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Outcome and Prognostic Factors of High-Risk Acute Myeloid Leukemia After Allogeneic Hematopoietic Stem Cell Transplantation

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Background: Allogeneic transplantation remains one of the best therapies for high-risk acute myeloid leukemia (HR-AML).

Material/Methods: This study retrospectively analyzed 126 patients with HR-AML after allogeneic hematopoietic stem cell transplantation (allo-HCST).

Results: The disease-free survival (DFS) rates of 1 year and 3 years were 58.83% (95%CI: 50.75–68.20%) and 53.09% (95%CI: 44.59–63.22%) respectively. The cumulative relapse rates of 1 year and 3 years were 21.1% (95%CI: 14.4–28.8%) and 25.9% (95%CI: 18.1–34.5%) respectively. The cumulative incidences of III to IV acute graft-versus-host disease (aGVHD) for 100 days was 8.70% (95%CI: 4.6–14.5%). The cumulative rate of extensive chronic graft-versus-host disease (cGVHD) for 1-year was 4.1% (95%CI: 1.5–8.7%). The cumulative transplantation related mortality rate of 1 year and 3 years were 20.1% (95%CI: 13.6–27.6%) and 21.0% (95%CI: 14.3–28.6%) respectively. Univariate analysis revealed that lower overall survival was correlated with age, bacterial or fungal infection, disease status at transplantation, III–IV aGVHD, post-transplantation lymphoproliferative disorders (PTLD), white blood cell engraftment, and extramedullary involvement ($P<0.05$). The results of multivariate analysis were that the aforementioned factors were also related to lower overall survival except for PTLD ($P<0.05$). The results of univariate and multivariate analysis were that extramedullary involvement, III–IV aGVHD, and status pre-transplantation influenced DFS ($P<0.05$). The risk factors for relapse were status pre-transplantation and extramedullary involvement by univariate and multivariate analysis ($P<0.05$).

Conclusions: HR-AML has inferior prognosis. Our study indicated the necessity of achieving remission status prior to hematopoietic stem cell transplantation, and administration of preventive treatments on high-risk patients after hematopoietic stem cell transplantation. In addition, adequate prevention and treatment of complications are needed.

MeSH Keywords: **Disease-Free Survival • Graft *vs.* Host Disease • Hematopoietic Stem Cell Transplantation • Leukemia, Myeloid, Acute • Recurrence**

Abbreviations: **aGVHD** – acute graft-versus-host disease; **cGVHD** – chronic graft-versus-host disease

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Background

Acute myeloid leukemia (AML) is a malignant clonal tumor. Compared to favorable or intermediate AML, the treatment of high-risk AML (HR-AML) has many challenges [1]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been proven to be a post-remission therapy for HR-AML [2–4]. Advances in allo-HSCT have significantly reduced mortality, however, despite this, leukemia relapse still is a significant challenge for patients of HR-AML [5]. Patients with relapsed AML after transplantation usually have very poor prognosis [6,7].

Although many studies have been reported regarding HR-AML, quite a few of these reports have been very heterogeneous in terms of their definition of "high risk". Moreover, there have been few studies about prognosis and outcome for HR-AML after allo-HSCT. Owing to the aforementioned reasons, it is necessary to focus on identifying prognostic factors at transplantation, and devise strategies for prevention of relapse.

We retrospectively analyzed outcome and prognosis of HR-AML, and identified prognostic factors affecting outcomes.

Material and Methods

Patients

Medical records data of 126 patients who were diagnosed as HR-AML and underwent allo-HSCT between 05.01.2007 and 11.01.2018 at the Chinese PLA General Hospital were retrospectively analyzed in this research. The earliest time of diagnosis was 07.01.2007, and the earliest time of transplantation was 05.01.2008. Chinese PLA General Hospital ethical committee approved this study. Patients signed informed consent for gathering clinical information.

Selection criteria

HR-AML was defined according to institutional guidelines, the definition of HR-AML met at least 1 of the following criteria: 1) no remission or partial remission at transplantation; 2) patient in complete remission, but the complete remission was not the first; 3) adverse karyotype abnormalities according to cytogenetic stratification [8]; 4) relapse within 6 months after complete remission; 5) relapse more than 6 months after complete remission, but the original therapy could not make patients result in remission again; 6) leukemia with DNMT3a, TET2, or TP53 mutation [8–10].

Conditioning regimens

The conditioning regimens included busulfan (3.2 mg/kg/day, Days –10 to –8), cytarabine (4 g/m^2/day, Days –7 to –6), carmustine (250 mg/m^2, Day –5), cyclophosphamide (60 mg/kg/day, Days –5 to –2). Patients accepting haploidentical-related donor transplant or unrelated donor transplant were given anti-thymocyte globulin (ATG) (2.5 mg/kg/day, Days –4 to –2). Patients accepting HLA-matched sibling donor transplant were given the same conditioning regimen, but without ATG. If patients were not in complete remission at time of transplantation and did not suffer from II–IV aGVHD, they received prophylactic donor lymphocyte infusion (DLI).

Prophylaxis and management for graft-versus-host disease (GVHD)

Prophylaxis treatment consisted of mycophenolate mofetil (0.5 g, every 12 hours, on Day –1 for 28 days); cyclosporine (3 mg/kg, every 12 hours, starting on Day –9) and MTX (15 mg/m^2 on Day +1, 10 mg/m^2 on Days +3, +6, and +11). Grades II to IV aGVHD were treated with methylprednisolone 1–2 mg/kg/day, and the refractory aGVHD were treated with basiliximab. Extensive cGVHD was given prednisone 1 mg/kg/day alone or combined with mesenchymal stem cell.

Infection prevention and supportive care

All patients received acyclovir and cotrimoxazole for prophylaxis against cytomegalovirus and pneumocystis when absolute neutrophil count (ANC) was $<0.5\times10^9$/L. Red blood cell transfusions were administered to maintain hemoglobin levels >80 g/L. Patients were transfused with platelets if their platelets count was $<10\times10^9$/L, but if patients suffered from mucosa bleeding, organ bleeding or severe infection, platelet transfusion were administered to maintain platelet counts $>20\times10^9$/L. Patients was given recombinant human granulocyte macrophage colony stimulating factor after cell infusion.

Minimal residual disease (MRD) monitoring

Minimal residual disease (MRD) was monitored by bone marrow aspiration and biopsy which was conducted before transplantation and on Days 30, 60, 90, and 180 after transplantation by multiparameter flow cytometry and cytogenetics assays.

Treatment for relapse

HR-AML patients without hematologic relapse would be given DLI in 2 to 3 months after transplantation if they did not suffer from II–IV aGVHD. Patients with hematologic relapse received chemotherapy alone or combined with DLI or the second transplantation.

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Definition

AML diagnosis was according to previously described definitions [11,12]. The definition of complete remission was bone marrow blasts less than 5%, without extramedullary disease, and absolute platelet number >100×10^9/L, ANC >1.0×10^9/L, and no need of red cell infusions. The definition of relapse was more than 5% bone marrow blasts reappeared, blasts of the peripheral blood recurred, or extramedullary tumor developed. Grading of aGVHD and cGVHD was based on the previously described scoring system [13,14]. The definition of transplantation-related mortality was that mortality was attributed to transplantation-related toxicities, but not disease recurrence. The definition of disease-free survival (DFS) was that patients had survival with complete remission from transplantation. The definition of overall survival (OS) was that patients were dead of any reason from transplantation. The definition of neutrophil recovery was ANC >0.5×10^9/L. The definition of platelet recovery was absolute platelet number >20×10^9/L, and independence of platelet infusion.

Statistical analysis

Descriptive statistical analysis of variables was done, and one-way ANOVA was examined for more than 2 groups. Fisher's test or chi-square test were examined for the difference between categorical data. The variables were entered into multivariate analysis when *P* value less than 0.15 using univariate analysis. Univariate and multivariate analysis of variables influencing OS and DFS used Cox proportional hazards model. The Kaplan-Meier method was used to compared DFS and OS. The Fine and Gray competing risk regression methods was used to analyze recurrence, II–IV aGVHD, extensive cGVHD, and transplantation-related mortality after transplantation, and competing risks were considered. *P*-values were 2-sided with the significant value of $P<0.05$. The statistical software was SPSS 18.0 and R version 3.4.3.

Results

Patients and clinical characteristics

There were 126 patients (40 females and 86 males) included in this study and the basic patient features are illustrated in Table 1. The median follow-up time from transplantation was 17.0 months (range, 0.3–90.2 months). The median age of patients was 34 years (range, 19–66 years), the median age of donors was 37 years (range, 20–64 years). There were 101 cases that were haploidentical related transplantation cases, 24 cases that were matched sibling transplantations, and 1 case that was categorized as an unrelated transplantation. Disease status at transplantation was: 53 cases (42.10%) that were MRD positive, 30 cases (23.80%) that were MRD negative, and 43 cases (34.10%) that were none remission (NR) disease. The median dose of $CD34^+$ cells was 3.95×10^6 (2.46–13.31×10^6)/kg, the median dose of MNC cells was 9.99×10^8 (4.82–22.00×10^6)/kg. There were 123 patients who had successful neutrophil engraftment, and the median time of neutrophil recovery was 13 days (range, 9–26 days). Platelet recovery was reached in 113 patients, the median time of platelet recovery was 15 days (9–77 days); 13 cases (10.32%) had grade III–IV aGVHD; 7 cases (5.56%) had extensive cGVHD, and 8 cases (6.35%) were diagnosed as PTLD.

Overall survival

Fifty-two patients died and 74 patients survived. The OS rates of 3 years and 5 years were 57.55% (95%CI: 48.78–67.89%) and 55.04% (95%CI: 45.66–66.35%) respectively (Figure 1A). Among the patients with complete remission, compared to MRD negative group, the OS of the MRD positive group was shorter ($P<0.05$) (Figure 1B). As shown in Table 2, the result of univariate analysis was that lower OS was correlated with age at transplantation (≥40 versus <40 years), bacterial or fungal infection, status at transplantation (none remission group versus complete remission group), III–IV aGVHD (yes versus no), PTLD (yes versus no), white blood cell (WBC) engraftment (failure versus success) and extramedullary involvement ($P<0.05$). By multivariate analysis, the results were that age (≥40 versus <40 years), bacterial or fungal infection (with versus without), III–IV aGVHD (yes versus no), status at transplantation (none remission group versus complete remission group), WBC engraftment (failure versus success), and extramedullary involvement were linked with lower OS ($P<0.05$). Figure 2 show the survival analysis of prognostic factor.

Disease-free survival (DFS)

During the follow-up time after transplantation, the disease-free and alive patients were 68 out of 126 patients (53.97%). The DFS rates of 1 year and 3 years were 58.83% (95%CI: 50.75–68.20%) and 53.09% (95%CI: 44.59–63.22%) respectively (Figure 3A). Compared with the complete remission group, DFS was significantly lower in the none remission group (Figure 3B). By univariate and multivariate method, III–IV aGVHD, status at transplantation and extramedullary involvement influenced DFS ($P<0.05$) (Table 3). Figure 4 showed the survival analysis of DFS under 3 prognosis factors.

Relapse

Thirty-one cases experienced relapse. The cumulative rates of relapse for 1 year and 3 year were 21.1% (95%CI: 14.4–28.8%) and 25.9% (95%CI: 18.1–34.5%) respectively (Figure 5A). The time of leukemia relapse was 4.7 months (0.9–70.9 months).

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Table 1. Patient and transplantation characteristics of study population.

Characteristics	N	%
Patient age, median (range)	34 (19–66) years	
Donor age, median (range)	37 (20–64) years	
Patient gender		
Male	86	68.25
Female	40	31.75
Diagnosis		
M1	6	4.76
M2	51	40..48
M4	22	17.46
M5	21	16.67
MDS-AML	15	11.90
NA	11	8.73
Conditioning regimen		
Bu/Cy	107	84.92
FB	12	9.52
TBI/Cy	7	5.56
Status pre-transplantation		
MRD–	30	23.80
MRD+	53	42.10
NR	43	34.10
Donor		
Haploidentical related	101	80.16
Match related	24	19.05
Mismatch unrelated	1	0.79
ABO compatibility		
Yes	64	50.79
No	62	49.21
Cytogenetic risk group		
Favorable	17	13.49
Intermediate	88	69.84
Poor	11	8.73
No results	10	7.94
Donor gender		
Female	40	31.75
Male	86	68.25

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Table 1 continued. Patient and transplantation characteristics of study population.

Characteristics	N	%
III–IV aGVHD		
Yes	13	10.32
No	113	89.68
Extensive cGVHD		
Yes	7	5.56
No	119	94.44
PTLD		
Yes	8	6.35
No	118	93.65
Bacterial or fungal infection after transplantation		
Yes	47	37.30
No	79	62.70
Relapse after transplantation		
Yes	31	24.60
No	95	75.40
MNC median (range) $\times 10^8$/kg	9.99 (4.82–22.00)	
$CD34^+$ cell count median (range) $\times 10^6$/kg	3.95 (2.46–13.31)	
Neutrophil recovery(days) $>0.5\times 10^9$/l median (range)	13 (9–26)	
Platelets recovery(days) $>20\times 10^9$/l median (range)	15 (9–77)	
WBC at diagnosis (range)	10.29 (0.51–456.2)	
HB at diagnosis	81 (2–160)	
PLT at diagnosis	61.5 (4–309)	

PTLD – post-transplant lymphoproliferative disorder; AML – acute myeloblastic leukemia; MDS – myelodysplastic syndrome; aGVHD – acute graft-*vs.*-host disease; cGVHD – chronic acute graft-*vs.*-host disease; Bu – busulfan; Cy – cyclophosphamide; FB – fludarabine+busulfan; MNC – mononuclear cells count; CR – complete remission; NR – none remission; MRD – minimal residual disease; WBC – white blood cell; HB – hemoglobin; PLT – platelet.

Relapse only took place in 26 patients, and relapses combined with extramedullary involvement were seen in 5 patients. The result of univariate and multivariate are illustrated in Table 4. Factors influencing relapse included status at transplantation (none remission group versus complete remission group) and extramedullary involvement (yes versus no) ($P<0.05$). For salvage therapy, 9 patients received chemotherapy, 13 patients received chemotherapy combined with donor lymphocyte infusion, 3 patients received chemotherapies combined with second transplantation, and 6 patients were only given best supportive care. Six patients were alive, and 25 patients died of AML progression after treatment.

Transplantation-related mortality

Twenty-seven patients died from transplantation-related mortality, the 1-year and 3-year cumulative incidences of transplantation-related mortality were 20.1% (95%CI: 13.6–27.6%) and 21.0% (95%CI: 14.3–28.6%) respectively (Figure 5B). Among 27 cases, 2 cases died of refractory aGVHD, 21 cases died of infection, 1 case died of multiorgan failure, 2 cases died of PTLD, and 1 case died of acute heart failure.

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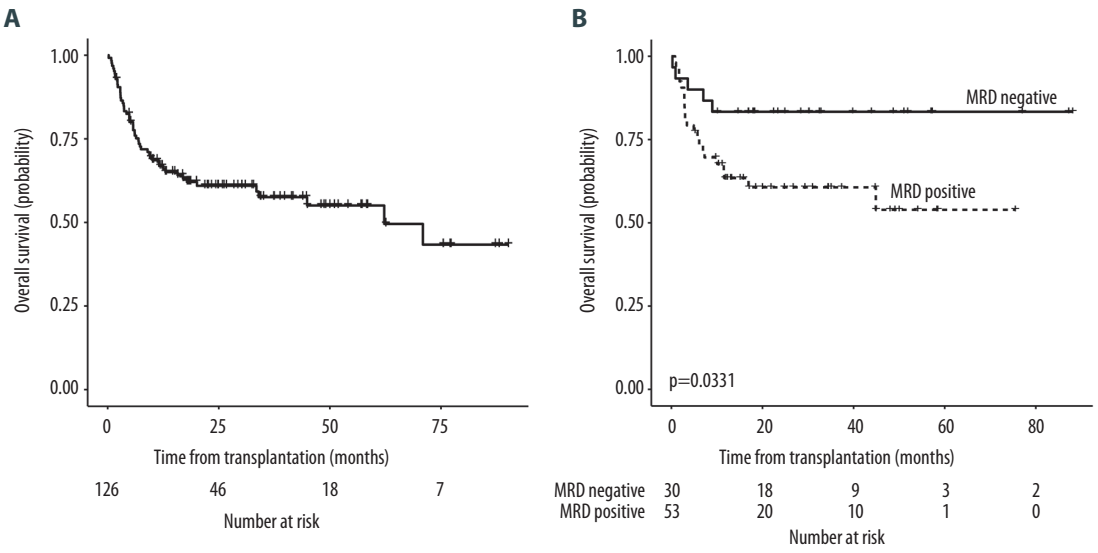

Figure 1. Kaplan-Meier estimates of overall survival for high-risk acute myeloid leukemia undergoing allogeneic hematopoietic cell transplantation. (**A**) overall survival; (**B**) overall survival between minimal residual disease (MRD) positive and MRD negative.

GVHD

Thirteen cases (10.32%) developed III–IV aGVHD, the cumulative incidence of grade III to IV aGVHD for 100-day period was 8.70% (95%CI: 4.6–14.5%) (Figure 5C). The clinical symptoms were skin rash, liver dysfunction, and diarrhea. Grades III to IV aGVHD were usually treated with methylprednisolone and methylprednisolone. Basiliximab was given to 3 cases with III aGVHD who were resistant to methylprednisolone, 2 cases died from infections, and 1 case was alive after treatment with basiliximab.

Seven patients (5.56%) had extensive cGVHD, the cumulative incidence of extensive chronic GVHD for 1-year was 4.1% (95%CI: 1.5–8.7%) (Figure 5D). Four patients were given prednisone 1 mg/kg/day, and 3 patients were given prednisone combined with mesenchymal stem cell. Seven patient's symptoms were relieved, and no patient died after treatment.

Discussion

AML is a heterogenous class of tumors that has different prognoses [11,15]. HR-AMLs are considered hard to go into remission and easy to go into relapse [16,17]. Allo-HSCT is considered a good therapy for HR-AML [18,19]. However, the problem of relapse remains one challenge, and relapse causes high mortality. Moreover, much less widely reported are the outcome and prognostic factors for HR-AML after allo-HSCT.

A few studies have shown that good prognosis has been seen in AML patients achieving complete remission at transplantation [20]. Failure for remission at transplantation is a bad factor for relapse [21,22]. In our study, the recurrence rate after transplantation was 44.2% (19 out of 43 cases) in the none remission group and 14.5% (12 out of 83 cases) in the complete remission group. Compared to the none remission group, the recurrence rate of the complete remission group was lower ($P<0.05$). The survival time was 13 months (range, 1.3–90.2 months) in the none remission group and 17.9 months (range, 0.2–88.1 months) in the complete remission group, and that of the complete remission group was longer than that of the none remission group ($P<0.05$). By univariate and multivariate analysis, result showed that DFS and OS of patients in the none remission group was shorter than that in the complete remission group before allo-HSCT, so it is necessary to make sure patients get complete remission at transplantation.

MRD was quantitatively evaluated for all patients enrolled, using flow cytometry or PCR. Some previously published studies have shown that MRD positive at transplantation can predict relapse after allo-HSCT [23,24]. Among patients with complete remission in our study, the median OS in MRD positive and MRD negative patients were 3.0 months (range, 0.8–75.5 months) and 26.7 months (range, 0.3–88.1 months) respectively. Compared to the MRD negative group, the DFS and OS were shorter in the MRD positive group ($P<0.05$). Therefore, further therapy in the MRD positive group, such as high dose conditioning regimens alone or combined with DLI or other treatment, should be considered.

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Table 2. Univariate and multivariate Cox proportional hazards regression techniques analyses for overall survival.

Factor	N (%)	Univariate			Multivariate		
		P	HR	95%CI	P	HR	95%CI
Age		0.004	2.245	1.300–3.874	0.001	2.708	1.483–4.946
≥40 years	45 (35.7)						
<40 years	81 (64.3)						
WBC		0.101	1.654	0.906–3.021	0.153	1.622	0.835–3.152
≥50×10⁶/L	26 (20.6)						
<50×10⁶/L	100 (79.4)						
ABO compatibility		0.476	0.819	0.474–1.417	–	–	–
No	62 (49.2)						
Yes	64 (50.8)						
Infection (bacteria or fungi)		<0.001	3.884	2.198–6.862	<0.001	3.442	1.915–6.187
Yes	52 (41.3)						
No	74 (58.7)						
PTLD		0.014	2.977	1.252–7.072	0.612	1.280	0.494–3.319
Yes	8 (6.3)						
No	118 (93.7)						
III–IV aGVHD		0.005	2.688	1.340–5.391	0.015	2.506	1.195–5.252
Yes	13 (10.3)						
No	113 (89.7)						
Extensive cGVHD		0.223	1.777	0.705–4.481	–	–	–
Yes	7 (5.6)						
No	119 (94.4)						
Status at transplantation		0.010	2.056	1.190–3.550	0.017	2.058	1.137–3.724
NR	43 (34.1)						
CR	83 (65.9)						
WBC graft		0.009	4.785	1.481–15.460	0.001	8.692	2.473–30.553
Success	122 (96.8)						
Failure	4 (3.2)						
Extramedullary involvement		0.006	2.483	1.294–4.764	0.017	2.253	1.155–4.397
Yes	17 (13.5)						
No	109 (86.5)						

PTLD – post-transplant lymphoproliferative disorder; AML – acute myeloblastic leukemia; MDS – myelodysplastic syndrome; aGVHD – acute graft-*vs.*-host disease; cGVHD – chronic acute graft-*vs.*-host disease; CR – complete remission; NR – none remission.

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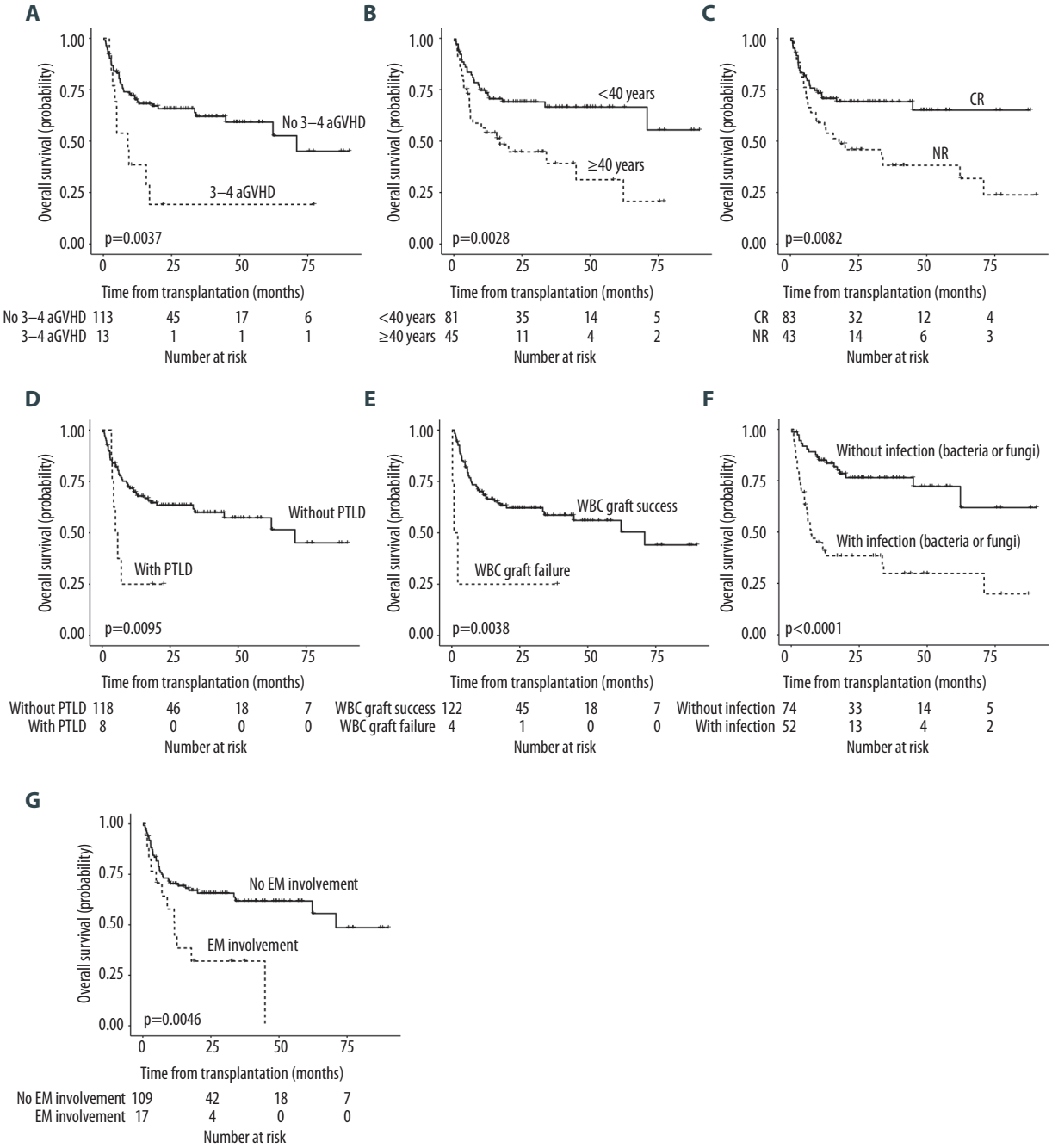

Figure 2. Overall survival (probability) of high-risk acute myeloid leukemia under 7 prognostic factors respectively following allogeneic stem cell transplantation, *P* significance is based on log-rank statistics: (**A**) stratified by III–IV aGVHD, *P*=0.0037; (**B**) stratified by age at transplantation, *P*=0.0028; (**C**) stratified by disease status at transplantation, *P*=0.0082; (**D**) stratified by post transplantation lymphoproliferative disorders, *P*=0.0095; (**E**) stratified by WBC engraftment, *P*=0.0038; (**F**) stratified by infection, *P*<0.0001; (**G**) stratified by EM involvement, *P*=0.0046. WBC – white blood cell; EM – extramedullary; aGVHD – acute graft-versus-host disease.

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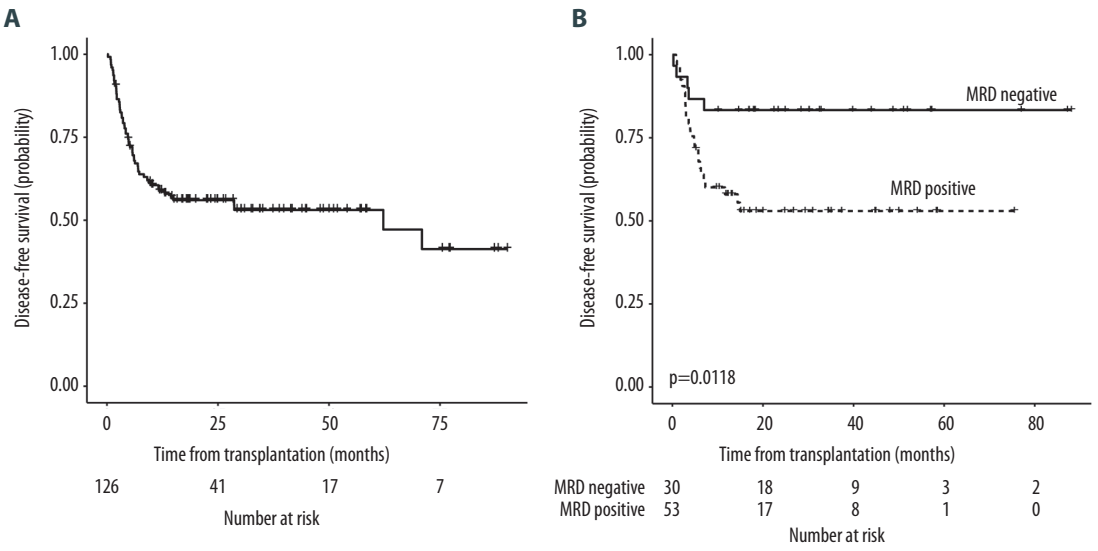

Figure 3. Kaplan-Meier estimates of disease-free survival for patients with high-risk acute myeloid leukemia of undergoing allogeneic hematopoietic cell transplantation: (**A**) disease-free survival; (**B**) disease-free survival between minimal residual disease (MRD) positive and MRD negative.

Table 3. Univariate and multivariate Cox proportional hazards regression techniques analyses for DFS.

Factor	N (%)	Univariate			Multivariate		
		P	HR	95%CI	P	HR	95%CI
WBC		0.228	1.437	0.797–2.592	–	–	–
≥50×10^9/L	26 (20.6)						
<50×10^9/L	100 (79.4)						
III–IV acute GVHD		0.009	2.415	1.246–4.678	0.038	2.026	1.039–3.950
Yes	13 (10.3)						
No	113 (89.7)						
Extensive cGVHD		0.094	2.070	0.884–4.846	0.059	2.312	0.970–5.512
Yes	7 (5.6)						
No	119 (94.4)						
Status at transplantation		0.002	2.294	1.376–3.849	0.006	2.093	1.240–3.531
NR	43 (34.1)						
CR	83 (65.9)						
Extramedullary involvement		0.001	2.779	1.485–5.202	0.001	2.978	1.568–5.654
Yes	17 (13.5)						
No	109 (86.5)						

aGVHD – acute graft-*vs.*-host disease; cGVHD – chronic acute graft-*vs.*-host disease; CR – complete remission; NR – none remission.

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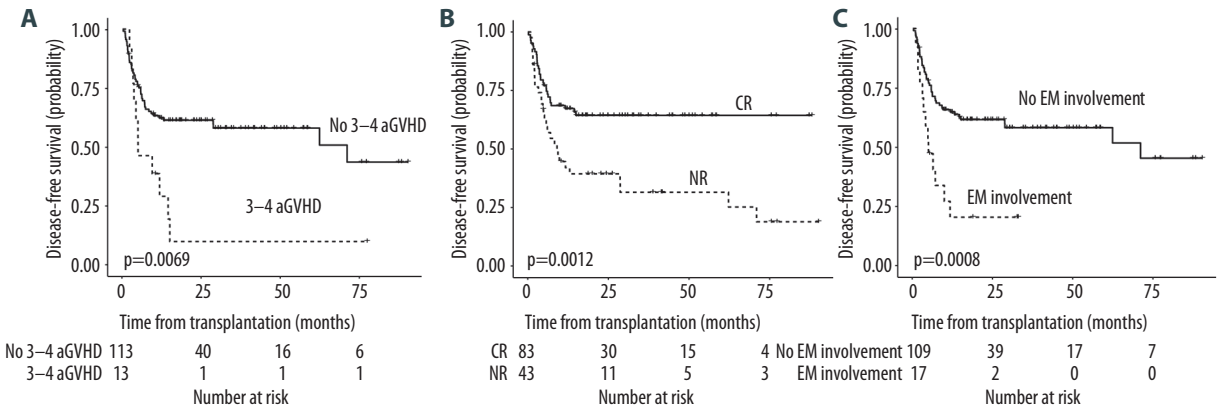

Figure 4. Disease-free survival (probability) of high-risk acute myeloid leukemia under 3 prognostic factors respectively following allogeneic stem cell transplantation, significance is based on log-rank statistics: (**A**) stratified by III–IV aGVHD, *P*=0.0069; (**B**) stratified by status at transplantation, *P*=0.0012; (**C**) stratified by EM involvement *P*=0.0008. WBC – white blood cell; EM – extramedullary; aGVHD – acute graft-versus-host disease.

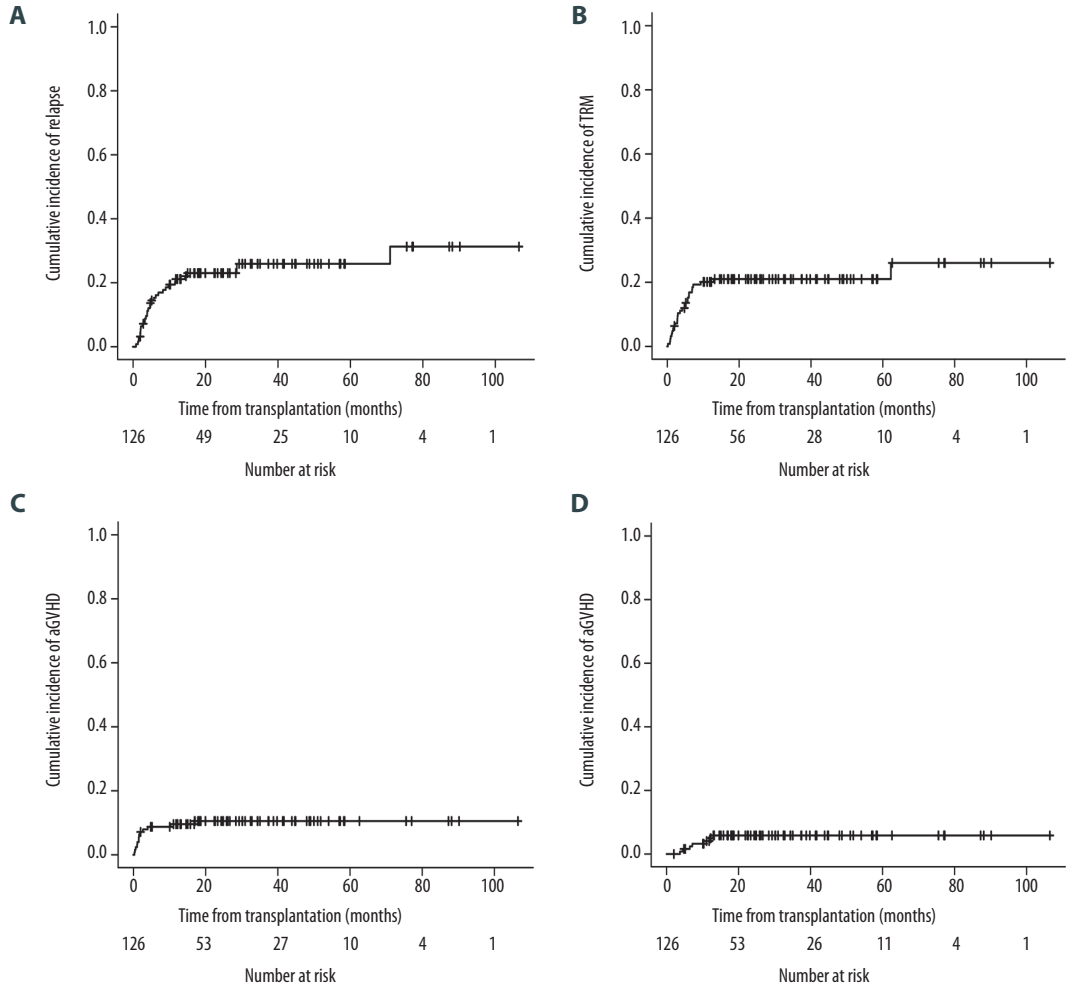

Figure 5. Estimates of cumulative incidence of (**A**) relapse, (**B**) transplantation related mortality, (**C**) aGVHD, and (**D**) cGVHD. aGVHD – acute graft-versus-host disease; cGVHD – chronic graft-versus-host disease.

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Table 4. Univariate and multivariate analysis of risk factors for relapse.

Factor	Univariate			Multivariate		
	P	HR	95%CI	P	HR	95%CI
WBC			0.447	–	–	–
≥50×10^9/L	8/26	30.8				
<50×10^9/L	23/100	23.0				
III–IV acute GVHD			0.305	–	–	–
Yes	5/13	38.5				
No	26/113	23.0				
Extensive cGVHD			0.362	–	–	–
Yes	3/7	42.9				
No	28/119	23.5				
Status at transplantation			<0.001	<0.001	5.319	2.131–13.275
NR	19/43	44.2				
CR	12/83	14.5				
Extramedullary involvement			0.007	0.004	5.481	1.710–17.570
Yes	9/17	52.9				
No	22/109	20.2				

aGVHD – acute graft-*vs.*-host disease; cGVHD – chronic acute graft-*vs.*-host disease; CR – complete remission; NR – none remission.

GVHD [25] is not only linked to transplantation related mortality, but also leads to poor quality of life [26]. Some previous studies showed the cumulative rate of aGVHD was approximately 30% to 75% [27,28], which was consistent with the results of our study that found a cumulative incidence of 32.54% (41 out of 126 cases). Moreover, III–IV aGVHD also leads to lower OS and DFS. Therefore, for HR-AML patients, it is necessary to strengthen prophylactic treatment for aGVHD to prolong OS and DFS. A few reports showed that basiliximab obtained satisfying response for treatment of refractory aGVHD [29,30]. However, basiliximab could lead to an increase in the incidence of fungal infection following transplantation [31]. In this study, 3 patients with steroid-refractory aGVHD died of fungal infection despite aGVHD symptoms relieved after treatment with basiliximab.

Chronic GVHD can result in death after allo-HSCT [32]. In our study, the OS and DFS were not affected by extensive cGVHD; there were 2 main reasons: one reason was possibly associated with the use of mesenchymal stem cells. It has been reported that mesenchymal stem cells can be used to treat GVHD [33,34]. The other reason was that in the 4 patients who were prednisone-sensitive, symptoms of all 4 patients were relieved after treatment with prednisone alone. Owing to our prompt active treatment and owning to extensive cGVHD considered sensitive to drugs, all patients with chronic extensive cGVHD in our study survived.

Extramedullary involvement refers to leukemia found in tissue or organs outside bone marrow or peripheral blood. Extramedullary involvement evaluation found that 3–8% of AML patients had extramedullary involvement, and a study showed that extramedullary involvement often occurred in older age patients [35]. In our study, the incidence of extramedullary involvement was 13.49% (17 out of 126 cases), which was higher than reported in former studies. The reason may be that our patients were HR-AML, which was different from previous studies. Extramedullary involvement was bad prognostic factors for AML [36,37]. In this study, among 17 patients with extramedullary involvement, the mortality rate was 70.59% (12 out of 17 patients), moreover, extramedullary involvement was closely related to lower OS, DFS, and high relapse (P<0.05).

In this study, 31 patients experienced relapse; 9 patients were treated with chemotherapy alone, 13 patients were given chemotherapy combined with DLI, 3 patients were given

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chemotherapy combined with second transplantation, and 6 patients was treatment with supportive care. Six patients were alive, and 25 patients died of AML progression after treatment. Therapeutic methods for patients who relapse after allo-HSCT included supportive care, chemotherapy, donor lymphocyte infusions, second transplantation, with the second transplantation noted to make numbers of patients achieve durable remission [38,39]. Eapen et al. [38] reported that the 1-year and 5-year OS after second transplantation for patients with leukemia relapsed were 41% and 28% respectively. In our study, 1 out of 3 patients survived long-term after a second transplantation, and 2 died of relapse. However, DFS of the dead 2 patients was 11.7 and 70.9 months respectively.

Conclusions

HR-AML has inferior prognosis. Therefore, it is necessary to focus on identifying prognostic factors at transplantation, and devise strategies for prevention of relapse. Particularly, this study found that the disease status before transplantation has impact on prognosis, which indicates the necessity of achieving remission status prior to HSCT, and administration of preventive treatments on high-risk patients after HSCT. In addition, common complications of HSCT, such as PTLD, III–IV aGVHD, and extensive cGVHD also affect OS. Thus, adequate prevention and treatment of complications are needed.

Conflict of interest

None.

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