European Group for Blood and Marrow Transplantation score correlates with outcomes of older patients undergoing allogeneic hematopoietic stem cell transplantation

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Abstract

Background: Acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are hematological diseases predominantly occurring in older patients. Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the curative therapy for refractory AML or high-risk MDS, old age is often a hurdle to the procedure. We conducted a retrospective study to analyze the prognostic factors predicting outcomes of older patients undergoing allo-HSCT for acute leukemia and MDS.

Methods: We collected data from patients diagnosed with acute leukemia or MDS, who underwent allo-HSCT at >50 years of age and reviewed clinical characteristics, including age, sex, underlying disease, European Group for Blood and Bone Marrow Transplantation (EBMT) risk score, and presence of acute graft-versus-host disease (aGVHD) or chronic GVHD (cGVHD). The Cox proportional hazard model was adopted to explore the independent prognostic factors for overall survival (OS), progression-free survival (PFS), and non-relapse mortality (NRM).

Results: A total of 85 older patients were included, with the median age at allo-HSCT being 55 years. The significant prognostic factors for worse OS or PFS were an EBMT risk score > 3 and grade III–IV aGVHD, while patients with moderate to severe cGVHD would have better OS or PFS. Interestingly, it is not cGVHD but grade III–IV aGVHD that significantly correlated with NRM.

Conclusion: This cohort study suggests that an EBMT risk score >3 and grade III–IV aGVHD predict poor outcomes, and careful management of GVHD may allow better survival for older patients undergoing allo-HSCT.

Keywords: Acute leukemia; Allogeneic hematopoietic stem cell transplantation; Myelodysplastic syndrome; Older patient

1. INTRODUCTION

Hematological malignancies are common in the elderly, and acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) are more popular in population of this age.[1] In Taiwan, the median age of diagnosis for AML in men and women is 62 years and 59 years, respectively. Furthermore, according to the American Cancer Society's Cancer Statistics Center report, the average age of patients with AML is 68 years in America. Older patients with AML or MDS would have poor prognosis and survival when compared with younger patients.[2] AML in older patients would have more unfavorable cytogenetics, frequently express drug resistance, respond less well to chemotherapy, and be more likely preceded by MDS. MDS is a malignant disease predominantly encountered in older patients, with a median age of approximately 75 years at diagnosis, and more than 80% of the patients with the diagnosis are older than 60 years.[2] In addition to AML and MDS, elderly patients with acute lymphoid leukemia (ALL) also had worse outcomes compared with young adults and adolescents. Although allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the curative therapy for AML, ALL, or high-risk MDS, old age had been a limitation to access this procedure. The introduction of reduced-intensity condition (RIC) or non-myeloablative conditioning regimens allows more older patients to undergo allo-HSCT, with reduced toxicities and transplantation-related mortality. However, the relapse and disease control rates are still major concerns with the use of less intensive conditioning regimens. Furthermore, as the impact of acute and chronic graft-versus-host disease (aGVHD and cGVHD) on non-relapse mortality (NRM) are not well known in older patients undergoing allo-HSCT. Here, we conducted a retrospective study to analyze the prognostic factors predicting outcomes of older patients undergoing allo-HSCT for acute leukemia or MDS at our institution in a 10-year period.

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2. METHODS

2.1. Study patient population

We retrospectively reviewed data of patients diagnosed with acute leukemia or MDS who underwent allo-HSCT at more than 50 years of age from January 2003 to December 2014 in Taipei Veterans General Hospital in Taiwan. Data of patient's clinical characteristics were collected, including sex, age, biological data, chronic underlying disease, healthy habit, nutrition status, comorbidities, type of allogeneic donors, disease diagnosis before transplantation, conditioning regimens, human leukocyte antigen (HLA) typing, European Group for Blood and Bone Marrow Transplantation (EBMT) risk scores,[3] and presence of aGVHD or cGVHD. Outcome analysis included overall survival (OS), progression-free survival (PFS), and NRM. OS is defined as the time from transplantation to death from any cause or lost follow-up. PFS indicates the length of time from transplantation to disease progression or death from any cause. NRM is the time from transplantation to death without disease relapse or progression. All patients were regularly followed until October 2015. The retrospective research was approved by the institutional ethical committee in agreement with the 1975 Declaration of Helsinki, revised in 2008.

2.2. Transplant details and conditioning regimens

Donor's source choices were matched sibling donors, or alternative donors, including matched unrelated donors, or haploidentical sibling donors. Selecting the sibling donors for allo-HSCT was based on low to intermediate resolution of HLA typing (HLA–A, HLA–B, HLA–DR, or HLA–C), while high resolution of HLA typing was preserved for unrelated donor selections. Myeloablative conditioning regimen consisted of intravenous busulfan (3.2 mg/kg/day for 4 days) and cyclophosphamide (60 mg/kg/day for 2 days) or cyclophosphamide (60 mg/kg/day for 2 days) combined with total body irradiation (TBI) of 12 Gy. Non-myeloablative conditioning regimen consisted of fludarabine, cyclophosphamide, and TBI < 2 Gy, while the RIC regimens consisted of fludarabine combined with alkylating agents, such as melphalan or busulfan.

2.3. GVHD prophylaxis and treatment

Prophylaxis against aGVHD consisted of cyclosporine with dosage titrated to keep trough plasma level at 100–250 μg/L, combined with short course low-dose methotrexate given with dosage of 15 mg/m^2 on day +1 and then10 mg/m^2 on days +3, +6, and +11 after allo-HSCT. Recipients of unrelated donor transplants would receive additional rabbit anti-thymocyte globulin (2–3 mg/kg/day) for 2 days before allo-HSCT. The aGVHD was evaluated by the system of Glucksberg et al.,[4] while severity of the cGVHD was assessed by National Institute of Health scoring system, defining the complications as mild, moderate, and severe.[5] Patients who developed greater than grade II aGVHD, alloimmune-related lung disease, or severe cGVHD would usually receive methylprednisolone of 1–2 mg/kg/day and other immunosuppressants depending on clinical conditions.

2.4. Infection prophylaxis during transplantation

Fluconazole or echinocandin for fungal infection prophylaxis was a routine in this cohort. An antifungal agent was administrated at the beginning of conditioning and would be maintained in the whole transplantation course until successful engraftment. Ganciclovir was initiated when cytomegalovirus (CMV) reactivation was detected by weekly surveillance using a quantitative real-time polymerase chain reaction method. After engraftment, trimethoprim-sulfamethoxazole was given for prophylaxis against *Pneumocystis jiroveci* infection in parallel with use of immunosuppressants for prophyalxis and treatment GVHD.

2.5. Study endpoints and statistical analysis

Patients' biological data, such as sex, age, comorbidities, conditioning regimens, donor sources, diagnosis before transplantation, GVHD, and EBMT score, were presented as the total number (n) and proportion (%). Continuous variables were reported as medians and interquartile ranges (IQR). Univariate and multivariate analyses were conducted using Cox proportional hazard models adjusted with age, sex, and other comorbidities to identify the independent predictors for OS, PFS, and NRM. All variables with a p-value <0.1 in the univariate analysis were further put into the multivariate analysis, and a p-value <0.05 in multivariate analysis was considered statistically significant. The survival analyses according to independent predictors were demonstrated by the Kaplan-Meier method. All analyses were conducted using SPSS statistical software version 17.0 (SPSS, Chicago, IL).

3. RESULTS

3.1. Patients' characteristics

A total of 85 patients undergoing allo-HSCT at age > 50 years were collected for analysis. The median age of this cohort was 55 years (IQR, 52–59), and the median follow-up time after allo-HSCT was 12.4 months (IQR, 4.0–29.2). Patients with AML comprised 74% of this cohort. Totally, 51% patients underwent unrelated donor transplantation; 58% adopted myeloablative conditioning regimens; and 48% had an EBMT risk score >3. Grade III–IV aGVHD developed in 16% of patients, 26% had moderated to severe cGVHD, and 65% had CMV reactivation. The OS in this cohort was 22.2 months (Fig. 1). Detailed information is shown in Table 1.

3.2. Predictors relevant to overall survival analysis for older patients after allogeneic hematopoietic stem cell transplantation

The one- and two-year OS rate was 55.2% and 47.8%, respectively. Table 2 shows the OS analysis for older patients undergoing allo-HSCT. The univariate analysis revealed that the potential predictors relevant to inferior OS were EBMT risk score >3 (hazard ratio [HR], 2.03; 95% CI, 1.21–3.69; p = 0.019) and development of grade III–IV aGVHD (HR, 3.88;

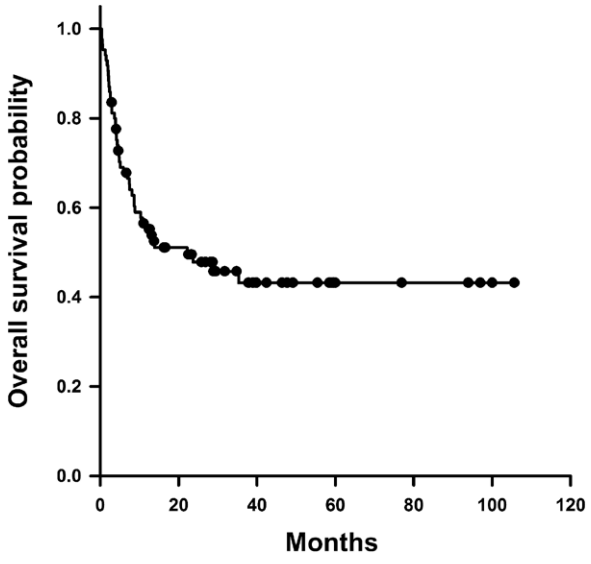

Fig. 1. Overall survival in elderly patients after allogeneic hematopoietic stem cell transplantation

Table 1.

Baseline characteristics of elderly patients receiving allogeneic hematopoietic stem cell transplantation (n = 85)

Characteristics	
Age at SCT, years, medium (interquartile-range)	55 (52–59)
Sex, male, n (%)	44 (51)
Diagnosis, n (%)	
Acute myeloid leukemia	63 (74)
Acute lymphoid leukemia	10 (12)
Chronic myeloid leukemia with accelerated phase	3 (4)
Myelodysplastic syndrome	9 (10)
Donor source, n (%)	
Matched sibling donors	39 (45)
Haploidentical sibling donors	3 (4)
Unrelated donors	43 (51)
HLA typing, n (%)	
Full match	48 (57)
Mismatch	37 (43)
Gene features, n (%)	
Activation of Hox 11	4 (5)
BCR-ABL	4 (5)
dupMLL(11q23)	4 (5)
FLT3-ITD/NPM1	8 (9)
FLT3-ITD	1 (1)
NPM1	3 (4)
No identified	61 (71)
Chromosome, n (%)	
t(8;21)(q22;q22)	3 (4)
t(9;22)(q34;q11)	4 (5)
t(9;11)(p22;q23)	2 (2)
Monosomy 5 or del(5q)	1 (1)
Monosomy 7 or del(7q)	4 (5)
Trisomy[a]	3 (4)
Others[b]	4 (5)
Complex karyotype	14 (16)
Normal karyotype	36 (42)
No metaphase	14 (16)
Chemotherapy before transplantation, n (%)	
High dose cytarabine	24 (28)
High dose cytarabine + anthracycline	19 (23)
Continuous cytarabine infusion + antracycline	17 (20)
Low-dose cytarabine	1 (1)
Hydroxyurea	4 (5)
Hypomethylation agents	5 (6)
Hyper-CVAD/MTX/AraC or E-SHAP[c]	8 (9)
High dose steroid + vincristine	1 (1)
Fludarabine+cytarabine+ G-CSF+idarubicin	2 (2)
Supportive care without chemotherapy	4 (5)
Disease status before transplantation, n (%)	
Acute leukemia	
Complete remission	38 (45)
Non-complete remission	25 (29)
Acute lymphoid leukemia	
Complete remission	9 (10)
Non-complete remission	1 (1)
Myelodysplastic syndrome	
Stable disease	4 (5)
Progression	5 (6)
Chronic myeloid leukemia with accelerated phase	3 (4)
Conditioning regimens, n (%)	
Fludarabine-based conditioning	36 (42)
TBI-based conditioning	9 (10)
Myeloablative conditioning	49 (58)
GVHD status, n (%)	
Acute GVHD, grade III–IV	14 (16)
Chronic GVHD	36 (42)
Moderate to severe chronic GVHD	22 (26)
EBMT risk score > 3, n (%)	38 (48)
Cytomegalovirus reactivation, n (%)	55 (65)
Smoking, n (%)	11 (13)
Diabetic mellitus, n (%)	12 (14)
Albumin > 3.5 g/dl, n (%)	71 (83)

[a]trisomy: 47,XY,+8/47,XY,+add(8)(p23); 47,XY,+11; 47,XY,+13.

[b]Others: 46,XY,add(11)(p15); 46,XY,der(7)t(1;7)(q10;p10); 46,XY,dic(1;15)(p11;p11); 46,XX,t(4;8)(p16;q22).

[c]hyperfractionated cyclophosphadmide, vincristine, doxorubicin, dexamethasone, alternatively methotrexate and cytarabine (Hyper-CVAD/MTX/AraC) or etoposide, methylprednisolone, cisplatin and cytarabine (E-SHAP).

SCT = stem cell transplantation; HLA = human leukocyte antigen; BCR-ABL = breakpoint cluster region-Abelson; dupMLL = duplication mixed lineage leukemia; FLT3-ITD = FMS-like tyrosine kinase-internal tandem duplication; NPM1 = nucleophosmin; TBI = total body irradiation; GVHD = graft-versus-host disease; EBMT = European Group for Blood and Bone marrow Transplantation.

95% CI, 1.96–7.70; $p < 0.001$). Patients with moderate to severe cGVHD would have superior OS (HR, 0.43; 95% CI, 0.19–0.92; $p = 0.032$). By multivariate analysis adjusted by sex and age, the significant predictors for inferior OS were EBMT risk score >3 (HR, 2.10; 95% CI, 1.43–3.88; $p = 0.017$) and grade III–IV aGVHD development (HR, 4.36; 95% CI, 2.133–8.93; $p < 0.001$). Moderate to severe cGVHD development significantly correlated with superior OS (HR, 0.455; 95% CI, 0.20–0.99; $p = 0.048$). Other relevant variables, such as >60 years of age, myeloablative conditioning regimens, unrelated donor stem cell source, and CMV reactivation were not a determinant of OS. The OS for patients with EBMT risk score ≤3 was 35.3 months, while those with EBMT risk score >3 was 4.7 months. By log rank test, the OS curve of patients with EBMT risk score ≤3 was significantly better than those with EBMT risk score >3 ($p = 0.017$). The survival curve according to EBMT risk score is presented in Fig. 2.

3.3. Predictors relevant to progression-free survival analysis for older patients after allogeneic hematopoietic stem cell transplantation

The one- and two-year PFS was 47.6% and 38.4%, respectively. The significant predictors for PFS were quite similar to those for OS. In the univariate analysis, an EBMT risk score >3 (HR, 2.20; 95% CI, 1.28–3.76; $p = 0.004$) and grade III–IV aGVHD development (HR, 4.16; 95% CI, 2.18–7.92; $p < 0.001$) correlated with inferior PFS. Patients with moderate to severe cGVHD would have superior PFS (HR, 0.44; 95% CI, 0.22–0.86; $p = 0.017$). By multivariate analysis adjusted by sex and age, the significant predictors for inferior PFS were EBMT risk score >3 (HR, 2.27; 95% CI, 1.37–3.94; $p = 0.003$) and grade III–IV aGVHD development (HR, 4.70; 95% CI, 2.41–9.17; $p < 0.001$). Moderate to severe cGVHD occurrence significantly correlated with better PFS (HR, 0.46; 95% CI, 0.23–0.90; $p = 0.025$). The detailed information relevant to PFS is shown in Table 3.

3.4. Predictors relevant to non-relapse mortality analysis for older patients after allogeneic hematopoietic stem cell transplantation

We further analyzed the variables related to NRM. In the univariate analysis, patients with EBMT risk score >3 (HR, 2.03; 95% CI, 0.96–4.31; $p = 0.063$) and grade III–IV aGVHD (HR,

Table 2.

Overall survival analysis for elderly patients after allogeneic hematopoietic stem cell transplantation

	Univariate analysis		Multivariate analysis	
Predictive variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age > 60 years	0.949 (0.468–1.923)	0.885	1.155 (0.565–2.361)	0.693
Sex, male	0.986 (0.545–1.784)	0.964	0.979 (0.537–1.783)	0.944
HLA mismatch	1.434 (0.793–2.596)	0.233		
Unrelated donor source	1.558 (0.849–2.861)	0.153		
Fludarabine-based conditioning	1.063 (0.585–1.931)	0.841		
TBI-based conditioning	1.679 (0.748–3.768)	0.209		
Myeloablative conditioning	0.933 (0.515–1.690)	0.819		
EBMT risk score >3	2.036 (1.121–3.695)	0.019	2.108 (1.143–3.888)	0.017
Smoking	0.904 (0.381–2.145)	0.818		
Diabetic mellitus	0.495 (0.177–1.386)	0.181		
Albumin >3.5 g/dl	0.767 (0.356–1.652)	0.498		
Acute GVHD, grade III–IV	3.885 (1.960–7.703)	<0.001	4.366 (2.133–8.937)	<0.001
Moderate to severe chronic GVHD	0.430 (0.199–0.928)	0.032	0.455 (0.208–0.993)	0.048
Cytomegalovirus reactivation	1.037 (0.556–1.936)	0.909		

HR = hazard ratio; CI = confidence interval; HLA = human leukocyte antigen; TBI = total body irradiation; EBMT = European Group for Blood and Marrow Transplantation; GVHD = graft-versus-host disease.

4.77; 95% CI, 2.09–10.91; $p < 0.001$) would have relatively higher risk for NRM. In the multivariate analysis, only grade III–IV aGVHD (HR, 5.87; 95% CI, 2.43–14.13; $p < 0.001$) was found to be a significant predictor for NRM, while there was a trend for EBMT risk score >3 (HR, 2.41; 95% CI, 0.994–4.63; $p = 0.052$) predicting higher NRM. Of note, moderate to severe cGVHD (HR, 0.89; 95% CI, 0.354–1.84; $p = 0.614$) was not significantly correlated with NRM. The one- and two-year NRM was 29.9% and 37.1%, respectively. The detailed information for NRM is presented in Table 4.

4. DISCUSSION

Prospective studies focusing on older patients undergoing allo-HSCT are rare. Several recent retrospective cohort studies demonstrated that aging is no more a barrier for allo-HSCT.[6–9] A retrospective multicenter study divided 1,333 older patients with MDS or secondary acute leukemia undergoing allo-HSCT into the age groups of 50–60 years and older than 60 years for analysis and concluded that advanced age was not an adverse factor influencing the outcomes.[7] Another nationwide retrospective study in Japan examined the impact of age on outcomes of allo-HSCT and categorized patients into groups with age of 50–54, 55–59, 60–64, and >65 years old. The three-year OS and NRM were not significantly different among these four age groups.[8] Brunner et al.[9] even reported that allo-HSCT was a safe and effective option for carefully selected patients >70 years. They also showed the similar finding that age >60 years was not a significant adverse factor for allo-HSCT in either univariate or multivariate analysis. Conclusively speaking, older age is no more an absolute contraindication for allo-HSCT in current practice.

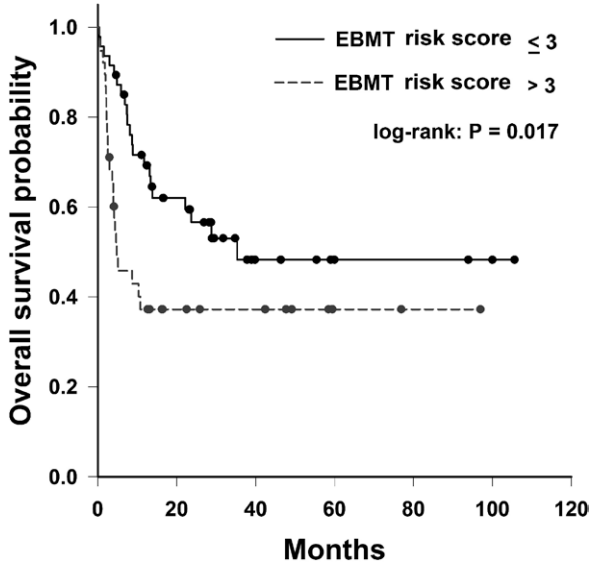

Fig. 2. Overall survival analysis according to European Group for Blood and Marrow Transplantation risk score

Pretransplant evaluation is important in selecting older patients for allo-HSCT, and several studies had investigated practical assessment tools for this population. Sorror et al.[10] had proposed hematopoiesis cell transplantation-specific comorbidity index (HCT-CI) as a scoring system for pretransplant risk assessments, and it was validated as a useful prognostic factor for patients undergoing allo-HSCT.[11–13] HCT-CI was further applied for older patients with allo-HSCT. In a retrospective review from 18 collaborating institutions, HCT-CI >0 significantly correlated with poor survival in patients >60 years receiving non-myeloablative allo-HSCT.[14] Another study reviewing 757 older patients undergoing allo-HSCT also found that HCT-CI ≥3 was an independent poor prognostic factor for OS and NRM.[8] In addition to HCT-CI, we identified a pretransplant risk factor for this population—EBMT risk score >3. The EBMT risk score comprised disease stage, age of patient, time interval from diagnosis to transplant, donor types, and donor-recipient sex mismatch.[3] This score was initially created in 1998 by the Chronic Myeloid Leukemia Working Party of the European Group for Blood and Marrow Transplantation.[15] It had been modified and validated in various hematological diseases during the following years. A high EBMT risk score is significantly associated with NRM and poor OS.[3,16–20] Our study validated the value of EBMT risk score in older patients undergoing allo-HSCT, and an EBMT risk score >3 was significantly associated with poor outcomes in OS, PFS, and NRM. This risk score is relatively simple and easy to apply clinically. In addition to HCT-CI, it provides rapid risk evaluation before transplantation in older patients.

GVHD is an important issue for older patients undergoing allo-HSCT.[21] Although GVHD are harmful and intensive

Table 3.

Progression-free survival analysis for elderly patients after allogeneic hematopoietic stem cell transplantation

	Univariate analysis		Multivariate analysis	
Predictive variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age > 60 years	0.895 (0.471–1.699)	0.753	1.055 (0.551–2.018)	0.872
Sex (Male)	1.401 (0.820–2.395)	0.217	1.400 (0.815–2.407)	0.223
HLA mismatch	1.218 (0.716–2.074)	0.467		
Unrelated donor source	1.423 (0.832–2.433)	0.198		
Fludarabine-based conditioning	1.071 (0.628–1.825)	0.802		
TBI-based conditioning	1.620 (0.762–3.445)	0.210		
Myeloablative conditioning	0.799 (0.471–1.357)	0.407		
EBMT risk score >3	2.202 (1.289–3.763)	0.004	2.278 (1.317–3.942)	0.003
Smoking	1.439 (0.721–2.874)	0.302		
Diabetic mellitus	0.728 (0.329–1.609)	0.432		
Albumin >3.5	0.574 (0.296–1.115)	0.101		
Acute GVHD (grade III–IV)	4.162 (2.186–7.923)	<0.001	4.703 (2.415–9.175)	<0.001
Moderate to severe chronic GVHD	0.444 (0.228–0.863)	0.017	0.461 (0.234–0.906)	0.025
Cytomegalovirus reactivation	1.161 (0.660–2.042)	0.604		

HR = hazard ratio; CI = confidence interval; HLA = human leukocyte antigen; TBI = total body irradiation; SCT = stem cell transplantation; EBMT = European Group for Blood and Marrow Transplantation; GVHD = graft-versus-host disease.

Table 4.

Non-relapse mortality analysis for elderly patients after allogeneic hematopoietic stem cell transplantation

	Univariate analysis		Multivariate analysis	
Predictive variables	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Age > 60 years	1.101 (0.467–2.597)	0.826	1.324 (0.554–3.164)	0.527
Sex, male	1.321 (0.624–2.798)	0.467	1.442 (0.663–3.137)	0.356
HLA mismatch	1.651 (0.784–3.476)	0.187		
Unrelated donor source	1.743 (0.804–3.780)	0.159		
Fludarabine-based conditioning	1.206 (0.574–2.536)	0.621		
TBI-based conditioning	1.938 (0.736–5.104)	0.180		
Myeloablative conditioning	0.903 (0.429–1.899)	0.787		
EBMT >3	2.039 (0.963–4.314)	0.063	2.416 (0.994–4.631)	0.052
Smoking	1.626 (0.656–4.031)	0.294		
Diabetic mellitus	0.597 (0.180–1.978)	0.398		
Albumin >3.5 g/dl	0.784 (0.298–2.066)	0.623		
Acute GVHD, grade III–IV	4.779 (2.092–10.91)	<0.001	5.872 (2.439–14.134)	<0.001
Moderate to severe chronic GVHD	0.809 (0.354–1.846)	0.614		
Cytomegalovirus reactivation	0.947 (0.437–2.054)	0.981		

HR = hazard ratio; CI = confidence interval; HLA = human leukocyte antigen; TBI = total body irradiation; EBMT = European Group for Blood and Marrow Transplantation; GVHD = graft-versus-host disease.

immunosuppressants are often required as organ damage worsens, it may be beneficial in reducing disease relapse via the mechanism of graft-versus-leukemia (GVL) effect. Many studies had demonstrated that patients developing GVHD would have superior disease free survival and lower relapse rate.[22–24] With high risk of morbidity and mortality after GVHD development in elderly patients, the risk and benefit of GVHD versus GVL effect is still an equivocal issue for this patient group. A study performed by the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation reviewed 1,859 patients of AML with a median age of 56.3 years, and found that grade I aGVHD was associated with lower disease relapse rate, translating into a trend of superior OS.[25] Grade II aGVHD had no influence on OS, while grade III–IV aGVHD correlated with poor OS because of high risk of NRM.[25] Regarding cGVHD, limited cGVHD presented a tendency to lower disease relapse rate, translating into a significantly superior OS, while extensive cGVHD correlated with a lower risk of relapse but also higher NRM and thus had no significant influence on OS.[25] Our study confirms that grade III–IV aGVHD is associated with poor OS and higher risk of NRM. The EBMT risk score includes age and sex mismatch between the donor and recipient, which are associated with both risk of GVHD and beneficial GVL effect. However, in our study, severe acute GVHD is still a risk factor independent of EBMT risk score, indicating that the detrimental effects of severe acute GVHD outweighed the potential benefits of the associated GVL effect. Our finding revealed that moderate to severe cGVHD correlated with better PFS, not increasing NRM, translating into a significantly better OS. NRM in older patients is probably decreased by use of RIC regimens or non-myeloablative conditioning regimens and improved managements of cGVHD. Moreover, improved care of cGVHD may also allow GVL effects to be dominant for older patients receiving RIC or non-myeloablative conditioning regimens. The results of our study suggest that prevention of severe aGVHD and appropriate manipulation of cGVHD may be beneficial for older patients undergoing allo-HSCT. Of note, although moderate to severe GVHD may cause somehow morbidities for recipients, it seems to have little influence on older patients. In a study investigating the impact of age on functional status, quality of life, and survival in patients with GVHD, the authors concluded that older patients with moderate or severe cGVHD may cope

well with their limited physical activities and accordingly have a reasonable quality of life.[26]

The RIC or non-myeloablative conditioning regimens were introduced to fragile patients with multiple comorbidities, leading to a growing number of transplantations in older patients.[27] Although the RIC regimen reduces toxicities, complications, and NRM as transplantation, it increases the relapse rate due to relatively lower intensity of chemotherapy. These balanced effects usually result in lower NRM, higher relapse rates, and no significant difference in OS when compared myeloablative conditioning regimens in older patients.[7,28] A recent retrospective study from Fred Hutchinson Cancer Research Center and data from Luger et al.[29] showed similar OS and PFS in patients receiving RIC or myeloablative conditioning regimens.[30] The results of those studies lend support to our finding and suggest that the GVL effects may play an important role in older patients receiving RIC regimens.[25] Although prospective randomized studies are lacking, data from available literature suggest that the outcome of transplantation after RIC or myeloablative conditioning regimen is dependent on patient's performance status and comorbidities rather than advanced age alone.

In conclusion, we identified EBMT risk score >3 and grade III–IV aGVHD as adversely prognostic factors for OS, and PFS in older patients undergoing allo-HSCT. Development of moderate to severe cGVHD allows older patients to have better OS as well as PFS, and interestingly, it would not increase NRM significantly. Our finding indicates that the GVL effect is important for survival and disease control in older patients undergoing allo-HSCT. This cohort study suggests that an EBMT risk score >3 predicts poor outcomes and careful management of GVHD may lead to better survival of older patients undergoing allo-HSCT.

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