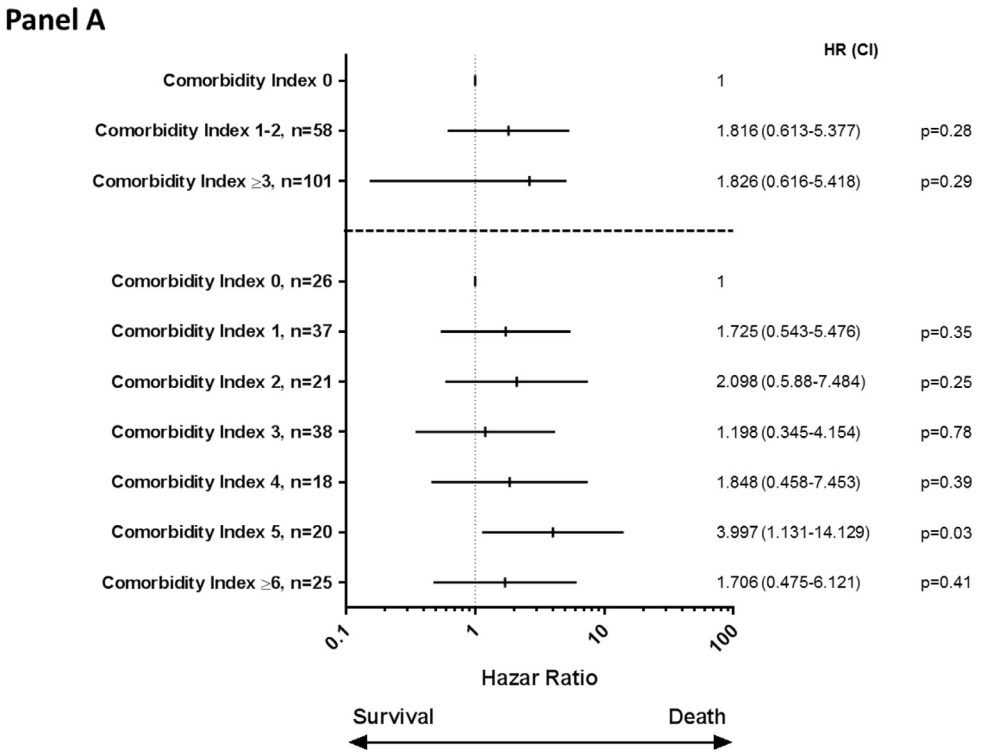
DISCUSSION

We report data on 185 subjects with AML > 65 years from our center. Transplants were reasonably well tolerated, with a median hospital stay of 27 days (range, 19 to 68) and a 100-day TRM of 11% (95% CI, 7 to 16). Two-year CIR was 41% (95% CI, 34 to 48) and 2-year survival, 37% (95% CI, 30 to 45).

The HCT-CI was a poor predictor of TRM in our study (Figure 2). There are several possible explanations. For example, the HCT-CI is based on the Charlson comorbidity score and predicts outcomes for a general population [30] and still includes some comorbidities irrelevant today such as peptic ulcer. Also, laboratory and diagnostic tests may require age-adapted cutoffs. For example, a moderate decline in pulmonary function should be age adjusted [31]. This may explain why the comorbidity pulmonary-moderate did not predict global TRM.

Older persons who receive a transplant are highly selected based on diverse objective, subjective, and fiscal criteria. These selection biases may explain why we found no correlation between increasing age or certain comorbidities and TRM. This underscores the need to develop a comorbidity score specific for elderly persons that should include frailty and geriatric assessments [32,33].

Persons with an MMC, defined as a medical event requiring admission to the intensive care unit for ventilatory or inotropic support or a medical event that prolonged the patient hospitalization for more than 2 weeks (see above), during prior chemotherapy had very high TRM and poor survival despite



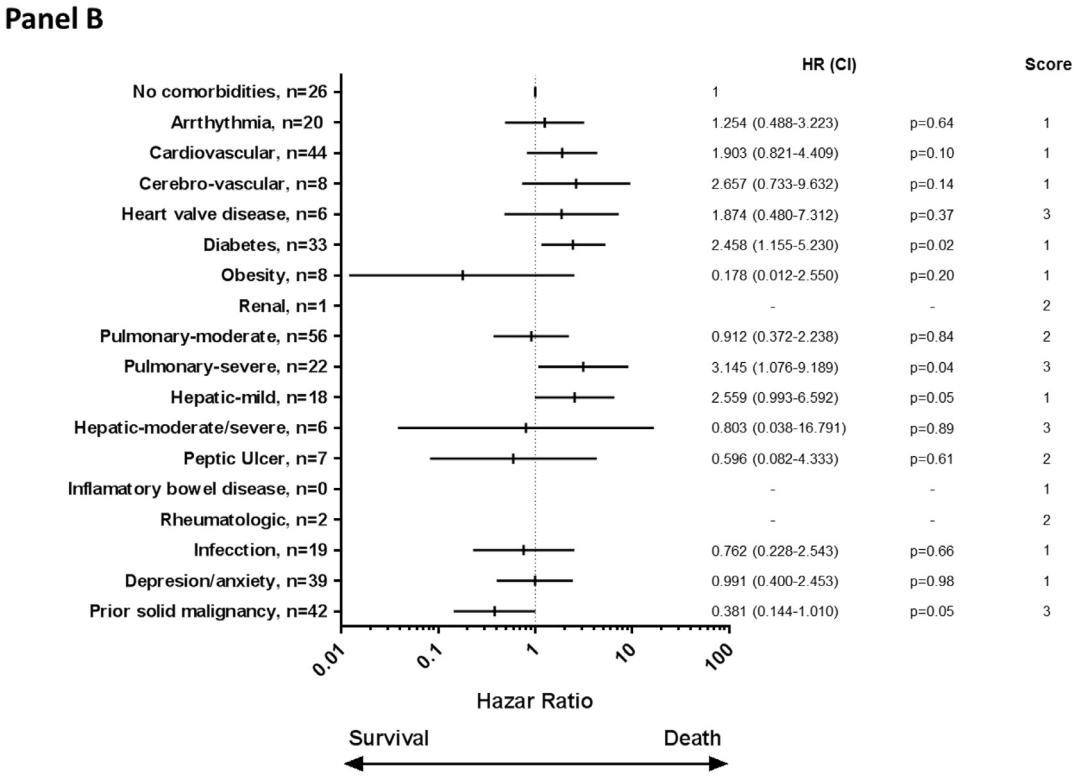


Figure 2. Adjusted HR for 2-year TRM according to HCT-CI. Forest plots show the adjusted HR for 2-year TRM according to the calculated HCT-CI (A) and the individual comorbidities that constitute the score (B). The numerical value of the score is calculated by adding the points assigned to each comorbidity. HRs were adjusted by age, conditioning regimen, genetic risk, MRD and remission status, and the other comorbidities. Vertical bars represents the HRs, whereas horizontal lines represent the 95% CIs. (A) The HCT-CI categorized into 3 groups (scores 0, 1 to 2, and ≥3) or 7 groups (scores 0, 1, 2, 3, 4, 5, and ≥6). The HCT-CI was not a statistically significant predictor for TRM, although there was a trend toward higher TRM for patients with scores of 1 to 2 and ≥3. This can be explained by the fact that only 7 comorbidities (arrhythmia, cardiovascular, cerebro-vascular, heart valve disease, diabetes, pulmonary, and moderate hepatic) were associated with an increased TRM (and only diabetes and pulmonary were statistically significant predictors), whereas the other comorbidities either did not have an influence on outcome or had a protective effect. Moreover, when we combined the comorbidities to calculate the score, we did not find an additive effect (ie, the TRM for patients with a score of 1 and for patients with a score ≥6 is practically identical [A]).

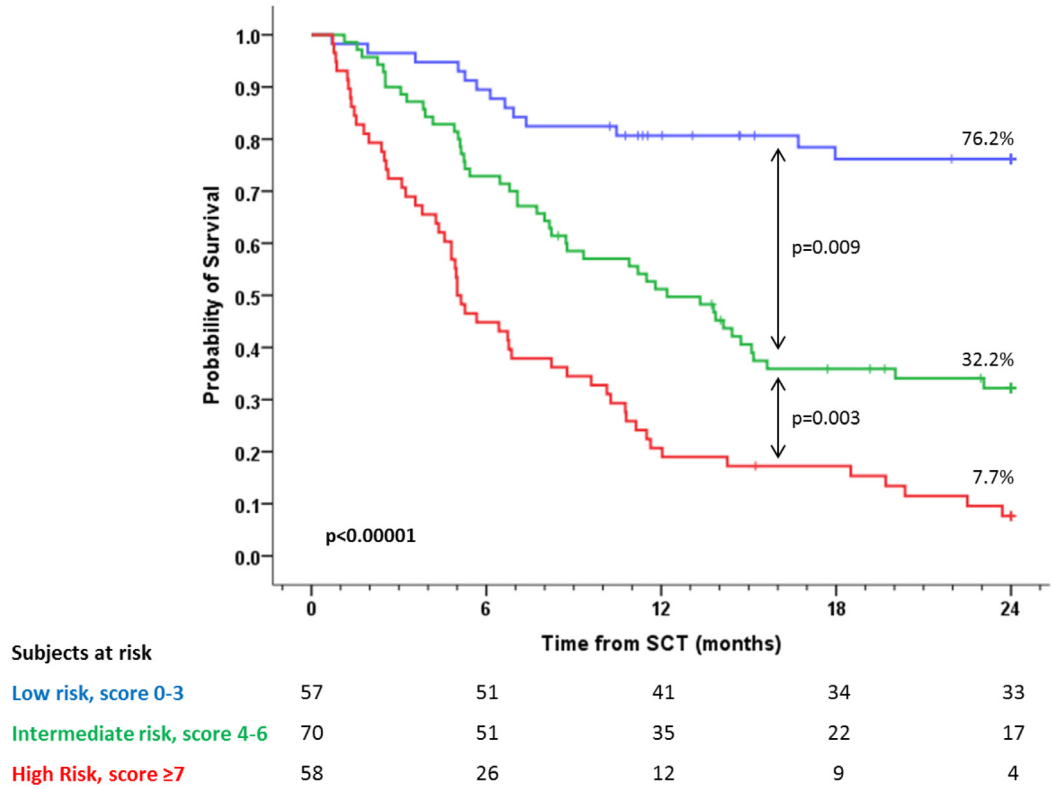


Figure 3. Survival according to prognostic groups. The 6 independent predictors identified in the multivariate analysis for 2-year OS (see text) were used to define 3 prognostic groups, low risk (n = 57, 30.8%), intermediate risk (n = 70, 37.8%), and high risk (n = 58, 31.4%). At 24 months the probabilities for survival, according to risk group, were 76.2% (95% CI, 63.3 to 85.6), 32.2% (95% CI, 22.1 to 44.3), and 7.7% (95% CI, 3.1 to 17.8; $P < .0001$). The HRs for survival for the low-, intermediate-, and high-risk groups were .262 (95% CI, .142 to .0486; $P < .0001$), 1, and 2.205 (95% CI, 1.481 to 3.283; $P < .0001$) respectively. Remarkably, the 23 MRD-negative patients from group A who had none of the above identified adverse prognostic factors had an excellent outcome (2-year OS, 96.7%; 95% CI, 78.7 to 99.3).

recovering from the complication. These subjects had similar organ function and HCT-CI scores as those without a preceding MMC, making identification possible only from the medical record. The most frequent causes of TRM in our series were recurrence of a cardiac event and multiorgan failure (data not shown).

In our study the 2-year CIR was 41%. Leukemia relapse was the most common cause of death after transplantation. In recent years the MRD status before transplantation, measured by multiparameter flow cytometry, has been identified as an emerging important predictor for outcome after SCT in AML patients [27,33–39]. In fact, MRD-positive patients in CR undergoing a MAC transplant have similar outcome as patients with active disease before transplantation [37]. We have confirmed this finding in our cohort of patients receiving either a RIC or a MAC transplant. In this cohort the failure to achieve MRD-negative remission before transplantation was the strongest independent predictor for relapse and OS and was also an independent predictor for higher TRM. This was not overcome by the intensity of the conditioning regimen. Other independent prognostic factors for OS were poor hematologic recovery during induction or consolidation therapy, high-risk genetics, degree of donor–recipient HLA matching, history of cardiovascular disease, and MMC.

We previously reported favorable results of Flu-Mel-RIC transplants in persons > 50 years with high-risk AML [40]. In the present study subjects who were MRD-negative and received this regimen had significantly better survival than similar subjects receiving a busulfan-based regimen and were more likely to achieve complete donor chimerism, also associated with better survival. However, these data need to be confirmed in a randomized trial.

Subjects receiving a transplant from an unrelated donor with >1 mismatch at HLA-DP or HLA-DRβ3/4/5 loci had worse survival compared with 13/14 or 14/14 HLA-matched donors. Adverse outcomes of nonpermissive HLA-DP mismatches and mismatches at the HLA-DRβ3/4/5 loci are described [24,41–43]. We believe that inclusion of these loci in the routine HLA matching for older patients with AML is critical because of the high mortality associated to the development of grades III to IV acute GVHD (median survival, 3.8 months).

We defined 3 cohorts based on prognostic variables for survival identified in multivariate analyses. Low-risk subjects were about 30% of the cohort, with 2-year survival of 76% (95% CI, 63.3 to 85.6). Intermediate-risk subjects, about 40%, had 2-year survival of 32% (95% CI, 22.1 to 44), whereas poor-risk subjects, about 30%, had 2-year survival of 8% (95% CI, 3 to 18).

There are a number of important limitations to our study. First, the subjects who underwent SCT were highly selected, and we do not know the true denominator from which they arose, either on the basis of referral to our center or referral for transplant within our center. Second, given the heterogenicity of subjects and of AML our sample size is relatively small, although this is the largest study to date to study risk factors for outcomes in elderly patients with AML. Third, there were no control subjects against which to compare transplant outcomes, and we lacked a validation cohort. However, our results compare very favorably with the reported outcome for elderly patients with high-risk AML (2-year survivals, 3% to 15%) [3,11–17]. We conclude that it is possible to identify persons

aged 65 years or older with high-risk AML and an HLA-identical sibling or HLA-matched unrelated donor who are likely to benefit from a transplant.

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