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Age is no Barrier for Adults undergoing HCT for AML in CR1: Contemporary CIBMTR Analysis

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Abstract

Acute Myeloid Leukemia (AML) has a median age at diagnosis of 67 years. The most common curative therapy remains an allogeneic hematopoietic stem cell transplantation (HCT), yet it is complicated by treatment-related mortality (TRM) and ongoing morbidity including graft versus host disease (GVHD) that may impact survival, particularly in older patients. We examined the outcomes and predictors of success in 1,321 patients aged 60 years and older receiving a HCT for AML in first complete remission (CR1) from 2007–2017 and reported to the CIBMTR. Outcomes were compared in three age cohorts (60–64; 65–69; 70+). With median follow-up of nearly 3 years, patients aged 60–64 had modestly, though significantly better OS, DFS and lower TRM than those either 65–69 or 70+; cohorts with similar outcomes. Three-year OS for the 3 cohorts was 49.4%, 42.3%, and 44.7% respectively (p=0.026). TRM was higher with increasing age, cord blood as graft source and HCT-CI score of ≥ 3. Conditioning intensity was not a significant predictor of OS in the 60–69 cohort with 3-year OS of 46% for RIC and 49% for MAC (p=0.38); MAC was rarely used over age 70. There was no difference in the relapse rate, incidence of Grade III/IV acute GVHD, or moderate-severe chronic GVHD across the age cohorts. After adjusting for other predictors, age had a small effect on OS and TRM. High-risk features including poor cytogenetics and measurable residual disease (MRD) prior to HCT were each significantly associated with relapse and accounted for most of the adverse impact on OS and DFS. Age did

not influence the incidence of either acute or chronic GVHD; while graft type and associated GVHD prophylaxis were most important. These data suggest that age alone is not a barrier to successful HCT for AML in CR1 and should not exclude patients from HCT. Efforts should focus on minimizing residual disease and better donor selection.

Introduction

Acute myeloid leukemia (AML) in the elderly carries a poor prognosis with median overall survival measured in months, even in those achieving remission [1]. Treatment of elderly patients with AML is often complicated by their increased burden of comorbid conditions making induction chemotherapy challenging. AML in the elderly is also characterized by higher risk cytogenetic and molecular abnormalities increasing the likelihood of chemoresistance and early relapse [2]. Currently, the only treatment modality that carries the potential for long-term survival remains hematopoietic stem cell transplantation (HCT), but patients are seldom offered transplant, either for lack of ability to achieve a complete remission (CR) or because they are deemed unsuitable for HCT, often without formal guidelines for this determination [3–5]. Elderly patients undergoing myeloablative conditioning (MAC) HCT may have unacceptable treatment-related mortality (TRM). [6] The advent of reduced intensity conditioning (RIC) has increased access to HCT[7], but evidence-based patient selection remains a challenge and a barrier to broader HCT access. The assignment to RIC, MAC, or no transplant is not uniform across transplant centers. Furthermore, relapse remains frequent following RIC HCT and overall mortality remains high. Therefore, observational studies are needed to probe how age, comorbidity, and/or disease factors may inform the optimal approach to transplantation in the older patient population.

Methods

We analyzed prospectively collected data on patients ≥ 60 years old with a diagnosis of AML in first complete remission (CR1) who underwent HCT and were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). The CIBMTR is a working group of more than 500 transplantation centers worldwide that contribute detailed data on HCT to a statistical center at the Medical College of Wisconsin (MCW). Participating centers are required to report all transplantations consecutively and compliance is monitored by on-site audits. Definitions used for case report forms are displayed on the CIBMTR website. Eligibility for HCT is determined by the treating center. MRD is reported by each center when available. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. The MCW and National Marrow Donor Program, Institutional Review Boards approved this study.

Three age groups were considered [60–64] vs [65–69] vs [70+] comparing patient, disease, and HCT treatment characteristics. Consensus criteria were used to define conditioning

intensity [8]. The primary endpoint is overall survival (OS) with death from any cause considered an event. Surviving patients were censored at the time of last follow up. Secondary endpoints included cumulative incidence of acute graft versus host disease (GVHD), chronic GVHD, treatment related mortality (TRM), relapse, and disease-free survival (DFS). TRM was defined as death without preceding disease relapse or death within 28 days regardless of cause. Relapse of AML was defined as clinically detectable disease after HCT with TRM considered a competing event. DFS was defined as survival without relapse or progression.

The incidence of GVHD, relapse, and TRM were calculated using the cumulative incidence estimator to accommodate competing risks. Probabilities of OS and DFS were calculated using the Kaplan-Meier method for univariable analysis. Multivariable regression analysis was performed using regression for acute GVHD, chronic GVHD, relapse, and TRM, and the Cox proportional hazards model for DFS and OS. The assumption of proportional hazards for each factor was tested and forward stepwise selection was used to select significant risk factors. Factors that were significant at a 5% level were retained in the final model. The interaction between the main effect of age and the other significant variables were examined. The variables that were considered in the multivariable models included recipient age, Karnofsky performance status (KPS), comorbidity index (HCT- CI), disease status at transplant, conditioning regimen intensity, GVHD prophylaxis, donor type, graft source, and year of transplant. Adjusted probabilities were calculated based on the final regression models for OS, DFS, relapse, and TRM.

Results

A total of 1,321 patients undergoing HCT for AML in CR1 from 2007–2017 were included. The three age cohorts were comparable in terms of clinical characteristics and comorbidities prior to HCT. Patients aged 70+ had more males, more secondary AML, and a higher incidence of MRD pre-HCT. Fewer in the oldest groups had sibling donors and more were performed in recent years. About half had an HCT-CI of 3 or greater. Data for modified ELN risk stratification was only available for about 35% of patients who received HCT in the later years (Table 1).

On univariate analysis, age, poor-risk cytogenetics, presence of MRD, donor type, and year of transplant were found to be associated with OS, while these same variables and graft, but not donor type were associated with DFS. After adjusting for these variables in a multivariate model, age remained a significant predictor of outcomes (Table 2). The youngest cohort age [60–64] had slightly better OS and DFS than the 2 other cohorts with a median follow-up of nearly 3 years (Figure 1). The overall survival of each age cohort is presented in table 3. Hazard ratio (HR) for mortality (worse OS) was 1.27 (p=0.02) for the middle cohort age [65–69] and HR 1.20 (p=0.10) for age 70+; each compared to age [60–64]. Patients age [65–69] and [70+] had similar outcomes with no difference in OS. On adjusted multivariate analysis, three-year OS for the 3 cohorts was 49.4%, 42.3%, and 44.7% respectively (p=0.026; figure 1).

Conditioning intensity was not a significant predictor of outcomes with HR for OS of RIC vs. MAC of 1.13 (CI: 0.93–1.38; p=0.21) for the combined [60–69] cohort with too few age [70+] receiving MAC. Three-year OS was 46% for RIC and 49% for MAC (p=0.38). HCT-CI did not impact OS while poor risk cytogenetics, detectable MRD prior to HCT, cord blood as graft source, and transplant prior to 2016 were each significantly associated with poor OS (Table 2). The use of ATG did not impact DFS or OS (data not shown).

TRM was higher with increasing age (Figure 2), cord blood as graft source and HCT-CI score of ≥ 3. Across the age cohorts there was no difference in the relapse rate, incidence of Grade III/IV acute GVHD, or of moderate-severe chronic GVHD (Figures 2, 3).

Discussion:

Increasing age is associated with a small decrement in OS after transplant that is substantially smaller than that due to other disease-related risk factors. In this large series of HCT for AML in CR1, we quantified the impact of increasing age on outcomes and showed that all age groups achieved 3-year OS of 40–50%; thus, HCT should be considered a standard of care option for patients of all ages with AML achieving CR1 with no upper age limit.

Elderly patients often have comorbid conditions that can complicate their therapy and increase TRM. Nearly 50% of our patients had HCT-CI ≥ 3 which was associated with increasing TRM, but not worse OS. HCT-CI has been shown to be correlated with survival outcomes in other cohorts [9]. This discrepancy is likely reflective of the fact that HCT-CI loses its discriminating power when comorbidities are common, as many older patients with HCT-CI > 3. It also likely reflects better management of comorbidities and improved recent supportive care, while likely influencing patient selection. Elderly AML patients often have higher risk disease with a cytogenetic and molecular profile that confers adverse risk and chemoresistance [2]. Similar to other HCT studies of elderly AML patients[7,10] we observed a high proportion of patients with poor cytogenetic risk profiles (32%) and detectable MRD at pre-HCT (32%). Presence of MRD was associated with more relapse and consequent worse OS, DFS, particularly using RIC conditioning[11]. MAC conditioning has been hypothesized to abrogate the adverse prognostic significance of MRD, though has not been well studied in this older population. Notably, increasing age was not associated with more frequent acute or chronic GVHD, which was dependent on the type of graft and the GVHD prophylaxis regimen. Patients who received peripheral blood stem cells and a tacrolimus-based prophylaxis regimens had an increased incidence of chronic GVHD, congruent with other reports [12,13].

After adjusting for cytogenetic risk, presence of MRD, donor type and year of transplantation, age remained a significant predictor of OS, albeit with a limited impact. Elderly patients with AML are often presumed to have inferior outcomes with treatment and are therefore often undertreated. In SEER database analyses, the reported 5-year OS for patients with AML > 65 years old is < 5% [1,14]. While this estimate of all patients with AML who are > 65 years, these poor outcomes reflect inability to achieve CR and frequent underutilization of HCT in this age cohort. In a National Cancer Database that looked at

17,000 patients, only 5.5% underwent HCT[15], and 0.8% in a SEER report [1]. These rates, though increasing recently[16], remain low despite a novel report showing improved outcomes of patients consolidated with HCT compared to chemotherapy consolidation on clinical trials[17]. The current cohort of elderly patients has a high prevalence of intermediate and poor risk cytogenetics, secondary AML, significant proportion with MRD, and high HCT-CI, all reflecting patients who are generally considered "high risk". These patients had an OS > 40% across all age cohorts despite the observed small decrement in survival for those older than 65.

Conditioning intensity did not significantly influence any of the outcomes, including OS, although few in the oldest group received MAC and the outcomes were adjusted for age and HCT-CI. This differs from a randomized trial comparing to MAC vs RIC[18]. We hypothesize that this reflects important, but perhaps clinically appropriate selection bias where patients deemed unfit for MAC are excluded or assigned a conditioning intensity suitable for their fitness. There is also a spectrum of intensities more refined than the dichotomous MAC vs RIC. Yet chronological age is the main guide to conditioning intensity and treatment options. The arbitrary and varying definitions of "elderly" range from 55 to 70 years [19,20]. MAC regimens in elderly patients have led to high TRM with early reports up to 50% [21,22]. In a randomized trial of the preferred conditioning intensity for patients with AML or MDS, patients who received MAC had higher TRM [18]. Some transplant programs have strict age limits for MAC vs. RIC while in recent years, chronological age has been supplemented with renewed focus on biological age as measured by frailty, sarcopenia, and other indices. Measures of frailty may correlate with survival better than other indices in older patients, and are less subjective than the commonly used KPS score [23]. Patients undergoing HCT in more recent years also had improved OS [24,25] and reflects numerous advances and improved supportive care, deeper understanding of mechanisms of failure of HCT and relapse mitigation strategies such as post-HCT maintenance therapy.

In this report, each age group still had 3-year OS > 40% and differences in outcome were better explained by covariates other than age. Because HCT remains the only curative therapy for higher risk AML, \all patients with AML should be referred early to a transplant center for evaluation, donor identification, optimization of their disease and organ function, and for psychosocial support planning to maximize the rates of success. More effort should be directed towards investigating barriers to transplant and early referrals [4]. Women were also underrepresented in this cohort and reasons should be elucidated. Some HCT practices in this patient population cannot be adequately answered by registry data including how to best assess frailty, how to best assess MRD and how to best select a donor for an older adult.

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Data Sharing

CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

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Conflicts of interests:

Dr. Weisdorf reports grants from FATE Therapeutics, grants from Incyte, outside the submitted work. Dr. Hourigan reports other from Sellas, outside the submitted work. Dr. Maakaron reports other from CRISPR, other from FortySeven Inc., other from TALARIS, outside the submitted work. Dr. de Lima reports grants from Pfizer grants from Celgene, personal fees from Kadmon personal fees from Pfizer, personal fees from Incyte, personal fees from BMS, outside the submitted work. Dr. Bhatt reports personal fees from Agios, grants and personal fees from Incyte, personal fees from Takeda, personal fees from Partner Therapeutics, personal fees from Omeros, grants and personal fees from Abbvie, grants from Jazz, grants from National Marrow Donor Program, other from Oncoceutics, personal fees from Partnership for health analytic research, LLC, grants and other from Pfizer, personal fees from CSL Behring, grants from Tolero Pharmaceuticals, personal fees from Rigel Pharmaceuticals, other from Novartis, personal fees from Genentech, outside the submitted work. Dr. Saad reports personal fees from Magenta Therapeutics, personal fees from Incyte Pharmaceuticals, personal fees from CareDx, outside the submitted work. Dr. Kebriaei reports grants from Amgen, grants from Ziopharm, other from Kite, other from Novartis, other from Jazz, other from Pfizer, outside the submitted work. Dr. Ustun reports not relevant, but honoria from Novartis and Blueprint for attending advisory board meeting. Dr. He reports personal fees from Magenta Therapeutics, outside the submitted work. Dr. Abhyankar reports other from Incyte Corporation, other from Therkos, outside the submitted work. Dr. Majhail reports personal fees from Incyte, personal fees from Anthem, Inc., personal fees from Nkarta, personal fees from Mallinckrodt, outside the submitted work.

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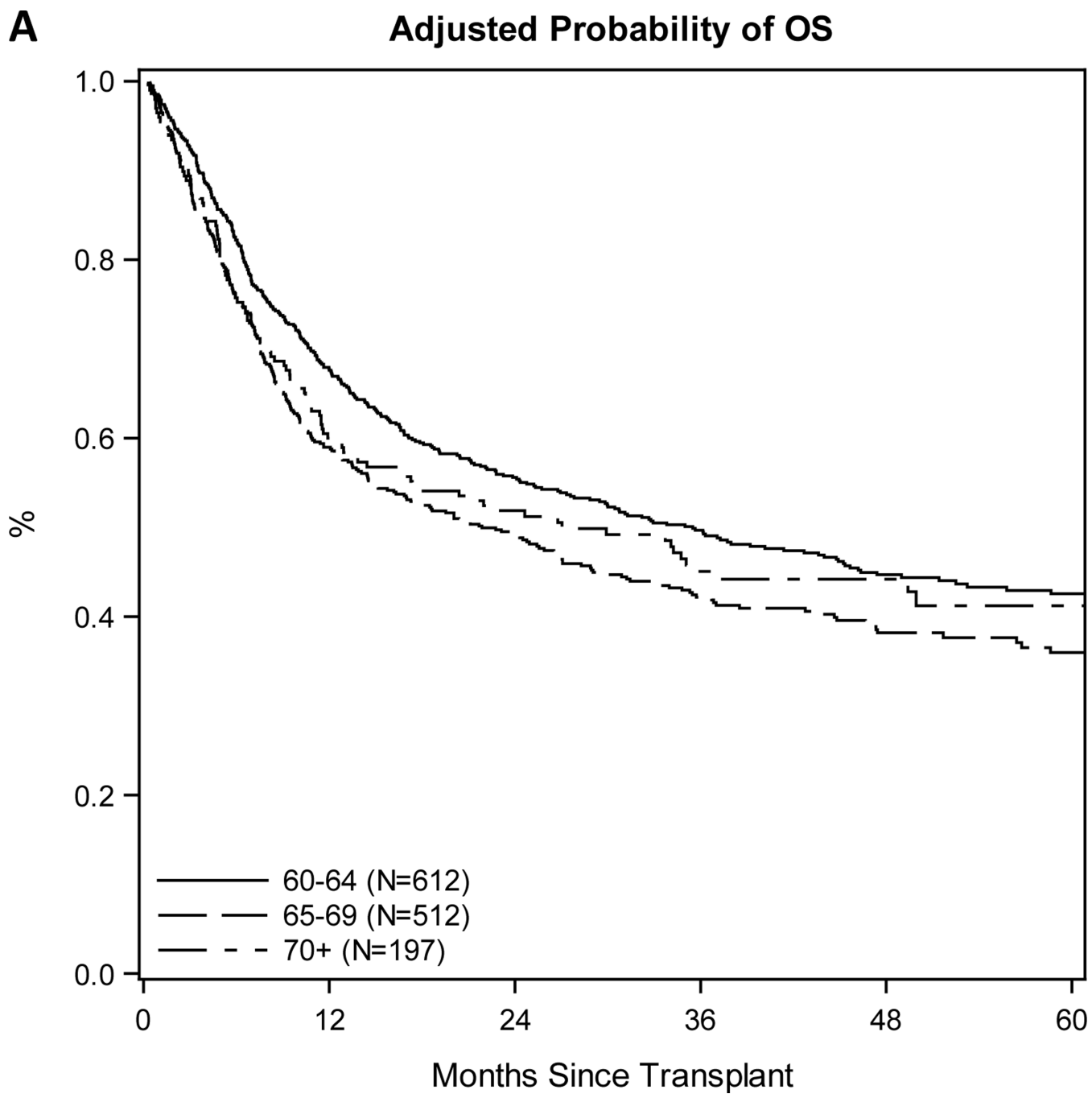


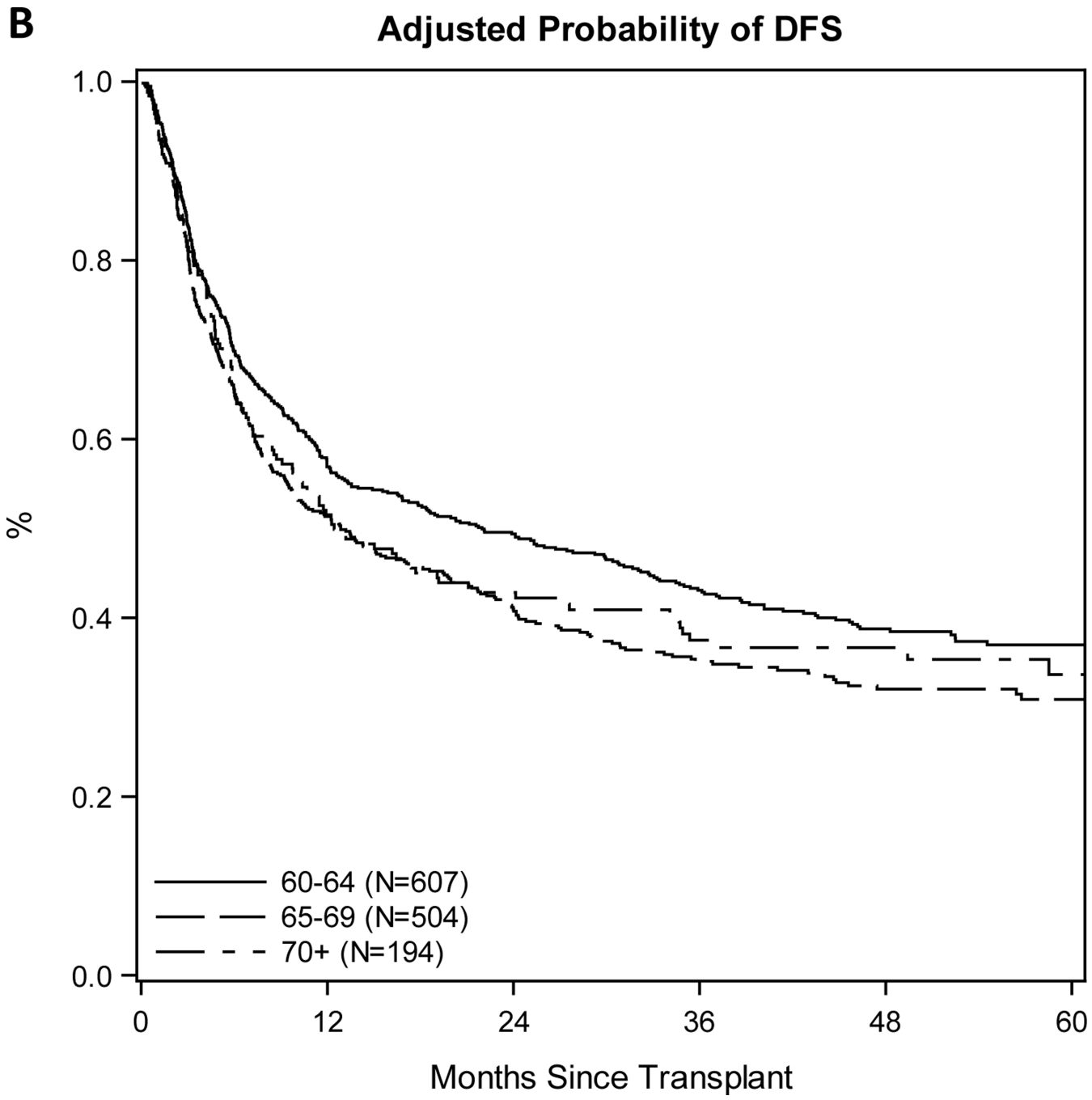
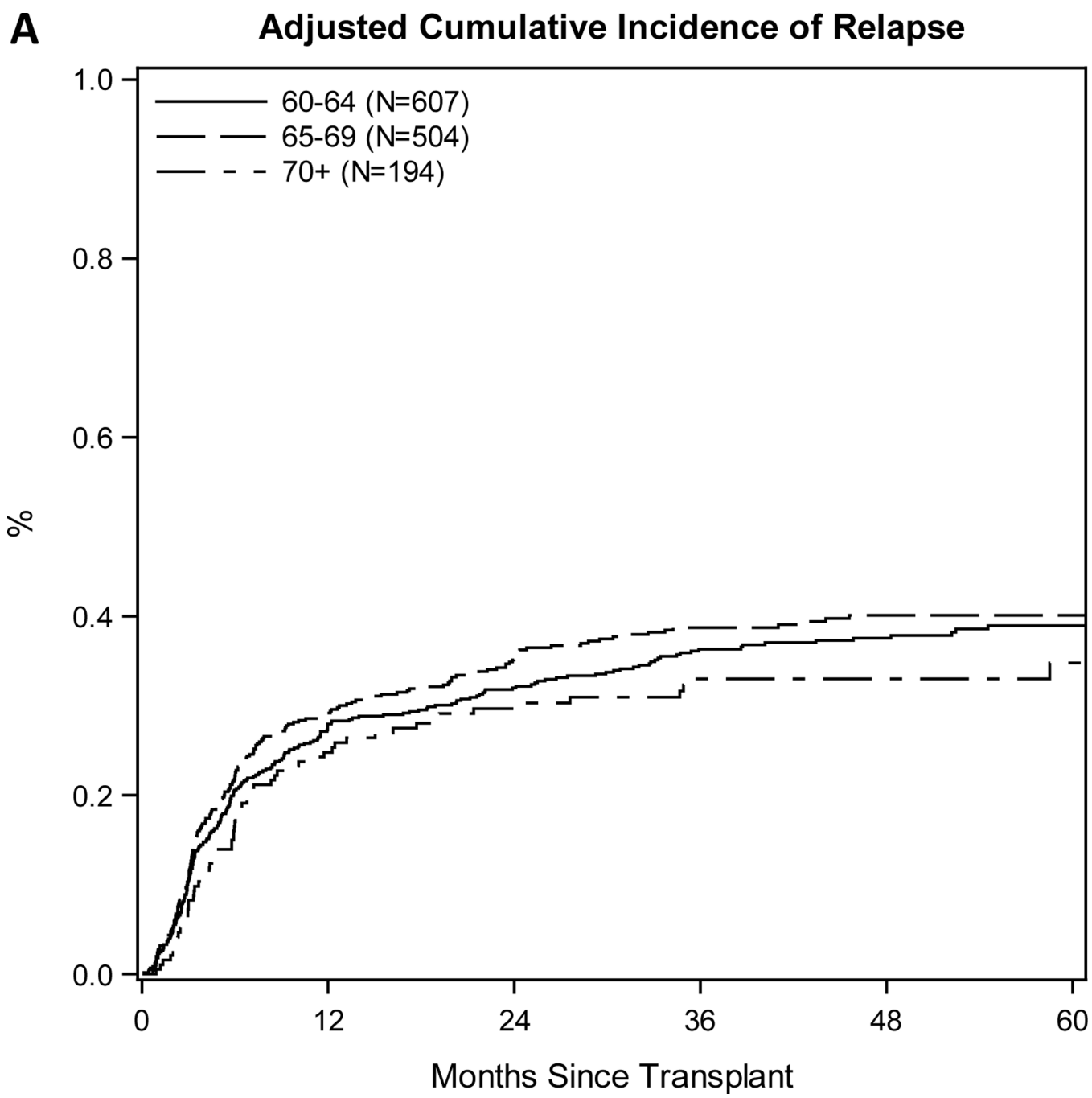


Figure 1.
A. Adjusted probability of OS stratified by age cohorts. B. Adjusted probability of DFS



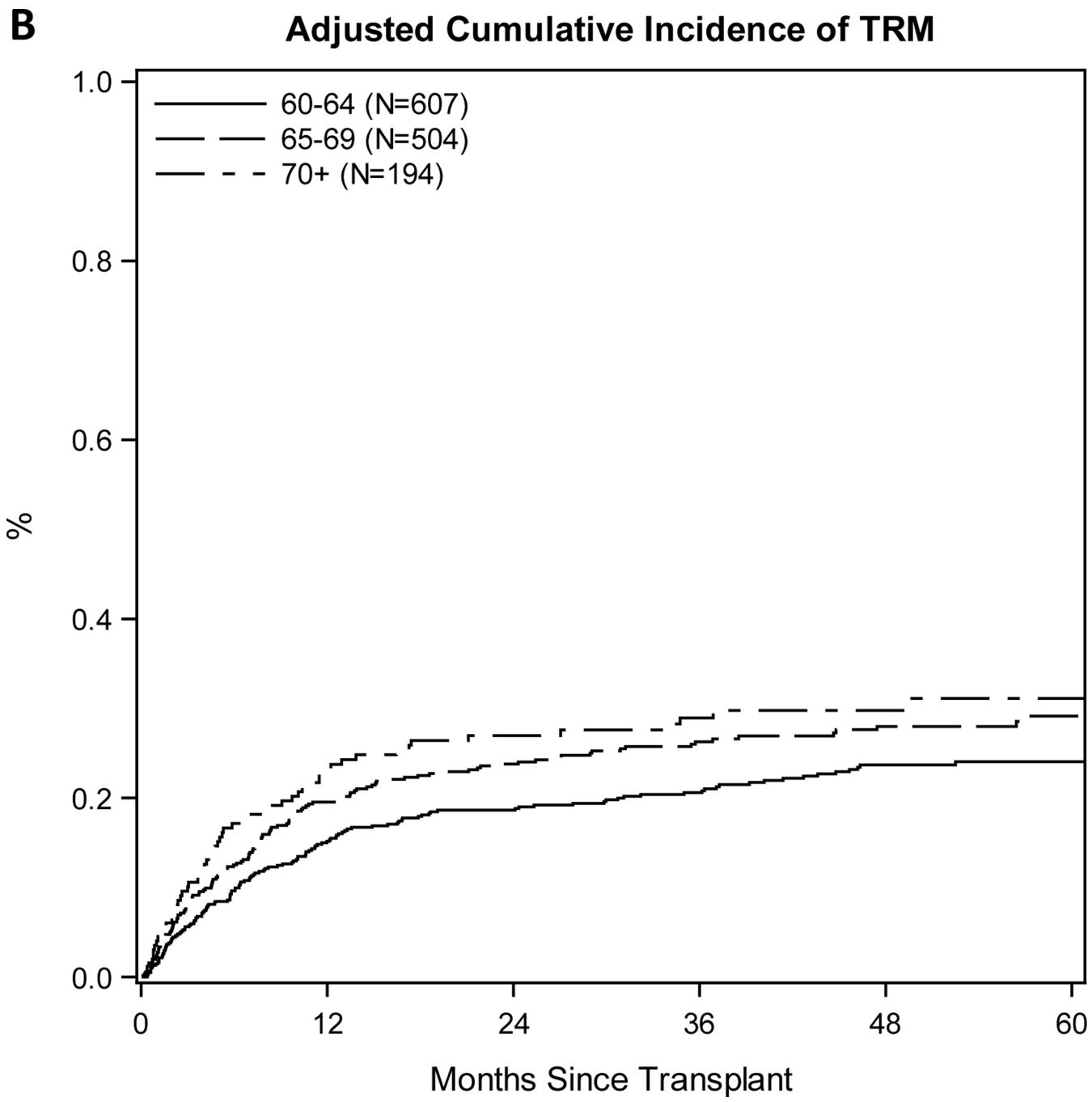
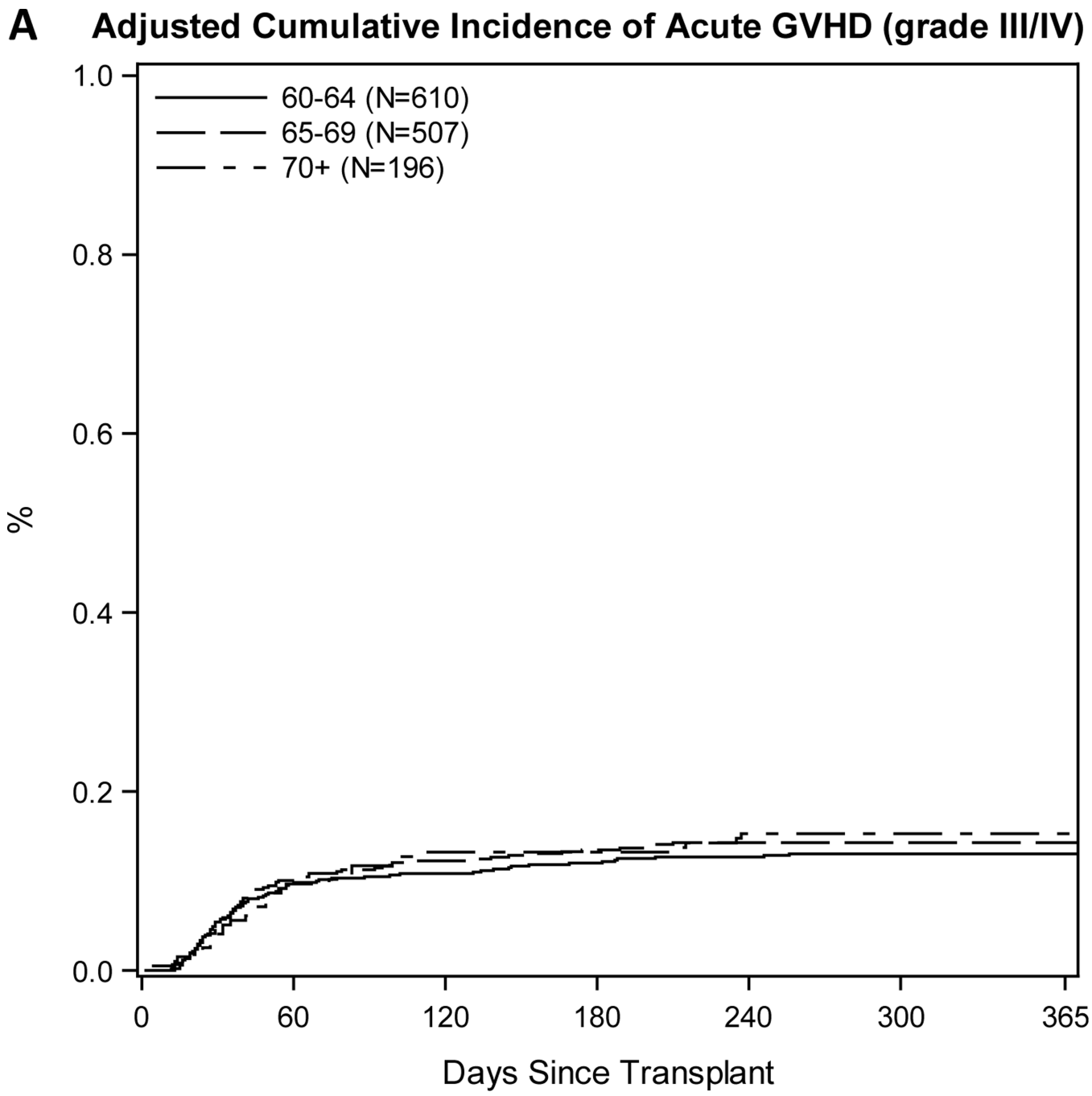


Figure 2.
A. Cumulative incidence of relapse and B. Cumulative incidence of TRM stratified by age



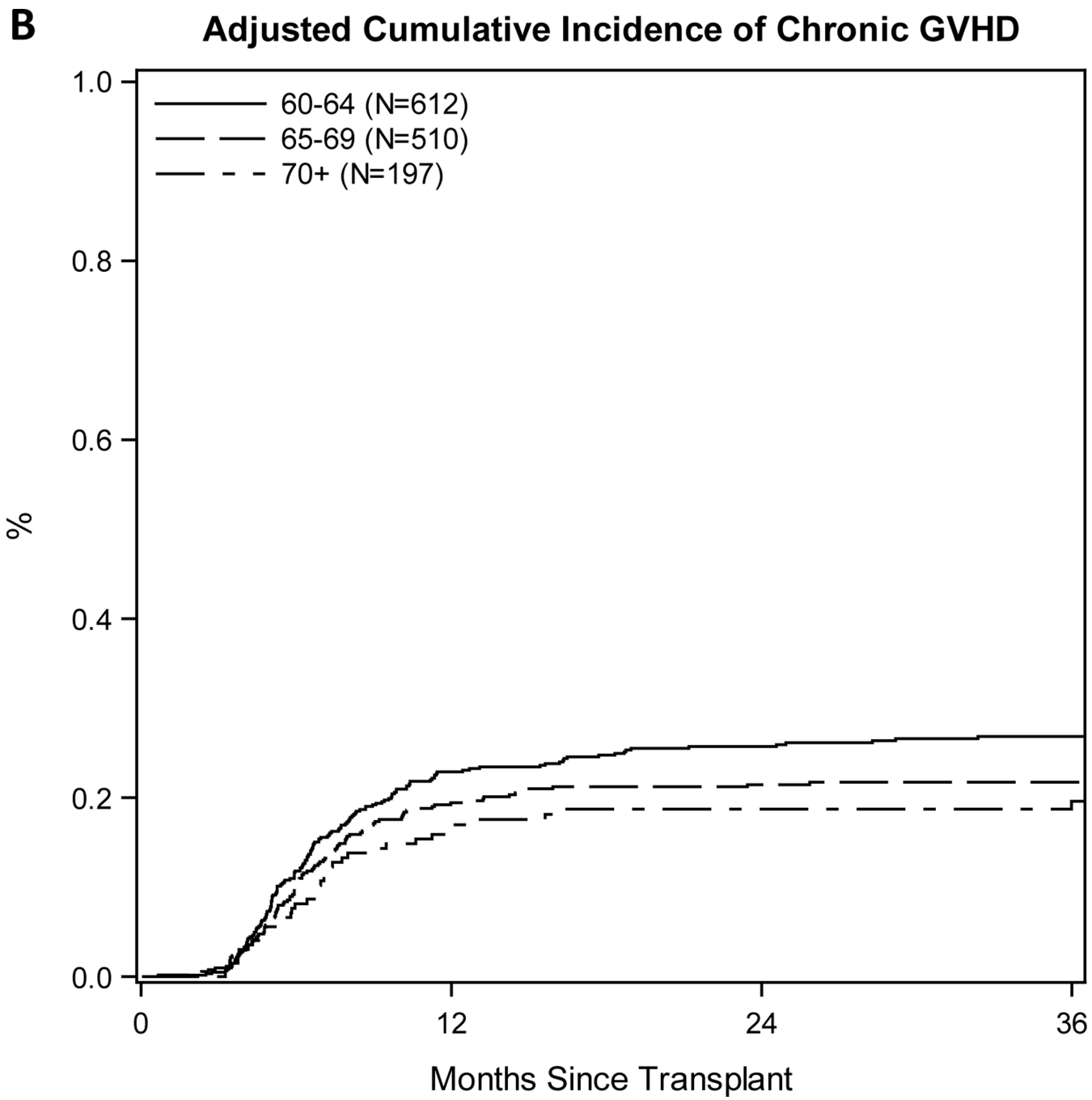


Figure 3.
A. Grade III/IV Acute GVHD and B. Moderate/Severe Chronic GVHD

Table 1.

Baseline characteristics

Characteristic	Age 60–64	65–69	≥70
No. of patients	612	512	197
Age at HCT (years) - median (range)	62 (60–65)	67 (65.1–69.9)	72 (70–77.7)
Gender - no. (%)			
Male	340 (56)	296 (58)	133 (68)
Female	272 (44)	216 (42)	64 (32)
Clinical onset of AML - no. (%)			
De-novo	467 (76)	376 (73)	139 (71)
sAML/tAML	145 (24)	136 (27)	58 (29)
Karnofsky score - no. (%)			
<90	251 (41)	236 (46)	78 (40)
>=90	355 (58)	271 (53)	119 (60)
Missing	6 (1)	5 (1)	0
HCT-CI - no. (%)			
0	115 (19)	80 (16)	31 (16)
1	93 (15)	74 (14)	20 (10)
2	94 (15)	67 (13)	39 (20)
3+	285 (47)	271 (53)	100 (51)
Missing	25 (4)	20 (4)	7 (4)
Cytogenetic risk group - no. (%)			
Favorable	8 (1)	8 (2)	5 (3)
Intermediate	401 (66)	325 (63)	131 (66)
Poor	191 (31)	168 (33)	59 (30)
Missing	12 (2)	11 (2)	2 (1)
No. of patients	612	512	197
ELN cytogenetic score			
Favorable	50 (8)	55 (11)	28 (14)
Intermediate	185 (30)	185 (36)	80 (41)
Adverse	109 (18)	107 (21)	48 (24)
Missing	268 (44)	165 (32)	41 (21)
MRD at time of HCT - no. (%)			
Negative	416 (68)	338 (66)	127 (64)
Positive	154 (25)	141 (28)	64 (32)
Missing	42 (7)	33 (6)	6 (3)
Donor type - no. (%)			
HLA-identical sibling	159 (26)	109 (21)	24 (12)
Haploidentical	57 (9)	46 (9)	21 (11)
Other relative	30 (5)	30 (6)	9 (5)
Well-matched URD (8/8 alleles)	240 (39)	228 (45)	110 (56)
Partially-matched URD (7/8)	24 (4)	23 (4)	5 (3)

Characteristic	Age 60–64	65–69	≥70
Cord blood	102 (17)	76 (15)	28 (14)
Graft type - no. (%)			
Bone marrow	69 (11)	53 (10)	23 (12)
Peripheral blood	441 (72)	383 (75)	146 (74)
Cord blood	102 (17)	76 (15)	28 (14)
Conditioning intensity - no. (%)			
MAC	184 (30)	82 (16)	13 (7)
RIC/NMA	428 (70)	430 (84)	184 (93)
ATG as part of regimen			
No	451 (74)	378 (74)	148 (75)
Yes	158 (26)	131 (26)	48 (24)
GVHD prophylaxis - no. (%)			
Post-cy +/− other	61 (10)	64 (13)	35 (18)
TAC/CSA +/− other	497 (81)	418 (82)	153 (78)
Other	54 (9)	30 (6)	9 (5)
Year of transplant - no. (%)			
2007–2013	261 (43)	156 (30)	40 (20)
2014–2015	225 (37)	217 (42)	96 (49)
2016–2017	126 (21)	139 (27)	61 (31)
Follow-up of survivors (months) - median (min-max)	49 (0.4–142.9)	47.9 (0.2–126.1)	43.6 (0.4–122.5)

sAML=secondary AML; tAML=Therapy-related AML; MAC=Myeloablative conditioning; RIC=Reduced intensity conditioning; URD=unrelated donor; mELN=modified European Leukemia Net classification; MRD=Minimal residual disease; Tac=tacrolimus; CSA=cyclosporine; Post-Cy=post-transplant cyclophosphamide

Table 2.

Multivariate model outcomes

Covariates	N	HR (95% CI)	p-value
Overall survival			
Age at HCT (years) - main effect			0.008
60–64	612	Reference	
65–69	512	1.27 (1.09–1.49)	0.002
≥70	197	1.20 (0.96–1.50)	0.11
Cytogenetic risk group			<0.001
Favorable/Intermediate	878	Reference	
Poor	418	1.42 (1.22–1.65)	<0.001
Missing	25	0.70 (0.40–1.22)	0.21
MRD status at HCT			0.004
Negative	881	Reference	
Positive	359	1.33 (1.12–1.57)	0.001
Missing	81	1.12 (0.83–1.52)	0.45
Donor type			<0.001
HLA-identical sibling	292	Reference	
Other relative	193	1.22 (0.95–1.57)	0.12
Well-matched URD (8/8)	578	0.90 (0.74–1.10)	0.29
Partially-matched URD (7/8)	52	0.98 (0.67–1.43)	0.91
Cord blood	206	1.49 (1.19–1.87)	0.001
Year of HCT			0.034
2007–2013	457	Reference	
2014–2015	538	0.96 (0.81–1.14)	0.63
2016–2017	326	0.76 (0.61–0.94)	0.01
Non-relapse mortality			
Age at HCT (years) - main effect			0.018
60–64	607	Reference	
65–69	504	1.34 (1.06–1.69)	0.016
≥70	194	1.44 (1.05–1.96)	0.023
HCT-CI			0.009
0–1	406	Reference	
2	199	1.10 (0.78–1.57)	0.58
3+	648	1.40 (1.09–1.79)	0.01
Missing	52	0.56 (0.26–1.22)	0.23
Donor type			0.001
HLA-identical sibling	286	Reference	
Other relative	189	0.91 (0.61–1.35)	0.63

Covariates	N	HR (95% CI)	p-value
Well-matched URD (8/8)	575	0.99 (0.74–1.32)	0.94
Partially-matched URD (7/8)	52	1.58 (0.98–2.56)	0.063
Cord blood	203	1.69 (1.20–2.37)	0.003
Relapse			
Age at HCT (years) - main effect			0.18
60–64	607	Reference	
65–69	504	1.19 (0.98–1.44)	0.083
≥70	194	0.99 (0.75–1.32)	0.95
Cytogenetic risk group			<0.001
Favorable/Intermediate	868	Reference	
Poor	412	1.83 (1.52–2.20)	<0.001
Missing	25	0.98 (0.50–1.90)	0.95
MRD status at HCT			<0.001
Negative	873	Reference	
Positive	352	1.54 (1.27–1.88)	<0.001
Missing	80	1.37 (0.96–1.97)	0.085
Donor type			0.013
HLA-identical sibling	286	Reference	
Other relative	189	1.06 (0.78–1.44)	0.72
Well-matched URD (8/8)	575	0.77 (0.61–0.97)	0.027
Partially-matched URD (7/8)	52	0.48 (0.27–0.88)	0.017
Cord blood	203	0.83 (0.56–1.23)	0.35
Graft type			0.02
Bone marrow	143	Reference	
Peripheral blood	959	0.72 (0.54–0.95)	0.02
Acute GVHD (grade III/IV			
Age at HCT (years) - main effect			0.65
60–64	610	Reference	
65–69	507	1.12 (0.81–1.54)	0.5
≥70	196	1.20 (0.79–1.82)	0.41
Chronic GVHD (moderate-severe)			
Age at HCT (years) - main effect			0.20
60–64	612	Reference	
65–69	510	0.84 (0.66–1.08)	0.17
≥70	197	0.76 (0.53–1.09)	0.14
Graft type			<0.001
Bone marrow	145	Reference	
Peripheral blood	968	1.74 (1.11–2.74)	0.017

Covariates	N	HR (95% CI)	p-value
Cord blood	206	0.61 (0.32–1.16)	0.13
GVHD prophylaxis			0.001
Post-cy +/− other	160	Reference	
TAC/CSA +/− other	1066	1.76 (1.15–2.70)	0.02
Other	73	0.37 (0.13–1.08)	0.068
Missing	20	1.48 (0.51–4.28)	0.47

Table 3.

Five-year overall survival

Prob (95% CI)	60–64 (n=612)	65–69 (n=512)	>=70 (n=197)	P Value
1-year	67.6 (63.9–71.3)%	59.2 (54.9–63.4)%	59.9 (53–66.6)%	0.008
2-year	55.4 (51.3–59.3)%	49.7 (45.3–54.1)%	51.7 (44.7–58.7)%	0.172
3-year	49.4 (45.3–53.5)%	42.3 (37.8–46.8)%	44.7 (37.5–52)%	0.068
4-year	44.3 (40.1–48.5)%	38.1 (33.6–42.8)%	43.8 (36.5–51.2)%	0.135
5-year	42 (37.7–46.4)%	35.8 (31–40.7)%	40.6 (32.7–48.7)%	0.166