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Outcomes of allogeneic stem cell transplantation for patients with hematologic diseases ≥60 years old

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Abstract

Hematologic diseases frequently affect people >60 years old, and allogeneic stem cell transplantation (allo-SCT) is a potentially curative treatment for these patients. Although several multicenter studies proposed the risk assessment of allo-SCT for the elderly, they receive different treatments and management at each facility. Therefore, accumulating data from institutions that exhibit relatively the same treatment policy and patient care is important. This retrospective study aimed to clarify the prognostic factors of allo-SCT for the elderly in our institution. Of the 104 patients, 51.0% were 60-64 years old, and 49.0% were ≥65 years old. The 3-year overall survival (OS) was 40.9% and 35.7% for patients 60-64 and ≥65 years old, respectively, which is not significant. While the disease status prior to allo-SCT demonstrated strong effects on the 3-year OS for patients that are 60-64 years old (in remission, 76.9%; non-remission, 15.7%, $p<0.001$), this effect was smaller for patients ≥65 years old (in remission, 43.1%; non-remission, 30.1%, $p=0.048$). Multivariate analysis revealed that the performance status (PS), not the disease status prior to allo-SCT, was the prognostic risk factor of OS for patients aged ≥65 years. Our data suggest that PS is a useful predictor of better OS following allo-SCT, especially for patients ≥65 years old.

Key words elder patients, hematopoietic stem cell transplantation, prognosis, risk factor

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Introduction

Hematologic diseases frequently affect people >60 years old[1,2]. For example, acute myeloid leukemia (AML), which is one of the major hematologic malignancies, and the median age of patients diagnosed with AML is 67 years[3]. Older hematologic disease patients were considered ineligible for allogeneic stem cell transplantation (allo-SCT) because of their frailties against treatment-related toxicities of allo-SCT[4,5]. In recent years, the development of reduced-intensity conditioning regimens, expanding donor availability including haplo-identical donors, and improvements in supportive care led to the extension of the age limit of allo-SCT to >70 years[6]. However, older patients are frail, and the outcomes of allo-SCT for older patients have not been satisfactory because of therapeutic toxicity or disease recurrence[6,7]. Therefore, deciding to strengthen the intensity of chemotherapies before allo-SCT to reduce the relapse risk of underlying disease following allo-SCT is difficult[1,5,6,8]. Although multiple institutions and organizations proposed various risk assessments and prognostic factors to improve allo-SCT outcomes in older patients[1,5,8-10], each facility presents different treatment policies and care for older patients; thus, interpreting and comparing the results of previous studies from such multiple facilities is not easy[5,9,10]. While large-scale studies by multiple institutions are indispensable for improving allo-SCT outcomes in older patients, accumulating and analyzing data from institutions that present relatively the same treatment policy and patient care is also important. Therefore, this retrospective study aims to clarify the prognostic factors of allo-SCT for older hematologic disease patients in our institution.

Materials and Methods

Patients and clinical data

From January 2015 to December 2020, a cumulative total of 104 cases of allo-SCT were performed in Hamanomachi Hospital. A set of complete clinical data required in this study such as patients' age, patients' sex, body-mass index (BMI), performance status (PS), hematopoietic cell transplantation-specific comorbidity index (HCT-CI), primary disease, disease status prior to allo-SCT, donor source, HLA disparity, previous allo-SCT, donors' age, donors' sex, and presence of graft-versus-host disease (GVHD) were available. The reduced-intensity conditioning was defined as a regimen with <8Gy total body irradiation, ≤140mg/sqm melphalan, and ≤8mg/kg oral busulfan (or intravenously in equivalent dosages)[11]. This retrospective study was approved by the institutional review board of Hamanomachi Hospital (No.2021-47).

Statistical analysis

The Fisher's exact test or the mxn Chi-square test was used for comparison of categorical variables and the Kruskal Wallis test was used for comparison of continuous variables. Survival was plotted using Kaplan-Meier curves, taking the interval from date of allo-SCT to death/relapse or last contact. Any patient who was alive at the last follow-up date was censored. Comparisons between each group were performed using the log-rank test. Relapse and treatment-related mortality were considered competing risk events and were analyzed using Fine & Gray's test. Univariate analysis was performed using logistic or exact logistic regression, and the parameters <0.05 were re-evaluated using multivariate analysis. Multivariate analysis was performed using logistic regression applying Firth's bias reduction. A p value<0.05 was considered as statistically significant. Statistical analyses were performed using EZR[12] and GraphPad Prism version 9 (GraphPad Software, San Diego, California, USA).

Results

Patient characteristics

We identified 104 patients who received allo-SCT. The median age of the entire cohort was 64 (with a range of 60-74) years old. All patients received reduced-intensity conditioning regimens[8]. AML or myelodysplastic syndrome (MDS) is the main indication for allo-SCT, followed by non-Hodgkin lymphoma, acute lymphoblastic leukemia (ALL), and other hematologic diseases. Moreover, 41 patients received related-peripheral blood, five received unrelated-peripheral blood, one received related-bone marrow, 18 received unrelated-bone marrow, and 39 received cord blood as the stem cell source. BMI of the patients ranged from 12.94-21.33 (with a median of 16.59), indicating that most patients (n=87, 83%) were underweight (BMI < 18.5). With regards to the Eastern Cooperative Oncology Group performance status (ECOG-PS), 48, 45, seven, and four patients had a score of 0, 1, 2, and 3, respectively. Fifty-seven patients demonstrated a Karnofsky performance status (KPS) of ≥90. In this study, patients were stratified into three groups based on age: 60-64 years (n=53), 65-69 years (n=38), and ≥ 70 (n=13). **Table 1** shows the characteristics of patients grouped by age, and all clinical parameters except for patient age were not significantly different between these three age groups.

Survival, relapse, and treatment-related mortality

The 1-year overall survival (OS) was 61.6%, 52.7%, and 51.9%, and the 3-year OS was 40.9%, 39.5%, and 26.0% for patients 60-64, 65-69, and ≥70 years old, respectively. No significant difference was found in the OS among the three age groups (p=0.464) (**Figure 1A** and **Table 2**). The cumulative incidence of relapse (CIR) at one year was 37.0%, 47.5%, and 48.1%, and the 3-year CIR was 48.3%, 47.5%, and 48.1% in patients 60-64, 65-69, and ≥70 years old, respectively. No significant difference in the CIR was found among the three age groups (p=0.913) (**Figure 1B** and **Table 2**).

Because of frailty, the treatment-related mortality (TRM) is also a significant issue for older patients[6,13,14]. The 1-year cumulative incidence of TRM was 6.8%, 15.0%, and 12.5%, and the 3-year TRM was 19.8%, 27.2%, and 41.7% in patients 60-64, 65-69, and ≥70 years old, respectively. A significant difference in TRM was not observed among the three age groups (p= 0.281) (**Figure 1C** and **Table 2**).

Effect of disease control prior to allo-SCT on OS, relapse, and TRM

Previous studies reported that disease status prior to allo-SCT is one of the important factors for patients' survival following allo-SCT[15-18]. Therefore, we first evaluate the effect of disease status prior to allo-SCT on the survival of older patients. Overall, 44 (42.3%) patients achieved complete remission (CR) prior to allo-SCT, and 60 (57.7%) did not achieved CR (non-CR). The 1-year OS was 83.4% and 37.9%, and the 3-year OS was 60.7% and 20.9% for the CR and non-CR groups, respectively. The median OS was not reached in the CR group, and it was 233 days (0.64 year) in the non-CR group (p<0.001) (**Figure 2A** and **Table 2**). Moreover, survival was evaluated based on age groups. For the 60-64 years old group (22 patients with CR and 31 patients without CR prior to allo-SCT), the 1-year

Table 1. Patient Characteristics

	Age 60-64 (n=53)	Age 65-69 (n=38)	Age 70- (n=13)	*p*
Age, years, median (range)	63 (60-64)	67 (65-69)	71 (70-74)	<0.001
Recipient sex, Male	34 (64)	24 (63)	7 (54)	0.929
Body-Mass Index, kg/sqm, median (range)	16.59 (12.98-21.33)	16.38 (12.94-21.03)	16.90 (14.04-21.03)	0.236
ECOG Performance Status, median (range)	1 (0-3)	1 (0-3)	0 (0-2)	0.735
Karnofsky Performance Status, median (range)	90 (40-90)	90 (40-100)	90 (60-90)	0.936
HCT-CI, median (range)	0 (0-5)	0 (0-5)	0 (0-5)	0.957
Disease				0.205
AML or MDS	29 (55)	27 (71)	12 (92)	
ALL	2 (4)	5 (13)	0 (0)	
ML	17 (32)	5 (13)	1 (8)	
others	5 (9)	1 (3)	0 (0)	
Disease status pre-SCT, CR	22 (42)	17 (45)	5 (38)	0.990
Donor source				0.481
related-PB	25 (47)	13 (34)	3 (23)	
unrelated-PB	2 (4)	3 (8)	0 (0)	
related-BM	0 (0)	1 (3)	0 (0)	
unrelated-BM	12 (23)	3 (8)	3 (23)	
CB	14 (26)	18 (47)	7 (54)	
HLA disparity				0.088
full match (8/8)	13	9	3	
7/8	7	3	3	
6/8	6	6	1	
5/8	9	15	3	
4/8	18	5	3	
Previous allo-SCT	5 (9)	1 (3)	3 (23)	0.234
Donor Age, years, median (range)	32 (0-60)	25 (0-62)	0 (0-48)	0.347
Donor sex, Male	33 (62)	23 (61)	7 (54)	0.959

All values are n (%) unless otherwise noted. The donor age of cord blood was defined as 0.

ECOG, Eastern Cooperative Oncology Group; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; ML, malignant lymphoma; SCT, stem cell transplantation; CR, complete remission; PB, peripheral blood; BM, bone marrow; CB, cord blood; allo-SCT, allogeneic stem cell transplantation

OS was 95.5% and 36.8%, and the 3-year OS was 76.9% and 15.7% for the CR and non-CR groups, respectively. The median OS was not reached in the CR group, and it was 233 days (0.64 year) in the non-CR group (p<0.001) (**Figure 2B** and **Table 2**). For the 65-69 years old group (17 patients with CR and 21 patients without CR prior to allo-SCT), the 1-year OS was 67.0% and 41.3%, and the 3-year OS was 44.7% and 35.4% for the CR and non-CR groups, respectively. The median OS was 493 days (1.35 years) for the CR group and 248 days (0.68 year) for the non-CR group (p=0.135) (**Figure 2C** and **Table 2**). For the ≥70 years old group (5 patients with CR and 8 patients without CR prior to allo-SCT), the 1-year OS was 80.0% and 33.3%, and the 3-year OS was 40.0% and 16.7% for the CR and non-CR groups, respectively. The median OS was 425 days (1.16 years) and 239 days (0.66 year) for the CR and non-CR groups (p=0.202), respectively (**Figure 2D** and **Table 2**).

Given that the disease status prior to allo-SCT significantly affected the 60-64 years old group, we combined the 65-69 years old and ≥70 years old groups into the ≥65 years old group for further analysis. The 1-year and 3-year OS in the ≥65 years old group (n = 51) was 52.3% and 35.7%, respectively. The median OS of the ≥65 years old group was 370 days (1.01 years), with no significant difference when compared to that of the 60-64 years old group (p=0.276) (**Figure 2E**). The OS of the 60-64 years old and ≥65 years old group were also compared according to the disease status prior to allo-SCT. For the ≥65 years old group (22 patients with CR and 29 patients without CR prior to allo-SCT), the 1-year OS was 70.0% and 39.1%, and the 3-year OS was 43.1% and 30.4% for the CR and non-CR groups, respectively; and the median OS was 479 days (1.31 years) and 248 days (0.68 year) for the CR and non-CR groups (p=0.048), respectively (**Figure 2F** and **Table 2**). For patients with CR prior to allo-SCT, a significant difference was found between the 60-64 years old and the ≥65 years old groups (p=0.015)

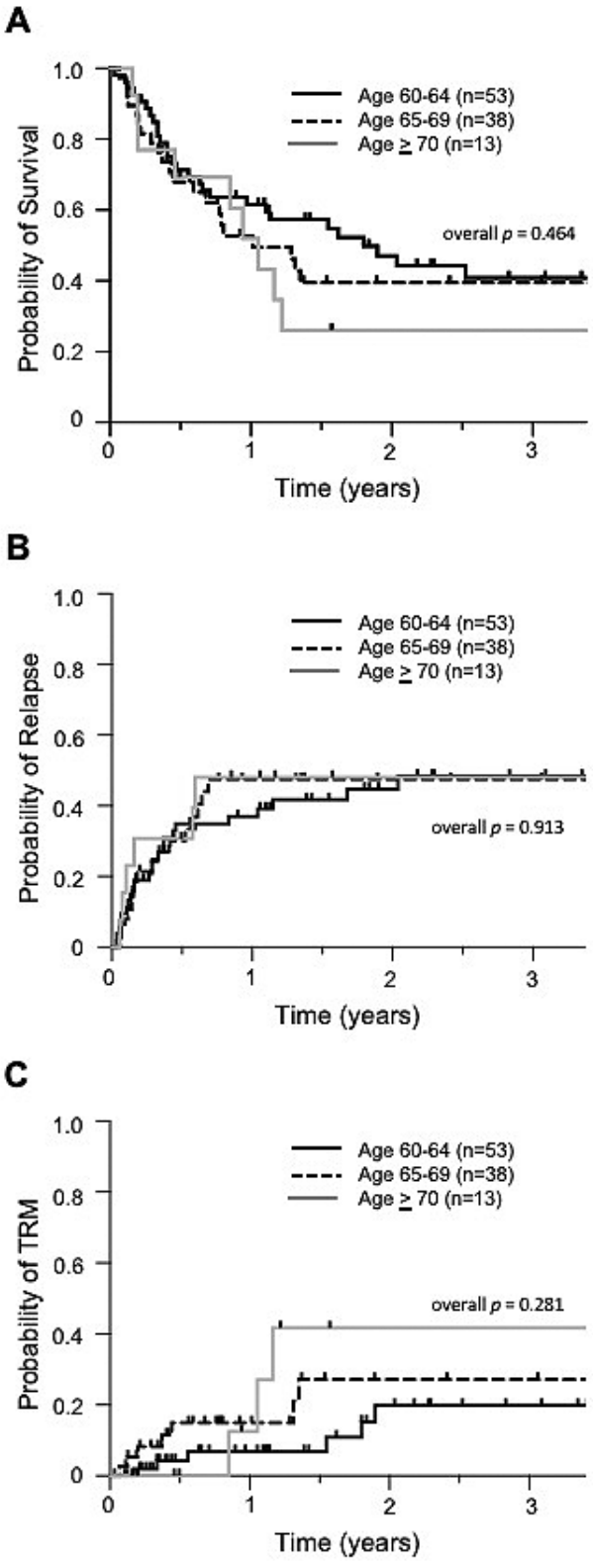

Figure 1. Age-classified outcome of allo-SCT
The overall survival (A), the cumulative incidence of relapse (B), and the cumulative incidence of the treatment-related mortality (TRM) (C) stratified by age groups.

(**Figure 2F**). This data indicates that disease status prior to allo-SCT is important for better OS; however, this effect is less observed in the ≥65 years old group than in the 60-64 years old group.

The 1-year CIR was 18.8% and 60.0%, and the 3-year CIR was 25.3% and 66.8% for the CR and non-CR groups, respectively. The median relapse-free survival (RFS) was not reached in the CR group, and it was 210 days (0.58 year) in the non-CR group ($p<$ 0.001) (**Figure 3A** and **Table 2**). For the 60-64 years old group, the 1-year CIR was 9.1% and 58.7%, and the 3-year CIR was 20.5% and 70.6% for the CR and non-CR groups, respectively. The median RFS was not reached in the CR group, and it was 134 days (0.37 year) in the non-CR group ($p<0.001$) (**Figure 3B** and **Table 2**). For the 65-69 years old group, the 1-year CIR was 32.1% and 60.5%, and the 3-year CIR was the same as those at one year for the CR and non-CR groups, respectively. The median RFS was not reached in the CR group, and it was 224 days (0.61 year) in the non-CR group ($p=0.029$) (**Figure 3C** and **Table 2**). For the ≥70 years old group, the 1-year CIR was 20.0% and 66.7%, and the 3-year CIR was same as those at 1 year for the CR and non-CR groups, respectively. The median RFS was not reached in the CR group, and it was 134 days (0.37 year) in the non-CR group ($p=0.078$) (**Figure 3D** and **Table 2**). The 1-year and 3-year CIR in the ≥65 years old group was 47.5%. The median RFS of the ≥65 years old group was 1,453 days (3.98 years) with no significant difference when compared to that of the 60-64 years old group ($p=0.688$) (**Figure 3 E**). The CIR of the 60-64 years old and ≥65 years old groups was also compared according to the disease status prior to allo-SCT. For the ≥65 years old group, the 1-year CIR was 29.6% and 62.0%, and the 3-year CIRs were the same as those at 1 year in the CR and non-CR groups, respectively. In the ≥65 years old group, the median RFS was not reached in the CR group, and it was 217 days (0.59 year) in the non-CR group ($p=0.007$) (**Figure 3F** and **Table 2**). For patients with CR prior to allo-SCT, no significant difference was found in the CIR between the 60-64 years old and the ≥65 years old groups ($p=0.332$) (**Figure 3F**). For non-CR patients prior to allo-SCT, no significant difference was noted in the CIR between the 60-64 years old and ≥65 years old groups ($p=0.771$) (**Figure 3F**). This data indicates that disease status prior to allo-SCT is important for providing better RFS; however, this effect is much less for older patients.

The 1-year cumulative incidence of TRM was 2.4% and 18.7%, and the 3-year TRM was 18.4% and 32.9% for the CR and non-CR groups, respectively ($p=0.135$) (**Figure 4A** and **Table 2**). For the 60-64 years old group, the 1-year TRM was 0% and 13.4%, and the 3-year TRM was 6.7% and 38.2% for the CR and non-CR groups, respectively ($p=0.039$) (**Figure 4B** and **Ta-**

Table 2. Summary of transplantation outcomes

	1-year OS (%)	3-year OS (%)	*p*	1-year CIR (%)	3-year CIR (%)	*p*	1-year TRM (%)	3-year TRM (%)	*p*
Age 60-64 (n=53)	61.6	40.9	0.464	37.0	48.3	0.913	6.8	19.8	0.281
Age 65-69 (n=38)	52.7	39.5		47.5	47.5		15.0	27.2	
Age 70- (n=13)	51.9	26.0		48.1	48.1		12.5	41.7	
CR (n=44)	83.4	60.7	<0.001	18.8	25.3	<0.001	2.4	18.4	0.135
non-CR (n=60)	37.9	20.9		60.0	66.8		18.7	32.9	
Age 60-64, CR (n=22)	95.5	76.9	<0.001	9.1	20.5	<0.001	0.0	6.7	0.039
Age 60-64, non-CR (n=31)	36.8	15.7		58.7	70.6		13.4	38.2	
Age 65-69, CR (n=17)	67.0	44.7	0.135	32.1	32.1	0.029	6.2	29.7	0.629
Age 65-69, non-CR (n=21)	41.3	35.4		60.5	60.5		22.5	22.5	
Age 70-, CR (n=5)	80.0	40.0	0.202	20.0	20.0	0.078	0.0	50.0	0.897
Age 70-, non-CR (n=8)	33.3	16.7		66.7	66.7		33.3	33.3	
Age ≥65 (n=51)	52.3	35.7		47.5	47.5		14.8	32.0	
Age ≥65, CR (n=22)	70.0	43.1	0.048	29.6	29.6	0.007	4.8	35.5	0.804
Age ≥65, non-CR (n=29)	39.1	30.4		62.0	62.0		24.2	24.2	

OS, overall survival; CIR, cumulative incidence of relapse; TRM, treatment-related mortality; CR, complete remission priro to transplantation; non-CR, without remission priro to transplantation

ble 2). For the 65-69 years old group, the 1-year TRM was 6.2% and 22.5%, and the 3-year TRM was 29.7% and 22.5% for the CR and non-CR groups, respectively (p=0.629) (**Figure 4C** and **Table 2**). For the ≥70 years old group, the 1-year TRM was 0% and 33.3%, and the 3-year TRM was 50.0% and 33.3% for the CR and non-CR groups, respectively (p=0.897) (**Figure 4D** and **Table 2**). The 1-year TRM in the ≥65 years old group was 14.8%, with no significant difference when compared to that of the 60-64 years old group (p=0.130) (**Figure 4E**). The TRM of the 60-64 years old and ≥65 years old groups were also compared according to the disease status prior to allo-SCT. For the ≥65 years old group, the 1-year TRM was 4.8% and 24.2%, and the 3-year TRM was 35.5% and 24.2% for the CR and non-CR groups, respectively (p=0.804) (**Figure 4F** and **Table 2**). For patients in the 60-64 years old and ≥65 years old groups with CR prior to allo-SCT, the TRM was 0% and 4.8% at one year and 6.7% and 35.5% at three years, respectively (p=0.031) (**Figure 4F**). For patients in the 60-64 years old and ≥65 years old groups with non-CR prior to allo-SCT, the TRM was 0% and 4.8% at one year and 6.7% and 35.5% at three years, respectively (p=0.031) (**Figure 4F**). For patients in the 60-64 years old and ≥65 years old groups with non-CR prior to allo-SCT, the TRM was 13.4% and 24.2% at one year and 38.2% and 24.2% at three years, respectively (p=0.784) (**Figure 4F**). This data indicates that disease status prior to allo-SCT is important for providing less TRM only for the younger (60-64) patients.

Risk and prognostic factors

To reveal the survival risk factors in older patients following allo-SCT, we analyzed the relationship between OS and several factors including age, BMI, ECOG-PS, KPS, HCT-CI, underlying diseases, disease status prior to allo-SCT, donor source, and the presence of grade II-IV GVHD using univariate and multivariate analyses. These analyses were performed at one year and at three years, respectively. The disease status prior to allo-SCT is the only risk factor for OS both at one year (odds ratio (OR)=6.00, 95%CI 2.52-14.30, and p< 0.001) and three years (OR=4.66, 95%CI 1.63-13.30, and p<0.01) (**Table 3**).

The same analyses were performed only for the ≥65 years old group because the effect of disease status prior to allo-SCT on OS of this age group was not very strong compared to that of the 60-64 years old group (**Figure 2B-D, and 2F**). Regarding the 1-year OS, the multivariate analysis showed that KPS was the only risk factor for OS (OR=1.08, 95%CI 1.00-1.17, and p< 0.05), although the probability of disease status prior to allo-SCT is close to p<0.05 (OR=3.23, 95%CI 0.94-11.10, and p<0.06) (**Table 4**). Regarding the 3-year OS, the univariate analysis showed that ECOG-PS prior to allo-SCT was the only risk factor for OS (OR=0.20,

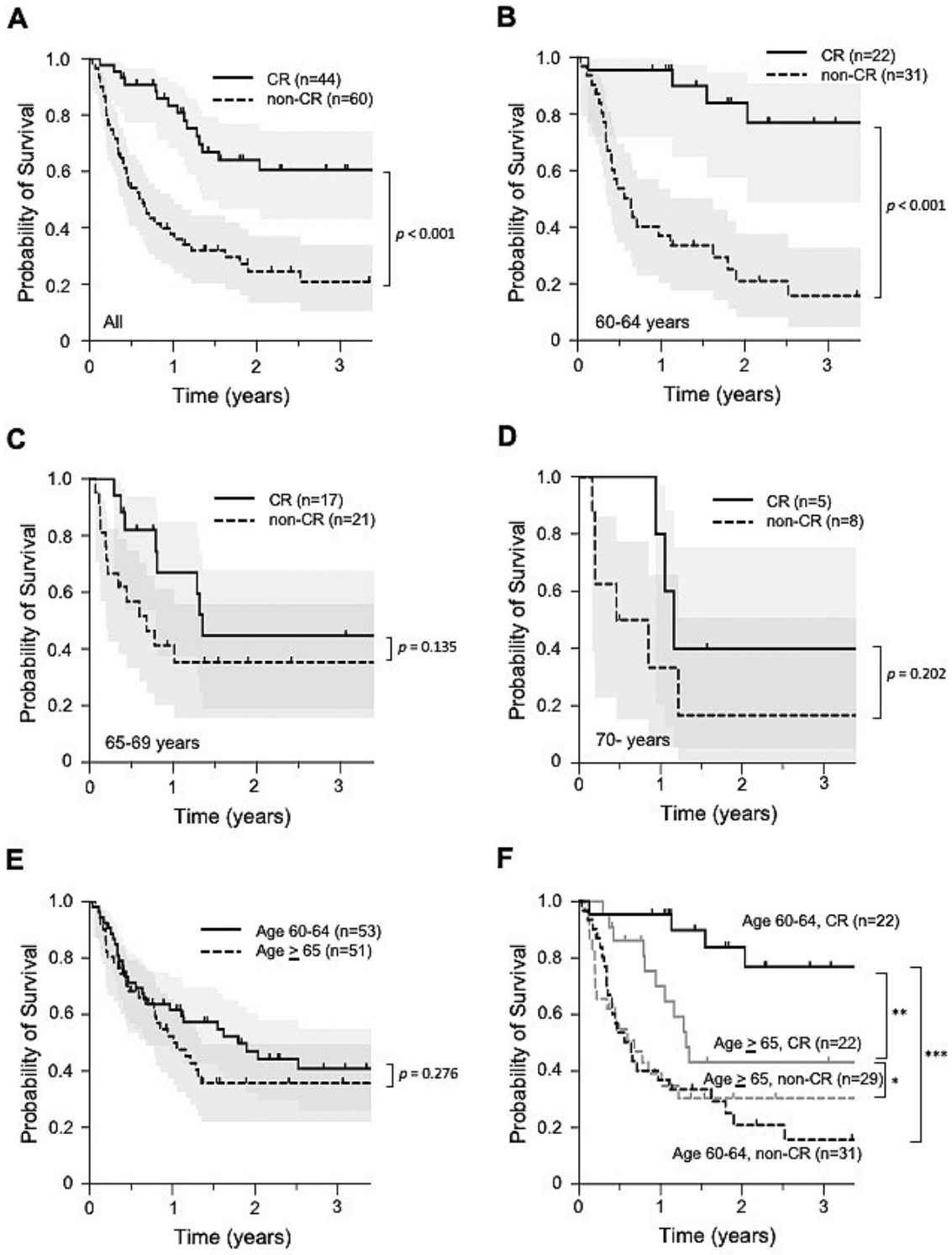

Figure 2. OS in CR and non-CR patients
The overall survival (OS) of all (A), Age 60-64 group (B), Age 65-69 group (C), and Age ≥ 70 group (D) patients with or without complete remission (CR). (E) The OS of Age 60-64 group and Age ≥ 65 group patients. (F) The OS for the CR patients and the non-CR patients in Age 60-64 group and in Age ≥ 65 group.

95%CI 0.04-0.97, and $p<0.05$) (**Table 4**).

Discussion

While older patients were not considered to receive allo-SCT previously, recent advances in transplantation methods, supportive care, and donor availability allow older patients to receive allo-SCT[4-6]. However, given the fragility of older patients and the difficulty of care they need compared to younger patients, clarifying useful

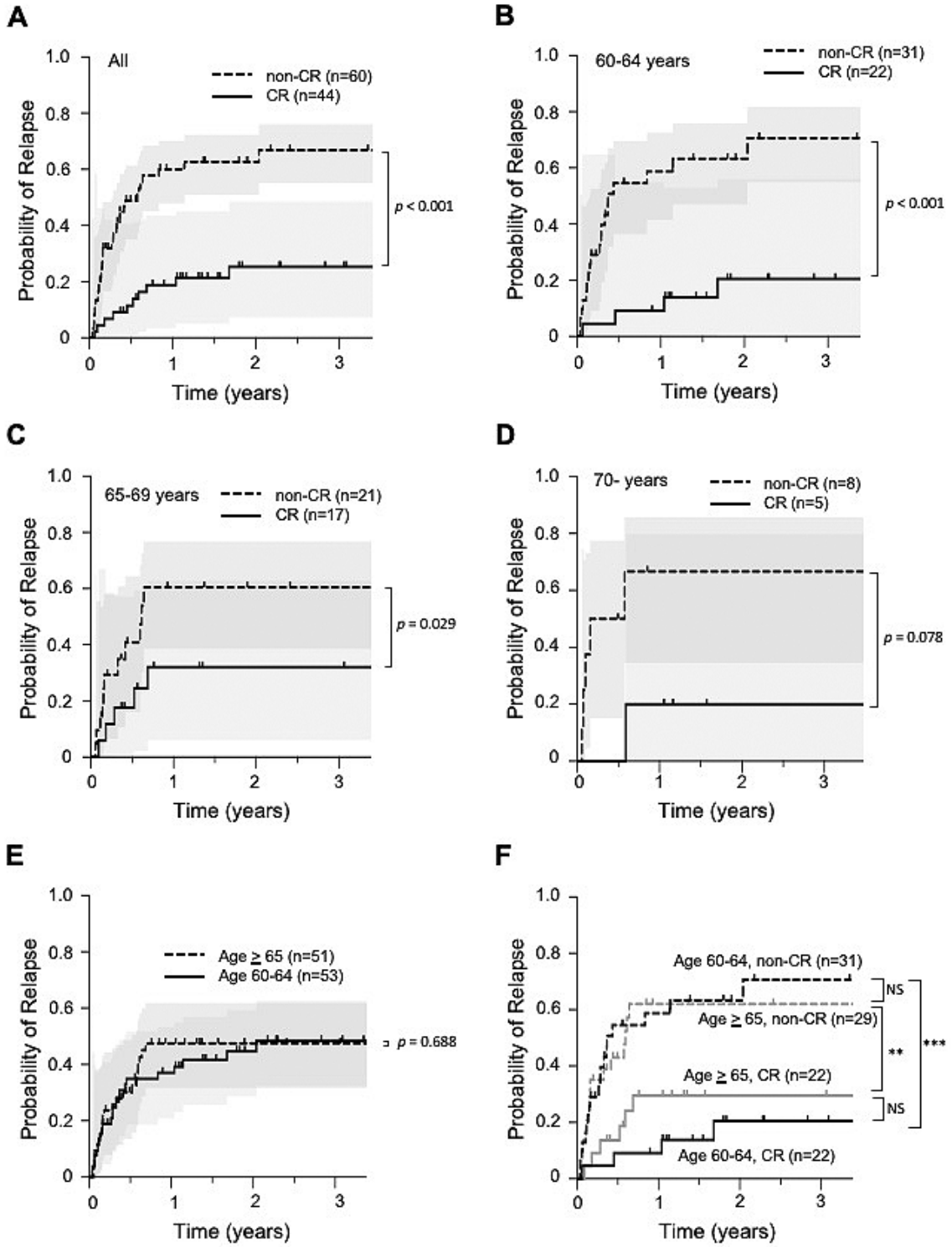

Figure 3. The incidence of relapse in CR and non-CR patients
The cumulative incidence of relapse of all (A), Age 60-64 group (B), Age 65-69 group (C), and Age ≥ 70 group (D) patients with or without CR. (E) The cumulative incidence of relapse of Age 60-64 group and Age ≥ 65 group patients. (F) The cumulative incidence of relapse for the complete remission (CR) patients and the non-CR patients in Age 60-64 group and in Age ≥ 65 group.

prognostic factors is necessary to improve the outcomes of allo-SCT in older patients. Some studies have focused on allo-SCT in older patients, and several potential prognostic factors have been suggested[1,5,8-10]; however, they have not been well investigated. Notably, large differences potentially exist among facilities regarding transplantation indications, treatment policies, and supportive care provision methods to older people;

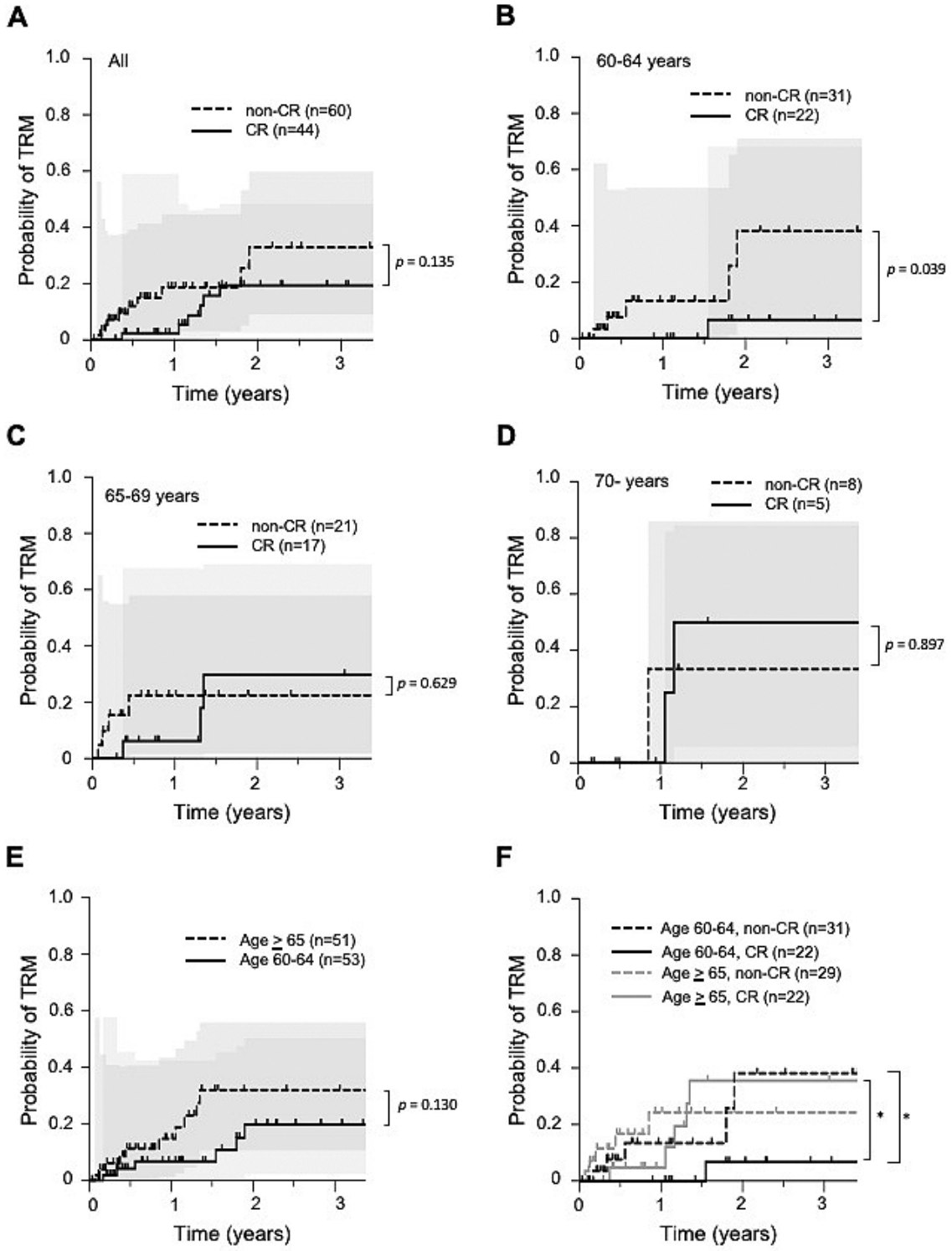

Figure 4. Treatment-related mortality in CR and non-CR patients
The treatment-related mortality (TRM) of all (A), Age 60-64 group (B), Age 65-69 group (C), and Age ≥ 70 group (D) patients with or without complete remission (CR). (E) The TRM of Age 60-64 group and Age ≥ 65 group patients. (F) The TRM for the CR patients and the non-CR patients in Age 60-64 group and in Age ≥ 65 group.

therefore, analyzing data at each facility that provides a relatively unified treatment and supportive care to older people is important[5,9,10].

The 3-year OS, CIR, and TRM in our cohort were comparable with those reported in previous studies[1,7,8], and no significant difference was found between each age group (**Figure 1A-C**). Generally, patients ≥60 years old are often regarded as the "elderly"[19], but when they are divided into three groups according to age, it is different. The effect of disease status prior to

Table 3. Risk factors for 1-year and 3-year survivals

	1-year survival		3-year survival	
	Unvariate		Unvariate	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age	0.93 (0.83-1.04)	0.222	0.95 (0.82-1.09)	0.454
Body-Mass Index	1.06 (0.86-1.31)	0.565	1.09 (0.85-1.41)	0.500
ECOG Performance Status	0.76 (0.45-1.26)	0.286	0.60 (0.28-1.25)	0.171
Karnofsky Performance Status	1.03 (1.00-1.07)	0.073	1.05 (0.99-1.11)	0.108
HCT-CI	0.94 (0.72-1.24)	0.676	0.81 (0.55-1.19)	0.275
Disease				
AML or MDS	reference		reference	
ALL	1.12 (0.23-5.38)	0.890	3.17 (0.63-15.90)	0.161
ML	0.54 (0.21-1.41)	0.208	0.89 (0.26-3.07)	0.854
others	0.84 (0.16-4.45)	0.840	0.85 (0.09-7.87)	0.883
Disease status pre-SCT, CR/non-CR	**6.00 (2.52-14.30)**	**<0.001**	**4.66 (1.63-13.30)**	**<0.01**
Donor source				
related-PB	reference		reference	
unrelated-PB	0.58 (0.09-3.82)	0.567	<0.01 (0.00-inf)	0.993
related-BM	>1×10^6 (0.00-inf)	0.992	<0.01 (0.00-inf)	0.997
unrelated-BM	0.69 (0.23-2.11)	0.515	1.02 (0.27-3.86)	0.982
CB	0.91 (0.38-2.19)	0.832	0.92 (0.31-2.68)	0.875
Acute GVHD, Grade II-IV/0-I	0.64 (0.27-1.53)	0.317	0.23 (0.05-1.06)	0.060

ECOG, Eastern Cooperative Oncology Group; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; ML, malignant lymphoma; SCT, stem cell transplantation; CR, complete remission; PB, peripheral blood; BM, bone marrow; CB, cord blood; GVHD, graft-versus-host disease

Table 4. Risk factors for 1-year and 3-year survivals of 65≤ years patients based on univariate and multivariate analyses

	1-year survival				3-year survival	
	Unvariate		Multivariate		Unvariate	
	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*	Odds ratio (95% CI)	*p*
Age	0.95 (0.75-1.20)	0.645			0.72 (0.49-1.07)	0.105
Body-Mass Index	0.98 (0.72-1.34)	0.896			0.81 (0.53-1.24)	0.328
ECOG Performance Status	0.43 (0.17-1.11)	0.082			**0.20 (0.04-0.97)**	**0.046**
Karnofsky Performance Status	**1.09 (1.01-1.17)**	**0.032**	**1.08 (1.00-1.17)**	**0.04**	1.12 (0.00-1.26)	0.071
HCT-CI	**0.93 (0.62-1.40)**	**0.727**			**0.84 (0.47-1.48)**	**0.541**
Disease						
AML or MDS	reference				reference	
ALL	1.94 (0.291-13.00)	0.493			2.58 (0.37-18.20)	0.340
ML	0.65 (0.11-3.96)	0.638			<0.01 (0.00-inf)	0.995
others	<0.01 (0.00-inf)	0.992			<0.01 (0.00-inf)	0.998
Disease status pre-SCT, CR/non-CR	**3.21 (1.01-10.20)**	**0.048**	3.23 (0.94-11.10)	0.06	4.04 (0.91-18.00)	0.067
Donor source						
related-PB	reference				reference	
unrelated-PB	0.83 (0.06-11.30)	0.891			<0.01 (0.00-inf)	0.994
related-BM	>1×10^6 (0.00-inf)	0.991			<0.01 (0.00-inf)	0.997
unrelated-BM	1.67 (0.25-11.10)	0.597			2.17 (0.26-17.90)	0.473
CB	1.31 (0.36-4.73)	0.681			1.08 (0.22-5.33)	0.992
Acute GVHD, Grade II-IV/0-I	0.713 (0.21-2.39)	0.583			0.48 (0.09-2.58)	0.394

ECOG, Eastern Cooperative Oncology Group; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; ML, malignant lymphoma; SCT, stem cell transplantation; CR, complete remission; PB, peripheral blood; BM, bone marrow; CB, cord blood; GVHD, graft-versus-host disease

allo-SCT on OS declined with group age, and a significant difference was no longer observed between the CR and non-CR groups in 65-69 and ≥70 years old patients. However, the number of patients ≥70 years old is as small as 13; therefore, the lack of significant difference may be observed. As a result, we divided our cohort into two groups starting from 65 years old, which is considered the "elderly" in general society[20]. Interestingly, a large difference in the OS was found in patients <65 years old in the CR and non-CR groups, but the difference was smaller in patients ≥65 years old (**Figure 2F**). Moreover, we examined the causes of differences in the effect of pre-transplant disease status on OS between these age groups. Firstly, focusing on the CIR in our cohort, the CIR was higher in the non-CR group than in the CR group in both 60-64 years old and ≥65 years old groups, but the difference was smaller in the ≥65 years old group (**Figure 3F**). While the TRM for the non-CR group was higher for 60-64 years old patients, the TRM for the non-CR group was higher for ≥65 years old patients. This data suggests that at an age of <65 years old, in the non-CR group, the treatment intensity before allo-SCT could be increased to perform allo-SCT while in remission; however, the risk of complications and organ damage could increase, resulting in an increased TRM following allo-SCT[21-23]. While both strengthening the treatment intensity to prevent disease recurrence and keeping patients' general conditions are important to obtain better survival, the determining the setting of allo-SCT based on these two factors is challenging. Our data revealed that KPS and ECOG-PS are more important prognostic factors for OS than disease status prior to allo-SCT, especially in the ≥65 years old group, and the rapid shift to transplantation might provide much better OS in such patients (**Figure 5**).

Importantly, it is very hard to clarify the cause of poor PS (both ECOG-PS and KPS) because underlying disease, disease status prior to allo-SCT, and comorbidities are closely related to each other in allo-SCT[24]. Based on our data, there was no statistically significant relationship between PS and underlying disease, disease status prior to allo-SCT, and HCT-CI (data was not shown). Therefore, we assume PS could be one of the surrogate makers to comprehend the complicated status of older patients, and PS could be a useful indicator of better prognosis following allo-SCT for these patients.

Although the reason why KPS was the only risk factor for 1-year OS and ECOG-PS was the only risk factor for 3-year OS is not clear, the *p* values of ECOG-PS and KPS for survival were close to 0.05 (**Table 4**). This may indicate that much finer evaluation, such as using the KPS, could be more useful especially for early phases (1-year) of post-transplantation.

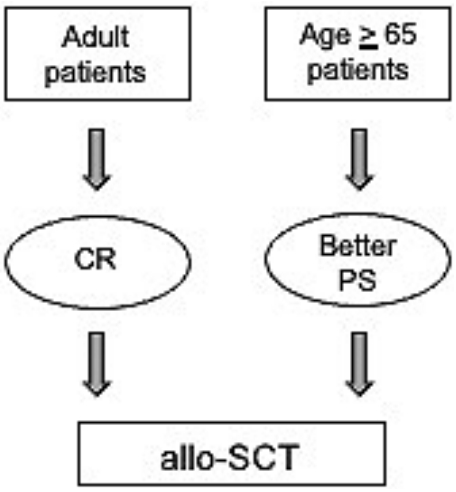

Figure 5. Stratification of transplantation for older patients
While allogeneic stem cell transplantation (allo-SCT) in complete remission (CR) generally provides favorable transplant outcome, allo-SCT with better performance status (PS) regardless of remission status prior to transplantation could contribute to better transplant outcome especially for older (≥ 65-year) patients according to this study.

Moreover, in the future, chemotherapy-reduced/free treatment strategies that combine new agents (e.g., molecular-targeted drug[25], bispecific CD19-directed CD3 T-cell engager[26], and chimeric antigen receptor T-cells[27]) to obtain CR before transplantation while maintaining better PS could be possible. These new treatments would lead to much better transplant outcomes.

Notably, most patients (n=87, 83%) were underweight (BMI <18.5) compared to a previous study for Japanese people[28]. It is reported that normal weight (BMI 18.5-23.9) and underweight contributed to better OS compared to overweight (BMI >24.0)[28]. Our cohort had no patient that was overweight, suggesting that our data could be potentially biased.

Despite the small sample size, and retrospective single-institutional experiences, our study suggests that PS before transplantation could be a useful prognostic factor for older patients. Therefore, PS might be one of the useful indicators for patients to make a decision on allo-SCT, especially for older patients. Therefore, we try to introduce exercise a tolerance test prior to allo-SCT to evaluate patients' activity in our institution. And we also try to introduce physical exercise for patients prior to allo-SCT to improve PS and the outcome of transplantation. Our findings should be confirmed by future prospective studies in a larger group of patients.

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Author Contributions

Contribution: T. Shima coordinated the project, performed the allo-SCT, designed and analyzed the data, and wrote the manuscript; K.T., S.U., T.Y., M.M., M.H., Y.M. and T.K. performed allo-SCT and reviewed the manuscript; M.N. organized patient information; and T.E. performed SCT, designed the study, and edited the manuscript.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

References

1. Hsu J, Chen Z, Shore T, Gergis U, Mayer S, Phillips A, et al. Outcomes of allogeneic stem cell transplant for elderly patients with hematologic malignancies. Biol Blood Marrow Transplant. 2020; **26**: 789-97.
2. Bron D, Ades L, Fulop T, Goede V, Stauder R; Elderly Task Force in Hematology EHA SWG. Aging and blood disorders: new perspectives, new challenges. Haematologica. 2015; **100**: 415-7.
3. Estey EH. Acute myeloid leukemia: 2013 update on risk-stratification and management. Am J Hematol. 2013; **88**: 318-27.
4. Podoltsev NA, Stahl M, Zeidan AM, Gore SD. Selecting initial treatment of acute myeloid leukaemia in older adults. Blood Rev. 2017; **31**: 43-62.
5. Duarte RF, Sánchez-Ortega I. HSCT in elderly patients. The EBMT Handbook-Hematopoietic Stem Cell Transplantation and Cellular Therapies, 7th edition. 2019. https://www.ncbi.nlm.nih.gov/books/NBK553964/
6. Lipof JJ, Loh KP, O'Dwyer K, Liesveld JL. Allogeneic hematopoietic cell transplantation for older adults with acute myeloid leukemia. Cancers (Basel). 2018; **10**: 179.
7. Muffly L, Pasquini MC, Martens M, Brazauskas R, Zhu X, Adekola K, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood. 2017; **130**: 1156-64.
8. Aoki J, Kanamori H, Tanaka M, Yamasaki S, Fukuda T, Ogawa H, et al. Impact of age on outcomes of allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning in elderly patients with acute myeloid leukemia. Am J Hematol. 2016; **91**: 302-7.
9. Basak GW, Sánchez-Ortega I, Beohou E, van der Werf S, Labopin M, van Biezen A, et al. Allogeneic hematopoietic cell transplantation in elderly patients aged 65 and older: A Retrospective Analysis By the Complications and Quality of Life Working Party of the EBMT. Blood. 2016; **128**: 681.
10. Rashidi A, Ebadi M, Colditz GA, DiPersio JF. Outcomes of allogeneic stem cell transplantation in elderly patients with acute myeloid leukemia: a systematic review and meta-analysis. Biol Blood Marrow Transplant. 2016; **22**: 651-7.
11. Giralt S, Ballen K, Rizzo D, Bacigalupo A, Horowitz M, Pasquini M, et al. Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2009; **15**: 367-9.
12. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013; **48**: 452-8.
13. Hahn T, McCarthy PL Jr, Hassebroek A, Bredeson C, Gajewski JL, Hale GA, et al. Significant improvement in survival after allogeneic hematopoietic cell transplantation during a period of significantly increased use, older recipient age, and use of unrelated donors. J Clin Oncol. 2013; **31**: 2437-49.
14. Zhao Y, Song Y, Yang F, Li F, Yang D, Wu T. Better outcomes of allogeneic hematopoietic stem cell transplantation with reduced-intensity conditioning in elderly patients with hematological malignancies. Blood. 2021; **138** (Suppl 1): 4864.
15. Armand P, Gibson CJ, Cutler C, Ho VT, Koreth J, Alyea EP, et al. A disease risk index for patients undergoing allogeneic stem cell transplantation. Blood. 2012; **120**: 905-13.
16. Murdock HM, Kim HT, Denlinger N, Vachhani P, Hambley B, Manning BS, et al. Impact of diagnostic genetics on remission MRD and transplantation outcomes in older patients with AML. Blood. 2022; **139**: 3546-57.
17. Moukalled NM, Kharfan-Dabaja MA. What is the role of a second allogeneic hematopoietic cell transplant in relapsed acute myeloid leukemia?. Bone Marrow Transplant. 2020; **55**: 325-31.
18. Sorror ML, Appelbaum FR. Risk assessment before allogeneic hematopoietic cell transplantation for older adults with acute myeloid leukemia. Expert Rev Hematol. 2013; **6**: 547-62.
19. Lazarevic VL. Acute myeloid leukaemia in patients we judge as being older and/or unfit. J Intern Med. 2021; **290**: 279-93.
20. Singh S, Bajorek B. Defining 'elderly' in clinical practice guidelines for pharmacotherapy. Pharm Pract (Granada). 2014; **12**: 489.
21. Ravanat JL, Remaud G, Cadet J. Measurement of the main photooxidation products of 2'-deoxyguanosine using chromatographic methods coupled to mass spectrometry. Arch Biochem Biophys. 2000; **374**: 118-27.
22. Grochow LB. Parenteral busulfan: Is therapeutic monitoring still warranted?. Biol Blood Marrow Transplant. 2002; **8**: 465-7.
23. De Lima M, Couriel D, Thall PF, Wang X, Madden T, Jones R, et al. Once-daily intravenous busulfan and fludarabine: clinical and pharmacokinetic results of a myeloablative, reduced-toxicity conditioning regimen for allogeneic stem cell transplantation in AML and MDS. Blood. 2004; **104**: 857-64.
24. Penack O, Peczynski C, Mohty M, Yakoub-Agha I, de la Camara R, Glass B, et al. Association of pre-existing comorbidities with outcome of allogeneic hematopoietic cell trans-

plantation. A retrospective analysis from the EBMT. Bone Marrow Transplant. 2022; **57**: 183-90.
25. Chi SG, Minami Y. Emerging targeted therapy for specific genomic abnormalities in acute myeloid leukemia. Int J Mol Sci. 2022; **23**: 2362.
26. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera JM, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017; **376**: 836-47.
27. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018; **378**: 439-48.
28. Yu J, Lin S, Luo Y, Shi J, Tan Y, Lai X, et al. Obesity is correlated with poor outcome after allogeneic hematopoietic stem cell transplantation in patients with acute leukemia. Jpn J Clin Oncol. 2020; **50**: 889-96.

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