Risk factors for positive post-transplantation measurable residual disease in patients with acute lymphoblastic leukemia

Yuewen Wang[1], Guomei Fu[2], Lanping Xu[1], Yu Wang[1], Yifei Cheng[1], Yuanyuan Zhang[1], Xiaohui Zhang[1], Yanrong Liu[1], Kaiyan Liu[1], Xiaojun Huang[1,2,3], Yingjun Chang[1]

[1]Department of Hematology, Peking University People's Hospital, Peking University Institute of Hematology, Beijing 100044, China;
[2]Department of Hematology, Peking University People's Hospital and National Clinical Research Center for Hematologic Disease, Beijing Key Laboratory of Hematopoietic Stem Cell Transplantation, Beijing 100044, China;
[3]Beijing Key Laboratory of Haematopoietic Stem Cell Transplantation, Research Unit of Key Technique for Diagnosis and Treatments of Hematologic Malignancies, Chinese Academy of Medical Sciences, Beijing 100730, China.

Abstract

Background: The level of measurable residual disease (MRD) before and after transplantation is related to inferior transplant outcomes, and post-hematopoietic stem cell transplantation measurable residual disease (post-HSCT MRD) has higher prognostic value in determining risk than pre-hematopoietic stem cell transplantation measurable residual disease (pre-HSCT MRD). However, only a few work has been devoted to the risk factors for positive post-HSCT MRD in patients with acute lymphoblastic leukemia (ALL). This study evaluated the risk factors for post-HSCT MRD positivity in patients with ALL who underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Methods: A total of 1683 ALL patients from Peking University People's Hospital between January 2009 and December 2019 were enrolled to evaluate the cumulative incidence of post-HSCT MRD. Cox proportional hazard regression models were built for time-to-event outcomes. Multivariable analysis was performed to determine independent influencing factors from the univariable analysis.

Results: Both in total patients and in T-cell ALL or B-cell ALL, pediatric or adult, human leukocyte antigen-matched sibling donor transplantation or haploidentical SCT subgroups, positive pre-HSCT MRD was a risk factor for post-HSCT MRD positivity (P <0.001 for all). Disease status (complete remission 1 [CR1] *vs.* ≥CR2) was also a risk factor for post-HSCT MRD positivity in all patients and in the B cell-ALL, pediatric, or haploidentical SCT subgroups (P = 0.027; P = 0.003; P = 0.035; P = 0.003, respectively). A risk score for post-HSCT MRD positivity was developed using the variables pre-HSCT MRD and disease status. The cumulative incidence of post-HSCT MRD positivity was 12.3%, 25.1%, and 38.8% for subjects with scores of 0, 1, and 2–3, respectively (P <0.001). Multivariable analysis confirmed the association of the risk score with the cumulative incidence of post-HSCT MRD positivity and relapse as well as leukemia-free survival and overall survival.

Conclusion: Our results indicated that positive pre-MRD and disease status were two independent risk factors for post-HSCT MRD positivity in patients with ALL who underwent allo-HSCT.

Keywords: Acute lymphoblastic leukemia; Measurable residual disease; Allogeneic hematopoietic stem cell transplantation; Posttransplantation; Risk factors; Relapse

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a curative treatment for patients with acute lymphoblastic leukemia (ALL), especially those with poor prognosis or relapse after initial chemotherapy.[1–6] However, relapse remains the major complication after transplantation, directly resulting in particularly poor clinical outcomes in ALL patients.[7–9] A handful of studies have indicated that the persistence of low-level leukemic blasts, also known as measurable residual disease (MRD), which cannot be detected by conventional cytomorphology, constitutes the cause of relapse either after chemotherapy or allo-HSCT.[9–14] Increasing evidence has demonstrated that the level of MRD at all-time points after transplantation is positively related to the cumulative incidence of relapse (CIR) and inversely associated with leukemia-free survival (LFS).[9,15,16] In addition, post-hematopoietic stem cell transplantation

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000003150

Yuewen Wang and Guomei Fu contributed equally to this work.

Correspondence to: Prof. Yingjun Chang, Peking University Institute of Hematology, Peking University People's Hospital, No. 11 Xizhimen South Street, Beijing 100044, China
E-Mail: rmcyj@bjmu.edu.cn

Chinese Medical Journal 2025;138(9)

Received: 03-02-2024; **Online:** 09-07-2024 **Edited by:** Sihan Zhou and Xiuyuan Hao

measurable residual disease (post-HSCT MRD) has a higher prognostic value in determining risk, even at low levels, than pre-hematopoietic stem cell transplantation measurable residual disease (pre-HSCT MRD). Previous studies have provided evidence that post-HSCT MRD-directed intervention could reduce the CIR and improve survival. Therefore, it is important to identify patients with a high risk of developing positive post-HSCT MRD before transplantation because these patients could be considered for early preemptive therapy.[17–22]

Presently, only a few studies have reported the correlation of pre-HSCT MRD with post-HSCT MRD in patients with ALL.[23,24] Previous studies showed that the cumulative incidence of post-HSCT MRD positivity was 26% and 44% in ALL patients with positive pre-HSCT MRD who underwent haploidentical stem cell transplantation (SCT) and those who received human leukocyte antigen (HLA)-matched HSCT, respectively.[24] However, the risk factors for positive post-HSCT MRD in patients with ALL remains to be explored. Thus, we performed this study to explore the risk factors for positive post-HSCT MRD in total patients and subgroup patient populations as well as in distinct periods of time after transplantation in ALL patients.

Methods

Patient population

In all, 1683 patients diagnosed with ALL who underwent either matched sibling donor transplantation (MSDT) (n = 337) or haploidentical stem cell transplantation (haplo-SCT) (n = 1346) from Peking University People's Hospital between January 2009 and December 2019 were enrolled in this study. All included patients provided written informed consent. The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Peking University People's Hospital (No. 2020PBH390-01). Informed consent was provided by all participants.

Transplant protocol

To mobilize the bone marrow (BM) and peripheral blood, granulocyte colony-stimulating factor (G-CSF, 5 μg·kg^{-1}·day^{-1}) were administered to healthy donors subcutaneously once daily at the same time for 5 or 6 consecutive days. After G-CSF mobilization, unmanipulated BM and peripheral blood stem cells (PBSCs) were harvested on Day 4 and Day 5, respectively. If the target mononuclear cell (MNC) count was not achieved in total allografts (4–6 × 10^8 cells/kg of recipient weight), PBSCs would be collected again on Day 6. The allografts were infused into the recipient on the day of collection. For unmanipulated haploidentical transplantation, the transplant procedures have been described in the previous research.[7,24] The conditioning regimen incorporated the combination of intravenous cytarabine (4 g·m^{-2}·day^{-1} on days –10 to –9), busulfan (3.2 mg·kg^{-1}·day^{-1} on days –8 to –6), intravenous cyclophosphamide (1.8 g·m^{-2}·day^{-1} on days –5 to –4), oral semustine (250 mg/m^2, once on day –3), and intravenous rabbit anti-thymocyte globulin (ATG, Sangstat, 2.5 mg·kg^{-1}·day^{-1} on days –5 to –2). The identical regimen aforesaid without ATG was employed for the patients who underwent HLA matched-sibling donor transplantation. They received oral hydroxycarbamide (80 mg/kg) on day –10 and a relatively low dose of cytarabine (2 g·m^{-2}·day^{-1}) on day –9.[7,24] In order to prevent graft-versus-host disease (GVHD), immunosuppressive agents including cyclosporine A (CsA), mycophenolate mofetil (MMF), and short-term methotrexate were administered. The detailed protocol regarding GVHD prophylaxis was described in the previous studies.[7,24]

Detection of MRD

MRD positivity and MRD negativity were defined as detectable and undetectable, respectively.[16,25] MRD detection was performed in all patients enrolled as a routine clinical test using multiparameter flow cytometry. BM aspirate samples were obtained 1 month before HSCT as well as +1.0, +2.0, +3.0, +4.5, +6.0, +9.0, and +12.0 months after HSCT. After 1 year of transplantation, BM MRD was evaluated every 3 months until 3 years after HSCT, and the evaluation was performed at any time according to changes in the patients' conditions.[26]

Endpoints

The primary endpoint was the cumulative incidence of post-HSCT MRD. The secondary endpoints included hematopoietic recovery, acute and chronic GVHD, CIR, LFS, and overall survival (OS). All these endpoints were defined according to the previous studies.[7,24] The end point of the last follow-up for all surviving patients was August 15th, 2022.

Definitions

A high white blood cell (WBC) count at diagnosis referred to ≥30 × 10^9 cells/L for those with B-cell ALL (B-ALL) and ≥100 × 10^9 cells/L for those with T-cell ALL (T-ALL).[27] High-risk cytogenetics and molecular genetics features were defined as hypodiploidy, BCR–ABL1 Philadelphia (Ph) chromosome-positive, lysine methyltransferase 2A (KMT2A) rearrangements, Transcription Factor 3 (TCF3)–HLF, complex karyotype (≥5 chromosomal abnormalities), IKAROS family zinc finger 1 (IKZF1) deletions or mutations, Ph chromosome-like, and Myocyte enhancer factor 2D (MEF2D)-rearrangement.[28] Intervention therapy after the emergence of post-HSCT MRD included interferon-α (IFN-α) subcutaneous injection, chemotherapy followed by donor lymphocyte infusion (DLI), tyrosine kinase inhibitor (TKI) oral administration, chimeric antigen receptor T-cell (CAR-T) immunotherapy, monoclonal antibody, and two or more aforementioned interventions.[7,24]

Statistical analysis

The Kaplan–Meier method was used to determine the probabilities of LFS and OS. The risk factors for positive post-HSCT MRD calculated for univariable analysis

included the immunophenotype of ALL, disease status, pre-HSCT MRD, WBC count at diagnosis, cytogenetics and molecular genetics features, recipient age, recipient sex, transplant modality, Ph chromosome positivity or negativity, HLA-A, B, DR mismatched loci, donor–recipient sex-matched graft, donor–recipient relationship, and ABO-matched graft. Cox proportional hazard regression models were built for time-to-event outcomes. The patient characteristics that were significant at the 10.0% level in the univariable analysis were selected for inclusion in the multivariable model. A forward selection procedure was implemented in the final model to select the remaining predictors with a *P* value of 0.05. Ninety-five percent confidence intervals (CIs) were calculated with log transformation. Calculations were performed using the SPSS 16.0 statistical package (Mathsoft, Seattle, WA, USA). R statistical software (R Core Team, Vienna, Austria) was used for competing risk analysis.

Results

Clinical and transplant characteristics

A total of 1683 patients were eligible for this study. Patient and donor characteristics are summarized in Table 1. The median age of the recipients was 25 years. The patients were either diagnosed with B-ALL (1345/1683, 79.9%) or T-ALL (338/1683, 20.1%). Most of these patients underwent haplo-SCT (1346/1683, 80.0%) compared to MSDT (337/1683, 20.0%). A majority of patients (1447/1683, 86.0%) were in complete remission 1 (CR1) at transplantation. Three hundred fifty-three patients (353/1683, 21.0%) had positive pre-HSCT MRD, and the median level of pre-HSCT MRD was 0.1% (range: 0–96.8%). Two hundred sixty-five patients (265/1683, 15.7%) experienced positive post-HSCT MRD. The median level of post-HSCT MRD was 0.1% (range: 0–18.9%), and the median time of the emergence of positive post-HSCT MRD was 141 days (range: 18–1613 days) after transplantation. The association of pre-HSCT MRD and post-HSCT MRD in the total patient population is shown in Figure 1. Among patients in CR1, 19.2% (278/1447) had positive pre-HSCT MRD. Among patients in ≥CR2, 31.8% (75/236) had positive pre-HSCT MRD. The incidence of pre-HSCT MRD positivity in patients in ≥CR2 was higher than that in patients in CR1 (P <0.001).

Overall outcomes

Seven hundred fifty-six patients (756/1683, 44.9%) developed acute GVHD, and 384 patients (384/1683, 22.8%) and 56 patients (56/1683, 3.3%) developed grades II–IV and grades III–IV acute GVHD, respectively. As of August 15th, 2022, 1144 patients (1144/1683, 68.0%) were alive. The median follow-up times for all patients and those who were alive were 1408 days (range: 8–4969 days) and 1955 days (range: 371–4969 days), respectively. The probabilities of OS and LFS at 5 years were 68.3% (1149/1683, 95% CI, 65.9–70.7%) and 62.6% (1053/1683, 95% CI, 60.2–65.0%), respectively. The cumulative incidences of transplantation-related mortality (TRM) and relapse at 5 years were 14.6% (245/1683, 95% CI, 12.6–16.6%) and

Table 1: Baseline characteristics of included ALL patients and donors.

Characteristics	Total	Post-HSCT MRD (+)
Patient number	1683	265
Median age (range, years)	25 (1–64)	25 (1–59)
Male, *n* (%)	1005 (59.7)	160 (60.4)
Immunophenotype of ALL, *n* (%)		
B-ALL	1345 (79.9)	213 (80.4)
T-ALL	338 (20.1)	52 (19.6)
Transplant modality, *n* (%)		
Haplo-SCT	1346 (80.0)	208 (78.5)
MSDT	337 (20.0)	57 (21.5)
Pre-HSCT MRD (+), *n* (%)	353 (21.0)	107 (40.4)
Ph+ ALL, *n* (%)	496 (29.5)	69 (26.0)
WBC count at diagnosis, *n* (%)		
High	466 (27.7)	83 (31.3)
Normal	1176 (69.9)	169 (63.8)
Unknown	41 (2.4)	13 (4.9)
Cytogenetics and molecular genetics features, *n* (%)		
High risk	706 (41.9)	123 (46.4)
Low risk	893 (53.1)	125 (47.2)
Unknown	84 (5.0)	17 (6.4)
Disease status, *n* (%)		
CR1	1447 (86.0)	212 (80.0)
≥CR2	236 (14.0)	53 (20.0)
HLA-A, B, DR mismatched loci, *n* (%)		
0	346 (20.6)	61 (23.0)
1	52 (3.1)	9 (3.4)
2	220 (13.1)	37 (14.0)
3	1065 (63.3)	158 (59.6)
Donor-recipient sex-matched graft, *n* (%)		
Male–male	676 (40.2)	116 (43.8)
Male–female	456 (27.1)	70 (26.4)
Female–male	331 (19.7)	46 (17.4)
Female–female	220 (13.1)	33 (12.5)
Donor-recipient relationship, *n* (%)		
Father–child	686 (40.8)	110 (41.5)
Mother–child	140 (8.3)	20 (7.5)
Sibling–sibling	664 (39.5)	104 (39.2)
Child–parent	164 (9.7)	25 (9.4)
Other	29 (1.7)	6 (2.3)
ABO matched graft, *n* (%)		
Matched	941 (55.9)	157 (59.2)
Major mismatch	343 (20.4)	53 (20.0)
Minor mismatch	312 (18.5)	43 (16.2)
Bi-directional mismatch	86 (5.1)	12 (4.5)
Acute GVHD (grades), *n* (%)		
II	328 (19.5)	42 (15.8)
III	30 (1.8)	3 (1.1)
IV	26 (1.5)	0
cGVHD, *n* (%)		
Moderate	106 (6.3)	72 (27.2)
Severe	24 (1.4)	23 (8.7)
Post-HSCT MRD (+), *n* (%)	265 (15.7)	265 (100)
Interventions for post-HSCT MRD (+), *n* (%)		
IFN-α	43 (16.2)	–
Chemotherapy + DLI	83 (31.3)	–
TKI	15 (5.7)	–
CAR-T	16 (6.0)	–
Monoclonal antibody	3 (1.1)	–

(*Continued*)

Table 1

(Continued)

Characteristics	Total	Post-HSCT MRD (+)
Two or more interventions mentioned above	25 (9.4)	–
Others	6 (2.3)	–
No intervention	29 (10.9)	–
Unknown	45 (17)	–

ALL: Acute lymphoblastic leukemia; B-ALL: B-cell ALL; CAR-T: Chimeric antigen receptor T-cell; cGVHD: Chronic GVHD; CR: Complete remission; DLI: Donor lymphocyte infusion; GVHD: Graft-versus-host disease; haplo-SCT: Haploidentical stem cell transplantation; HLA: Human leukocyte antigen; IFN-α: Interferon-α; MSDT: Matched sibling donor transplantation; Ph: Philadelphia; post-HSCT MRD: Post-hematopoietic stem cell transplantation measurable residual disease; pre-HSCT MRD: Pre-hematopoietic stem cell transplantation measurable residual disease; T-ALL: T-cell ALL; TKIs: Tyrosine kinase inhibitors; WBC: White blood cell; –: Not applicable.

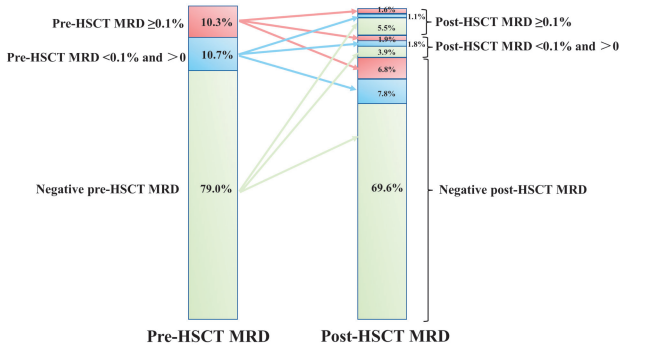

Figure 1: The association of pre-HSCT MRD and post-HSCT MRD in the total patient population. post-HSCT MRD: Post-hematopoietic stem cell transplantation measurable residual disease; pre-HSCT MRD: Pre-hematopoietic stem cell transplantation measurable residual disease.

23.0% (387/1683, 95% CI, 21.0–25.0%), respectively. Patients with positive post-HSCT MRD experienced a higher CIR and lower LFS and OS than those with negative post-HSCT MRD [Figure 2A–C]. Patients with positive post-HSCT MRD after 100 days following transplantation had a higher CIR as well as lower LFS and OS compared to positive post-HSCT MRD within 100 days following allo-HSCT and post-HSCT MRD-negative cases (all P <0.001) [Figure 2D–F].

Risk factors for positive post-HSCT MRD in the total patient population

In the total patient population, multivariable analysis demonstrated that positive pre-HSCT MRD (hazard ratio [HR] 3.053, 95% CI 2.347–3.971, P <0.001) and disease status (HR 1.458, 95% CI 1.044–2.053, P = 0.027) were associated with post-HSCT MRD positivity. As shown in Supplementary Figure 1A, http://links.lww.com/CM9/C19, the cumulative incidence of positive post-HSCT MRD was significantly higher in patients with positive pre-HSCT MRD compared with patients with negative pre-HSCT MRD. In Supplementary Figure 2A, http://links.lww.com/CM9/C19, the cumulative incidence of positive post-HSCT MRD was significantly higher in patients in ≥CR2 compared with patients in CR1. The association of pre-HSCT MRD and disease status with the transplant outcomes are shown in Supplementary Figure 1B–D and 2B–D, http://links.lww.com/CM9/C19, respectively.

Within 100 days after allo-HSCT, positive pre-HSCT MRD (HR 3.409, 95% CI 2.319–5.012, P <0.001) and disease status (HR 1.698, 95% CI 1.086–2.655, P = 0.020) were related to positive post-HSCT MRD after multivariable analyses. At 100 days following transplantation, multivariable analysis revealed that positive pre-HSCT MRD (HR 2.724, 95% CI 1.969–3.768, P <0.001) was the only risk factor for positive post-HSCT MRD.

Considering that the level of pre-HSCT MRD was a significant risk factor for CIR in our previous research,[25] we performed further subgroup analysis according to the level of pre-HSCT MRD specifically. The patients were stratified into three groups based on the degree of pre-HSCT MRD (negative pre-HSCT MRD, pre-HSCT MRD <0.1% and >0, and pre-HSCT MRD ≥0.1%). Multivariable analysis demonstrated that both pre-HSCT MRD <0.1% and >0 (HR 2.700, 95% CI, 1.930–3.779, P <0.001) and pre-HSCT MRD ≥0.1% (HR 3.714, 95% CI, 2.687–5.134, P <0.001) were associated with post-HSCT MRD positivity. The cumulative incidence of positive post-HSCT MRD as well as the transplant outcomes according to different levels of pre-HSCT MRD are shown in Supplementary Figure 3 A–D, http://links.lww.com/CM9/C19.

Risk factors for positive post-HSCT MRD in the B-ALL and T-ALL subgroups

In patients diagnosed with B-ALL, as shown in Supplementary Table 1, http://links.lww.com/CM9/C19, univariable analysis revealed that pre-HSCT MRD (P <0.001), disease status (P <0.001), and high WBC count at diagnosis (P = 0.031) were correlated with positive post-HSCT MRD. In multivariable analysis, it was subsequently demonstrated that positive pre-HSCT MRD (HR 3.167, 95% CI 2.392–4.194, P <0.001) and patients in ≥CR2 at HSCT (HR 1.655, 95% CI 1.185–2.311, P = 0.003) exhibited positive post-HSCT MRD. Within 100 days after transplantation, we found that positive pre-HSCT MRD (P <0.001) and disease status (P = 0.007) were associated with positive post-HSCT MRD in univariable analysis, while only pre-HSCT MRD (HR 3.969, 95% CI 2.642–6.002, P <0.001) was proven to be related to positive post-HSCT MRD in multivariable analysis. After 100 days following allo-HSCT, positive pre-HSCT MRD (HR 2.691, 95% CI 1.855–3.906, P <0.001), and disease status (HR 1.615, 95% CI 1.029–2.535, P = 0.037) were correlated with positive post-HSCT MRD, as demonstrated by both univariable and multivariable analyses.

With respect to the T-ALL patients [Supplementary Table 1, http://links.lww.com/CM9/C19], multivariable analysis showed that pre-HSCT MRD (HR 2.373, 95% CI 1.209–4.657, P = 0.012) and patient sex (HR 0.413, 95% CI 0.185–0.923, P = 0.031) were associated with positive post-HSCT MRD. No risk factors were observed to be related to positive post-HSCT MRD within 100 days after transplantation. After 100 days of transplantation,

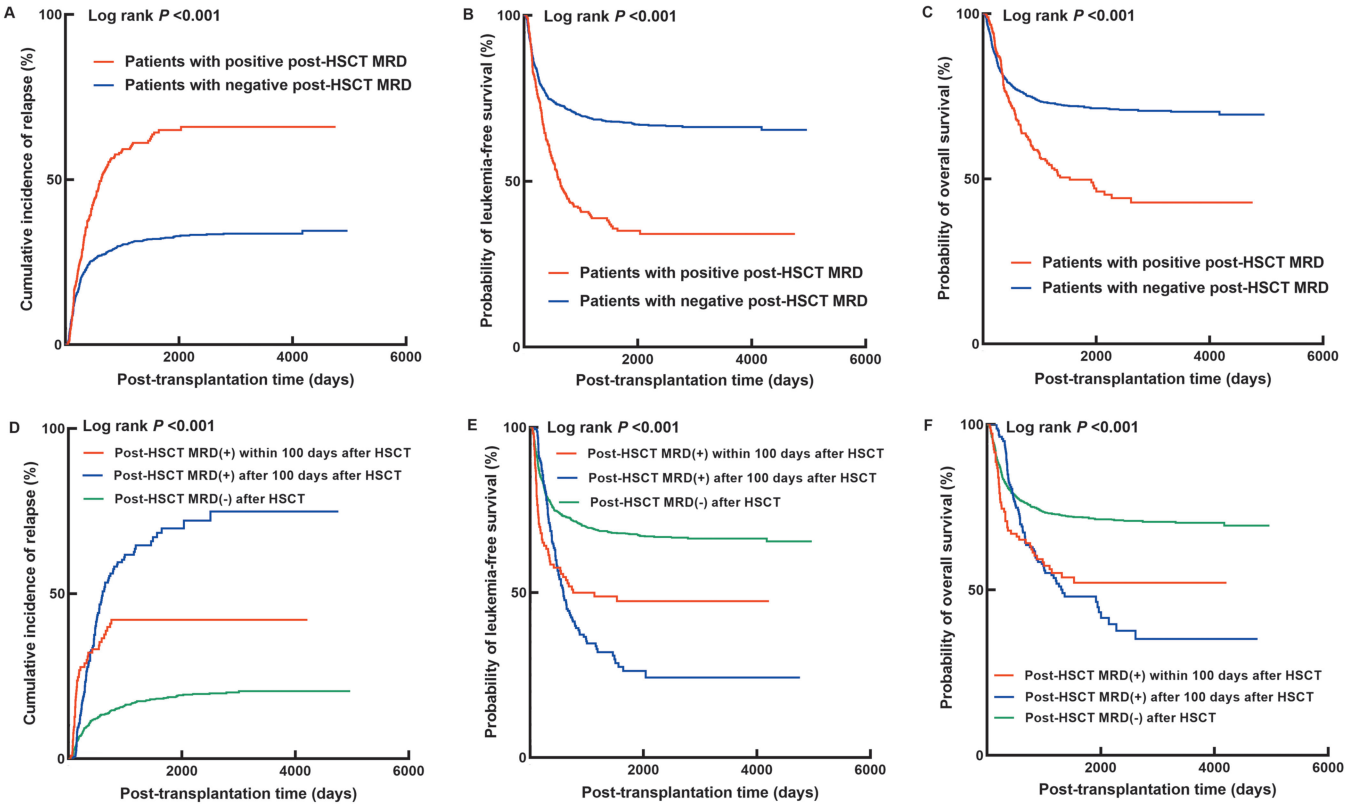

Figure 2: Kaplan–Meier analysis for correlation of post-HSCT MRD with clinical outcomes in the entire cohort (A–C). Transplant outcomes compared among positive post-HSCT MRD within and after 100 days following transplantation, as well as post-HSCT MRD negative cases (D–F). allo-HCT: Allogeneic cell transplantation; post-HSCT MRD: Post-hematopoietic stem cell transplantation measurable residual disease.

pre-HSCT MRD (HR 3.022, 95% CI 1.349–6.767, $P = 0.007$), high risk according to cytogenetic and molecular genetic features (HR 3.564, 95% CI 1.699–7.475, $P = 0.001$), and patient sex (HR 0.204, 95% CI 0.061–0.678, $P = 0.009$) were correlated with the emergence of post-HSCT MRD in multivariable analysis.

Risk factors for positive post-HSCT MRD in pediatric and adult subgroups

As shown in Supplementary Table 2, http://links.lww.com/CM9/C19, in the pediatric subgroup, pre-HSCT MRD (HR 2.229, 95% CI 1.370–3.625, $P = 0.001$), disease status (HR 1.682, 95% CI 1.038–2.725, $P = 0.035$), and immunophenotype of ALL (HR 1.855, 95% CI 1.127–3.054, $P = 0.015$) were correlated with positive post-HSCT MRD in multivariable analysis. In the early days post-transplantation, patients in ≥CR2 at HSCT (HR 2.735, 95% CI 1.278–5.855, $P = 0.010$) generally exhibited positive post-HSCT MRD, according to both univariable and multivariable analyses. After 100 days of allo-HSCT, positive pre-HSCT MRD (HR 2.793, 95% CI 1.549–5.037, $P = 0.001$) and patients diagnosed with T-ALL (HR 2.501, 95% CI 1.425–4.390 $P = 0.001$) were associated with positive post-HSCT MRD, as demonstrated in multivariable analysis.

With regard to the adult subgroup [Supplementary Table 2, http://links.lww.com/CM9/C19], multivariable analysis showed that positive pre-HSCT MRD (HR 3.514, 95% CI 2.578–4.791, P <0.001) and high risk according to cytogenetic and molecular genetic features (HR 1.390, 95% CI 1.019–1.898, $P = 0.038$) were related to positive post-HSCT MRD. Furthermore, in different periods of time, both within or after 100 days following transplantation, multivariable analysis showed that only positive pre-HSCT MRD (HR 4.525, 95% CI 2.854–7.176, P <0.001; HR 2.884, 95% CI 1.918–4.337, P <0.001) was a risk factor for post-HSCT MRD positivity.

Risk factors for positive post-HSCT MRD in the haplo-SCT and MSDT subgroups

The risk factors for positive post-HSCT MRD in the haplo-HCT and MSDT subgroups are shown in Supplementary Table 3, http://links.lww.com/CM9/C19. In the haplo-SCT subgroup, univariable analysis showed that positive pre-HSCT MRD (P <0.001), disease status (P <0.001), high WBC count at diagnosis ($P = 0.100$), and high risk in cytogenetic and molecular genetic features ($P = 0.077$) was correlated with positive post-HSCT MRD. In the subsequent multivariable analysis, only positive pre-HSCT MRD (HR 2.740, 95% CI 2.038–3.684, P <0.001) and disease status (HR 1.608, 95% CI 1.178–2.197, $P = 0.003$) were proven to be associated with positive post-HSCT MRD. Early after transplantation, positive pre-HSCT MRD (HR 2.713, 95% CI 1.742–4.226, P <0.001)

and ≥CR2 at HSCT (HR 1.923, 95% CI 1.299–2.845, P <0.001) were the two risk factors affecting post-HSCT MRD in both univariable and multivariable analyses. After 100 days following allo-HSCT, positive pre-HSCT MRD (HR 2.688, 95% CI 1.852–3.901, P <0.001) and immunophenotype of leukemia cells (HR 1.665, 95% CI 1.108–2.501, P = 0.014) were statistically related to post-HSCT MRD positivity in multivariable analysis.

For the MSDT subgroup, only positive pre-HSCT MRD (HR 4.720, 95% CI 2.787–7.992, P <0.001) was found to be correlated with positive post-HSCT MRD. In further demonstration concerning different times after transplantation, positive pre-HSCT MRD was the only risk factor for positive post-HSCT MRD within and after 100 days following allo-HSCT (HR 7.446, 95% CI 3.342–16.587, P <0.001; HR 3.205, 95% CI 1.531–6.786, P = 0.002).

Risk factors for positive post-HSCT MRD in the Ph+ and Ph– subgroups

Multivariable analysis showed that only pre-HSCT MRD (HR 4.367, 95% CI 2.682–7.111, P <0.001) was correlated with positive post-HSCT MRD in Ph+ patients. Pre-HSCT MRD positivity (HR 7.308, 95% CI 3.396–15.726, P <0.001) was associated with post-HSCT MRD positivity within 100 days following transplantation, while pre-HSCT MRD positivity (HR 2.985, 95% CI 1.551–5.746, P = 0.001) and high WBC count at diagnosis (HR 2.278, 95% CI 1.174–4.420, P = 0.015) were related to post-HSCT MRD positivity after 100 days following transplantation in the multivariable analysis.

In the subgroup analysis of Ph– patients, the multivariable analysis showed that positive pre-HSCT MRD (HR 2.567, 95% CI 1.891–3.486, P <0.001) and high risk in cytogenetics and molecular genetics features (HR 1.861, 95% CI 1.357–2.552, P <0.001) were related to positive post-HSCT MRD. Positive pre-HSCT MRD (HR 2.864, 95% CI 1.767–4.642, P <0.001) was the only risk factor for post-HSCT MRD positivity within 100 days following allo-HSCT in the multivariable analysis. Pre-HSCT MRD positivity (HR 2.500, 95% CI 1.688–3.702, P <0.001) and high risk in cytogenetics and molecular genetics features (HR 2.014, 95% CI 1.354–2.996, P = 0.001) were related to positive post-HSCT MRD after 100 days following allo-HSCT.

Association of the scoring system with post-HSCT MRD and transplant outcomes in the total patient population

In the total patient population, multivariable analysis showed that pre-HSCT MRD and disease status were positively associated with post-HSCT MRD. Therefore, we established a scoring system for post-HSCT MRD prediction using the variables pre-HSCT MRD and disease status. Pre-HSCT MRD negative scored 0, pre-HSCT MRD <0.1% and >0 scored 1, and pre-HSCT MRD ≥0.1% scored 2. Patients in CR1 scored 0, while those in ≥CR2 scored 1. Not surprisingly, as Figure 3A demonstrated, higher risk scores were associated with a higher incidence of positive post-HSCT MRD. The cumulative incidence of post-HSCT MRD positivity was 12.3% (207/1683), 25.1% (422/1683), and 38.8% (653/1683) for subjects with scores of 0, 1, and 2–3, respectively (P <0.001). Furthermore, we confirmed that this model could also be used to predict transplant outcomes. Higher scores were related to an increased CIR as well as lower LFS and OS [Figure 3B–D], and multivariable analysis showed that the risk score was associated with post-HSCT MRD and leukemia relapse, LFS, and OS [Table 2].

Discussion

In this study, we demonstrated that pre-HSCT MRD positivity was an independent risk factor for post-HSCT MRD positivity in the entire cohort of ALL patients as well as in subgroup patients according to different classifications, including immunophenotype of leukemia cells, recipient age, transplant modality, and Ph chromosome positivity or negativity. Except for pre-HSCT MRD, disease status at transplant was also a risk factor for post-HSCT MRD positivity. Moreover, we developed a new scoring system, using risk factors regarding pre-HSCT MRD positivity and disease status for predicting post-HSCT MRD positivity, which further stratified patients who underwent allo-HSCT into different subgroup cases with different cumulative incidences of post-HSCT MRD positivity.

In agreement with previous studies,[23,24] we provided further evidence indicating that pre-HSCT MRD positivity was strongly correlated with positive post-HSCT MRD positivity either in the total ALL population or in different subgroups. The residual leukemia cells before transplantation could represent those cells with chemoresistance,[29] which could prevent leukemia cells from being killed by

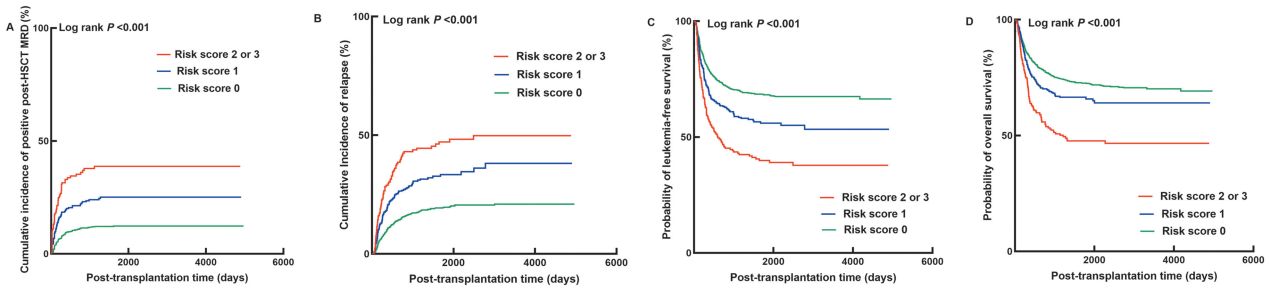

Figure 3: Estimates of (A) Cumulative incidence of positive post-HSCT MRD according to risk score. Transplant outcomes of the total patient population according to risk score. Estimates of (B) CIR, (C) probability of LFS, and (D) probability of OS. CIR: Cumulative incidence of relapse; LFS: Leukemia-free survival; OS: Overall survival; post-HSCT MRD: Post-hematopoietic stem cell transplantation measurable residual disease.

Table 2: Univariable and multivariable analysis of the scoring system with post-HSCT MRD and transplant outcomes in total ALL patients.

	Univariable analysis			Multivariable analysis		
Covariates*	**HR**	**95% CI**	***P* values**	**HR**	**95% CI**	***P* values**
Post-HSCT MRD						
The scoring system						
Risk score 0		1			1	
Risk score 1	2.243	1.676–3.001	<0.001	2.172	1.589–2.969	<0.001
Risk score 2 or 3	3.974	2.951–5.351	<0.001	3.956	2.886–5.422	<0.001
Disease status (≥CR2 *vs*. CR1)	1.777	1.314–2.401	<0.001	–	–	–
High WBC count at diagnosis (yes *vs*. no)	1.277	0.982–1.661	0.068	–	–	–
High risk in cytogenetics and molecular genetics features (yes *vs*. no)	1.246	0.971–1.598	0.083	–	–	–
Relapse						
The scoring system						
Risk score 0		1			1	
Risk score 1	1.925	1.509–2.455	<0.001	2.056	1.605–2.632	<0.001
Risk score 2 or 3	3.029	2.341–3.918	<0.001	3.132	2.419–4.056	<0.001
Immunophenotype of ALL (T-ALL *vs*. B-ALL)	1.305	1.029–1.654	0.028	1.501	1.179–1.911	0.001
Disease status (≥CR2 *vs*. CR1)	2.410	1.900–3.056	<0.001	–	–	–
Pre-HSCT MRD (positive *vs*. negative)	2.021	1.630–2.507	<0.001	–	–	–
High WBC count at diagnosis (yes *vs*. no)	1.399	1.128–1.736	0.002	–	–	–
Sex (female *vs*. male)	0.783	0.635–0.966	0.022	–	–	–
Ph+ ALL (yes *vs*. no)	0.820	0.653–1.030	0.088	–	–	–
LFS						
The scoring system						
Risk score 0		1			1	
Risk score 1	1.506	1.238–1.832	<0.001	1.292	1.008–1.657	0.043
Risk score 2 or 3	2.383	1.939–2.928	<0.001	2.128	1.682–2.693	<0.001
Immunophenotype of ALL (T-ALL *vs*. B-ALL)	1.241	1.029–1.496	0.024	1.416	1.168–1.716	<0.001
Disease status (≥CR2 *vs*. CR1)	1.951	1.606–2.370	<0.001	1.545	1.197–1.993	0.001
Pre-HSCT MRD (positive *vs*. negative)	1.699	1.429–2.019	<0.001	–	–	–
High WBC count at diagnosis (yes *vs*. no)	1.221	1.029–1.449	0.023	1.246	1.050–1.480	0.012
OS						
The scoring system						
Risk score 0		1			1	
Risk score 1	1.313	1.056–1.632	0.014	1.103	0.839–1.449	0.482
Risk score 2 or 3	2.242	1.797–2.796	<0.001	1.964	1.529–2.524	<0.001
Immunophenotype of ALL (T-ALL *vs*. B-ALL)	1.456	1.198–1.768	<0.001	1.594	1.308–1.942	<0.001
Disease status (≥CR2 *vs*. CR1)	1.852	1.500–2.285	<0.001	1.590	1.210–2.091	0.001
pre-HSCT MRD (positive *vs*. negative)	1.563	1.294–1.888	<0.001	–	–	–
Sex (female *vs*. male)	0.840	0.705–1.001	0.051	–	–	–

*All variables were first included in the univariable analysis; only variables with P <0.1 were included in the Cox proportional hazards model with time-dependent variables. ALL: Acute lymphoblastic leukemia; B-ALL: B-cell ALL; CI: Confidence interval; CR: Complete remission; HR: Hazard ratio; LFS: Leukemia-free survival; OS: Overall survival; Ph: Philadelphia; post-HSCT MRD: Post-hematopoietic stem cell transplantation measurable residual disease; pre-HSCT MRD: Pre-hematopoietic stem cell transplantation measurable residual disease; T-ALL: T-cell ALL; WBC: White blood cell; –: Not applicable.

the conditioning regimen in allo-HSCT settings. More recently, Pagliuca *et al*[30] showed that germline-determined class II HLA divergence and somatic class II HLA mutations, indels, or losses can enable an environment of graft-versus-leukemia resistance, immune evasion, and unfavorable outcomes. Therefore, elucidating the biological characteristics of residual leukemia cells before transplantation might help us identify those leukemia cells escaping the alloreactive immune response of donor immune effector cells, which would eventually result in post-HSCT MRD positivity, especially in cases with a high pre-HSCT MRD burden[17,25] because a high level of residual disease was correlated with a higher cumulative incidence of post-HSCT MRD positivity in our present study and a higher CIR in previous studies.[17,25]

Previous studies have demonstrated the association of disease status before transplantation with the CIR after allo-HSCT.[2,10,12,16,17,25,31,32] In our study, we found that disease status was a risk factor for post-HSCT MRD positivity in the total ALL population and B-ALL, pediatric, and haplo-SCT subgroup patients. Several reasons

might account for these findings. First, there were more MRD-positive patients in ≥CR2 before HSCT than those in CR1. Second, several studies indicated that patients in ≥CR2 before transplantation had a higher CIR than those in CR1,[25,33] which supported our results that pre-HSCT disease status (≥CR2 *vs*. CR1) was a risk factor for post-HSCT MRD positivity because the association of post-HSCT MRD positivity with the CIR after transplantation was already confirmed.[15–17] Moreover, in the present study, the CIR was higher in ≥CR2 patients with a negative pre-HSCT MRD than in CR1 patients with a negative pre-HSCT MRD, suggesting that more cases in ≥CR2 than in CR1 had undetectable residual disease before transplantation using MFC and that these existent but undetectable leukemia cells would eventually result in post-HSCT MRD positivity and cause subsequent relapse.

Except for positive pre-HSCT MRD and disease status,[16,25,31,32] we observed that some other risk factors were also associated with post-HSCT MRD positivity in subgroup cases. In the pediatric subgroup, patients diagnosed with T-ALL tended to experience positive post-HSCT MRD. Research by others and us demonstrated that the transplant outcomes of children with T-ALL were poor.[34,35] It is reasonable to speculate that in children with T-ALL after transplantation, the poor prognosis is partly associated with the tendency toward positive post-HSCT MRD. In the adult subgroup, high risk in cytogenetic and molecular genetic features was observed as a risk factor for post-HSCT MRD positivity. Previous research has reported that high-risk cytogenetic and molecular genetic features are some of the leading risk factors for poor transplant outcomes in adult ALL patients.[36,37] The present study suggested that adults with high-risk cytogenetic and molecular genetics features were more likely to develop positive post-HSCT MRD, confirming the value of cytogenetics and molecular genetics for stratifying patients into appropriate risk groups. In addition, the divergence of the risk factors for post-HSCT MRD positivity between the total ALL patients and subgroups might be attributed to the differences in disease characteristics displayed in various patients during distinct times. Therefore, our data suggested that, for different patient groups, the prediction of post-HSCT MRD positivity should use different risk factors to forecast the posttransplant MRD outcomes more precisely.

This analysis, although involving a large number of patients, was limited by the retrospective nature of the study. Therefore, a prospective, multicenter study is needed to corroborate our results in the future. In addition, our cohort was composed of the MSDT and haplo-SCT modalities based on G-CSF- and ATG-induced immune tolerance.[7,24] Future research could be performed on unrelated donors and cord blood transplantation as well as posttransplant cyclophosphamide (PTCy)-based haplo-SCT.[38,39] In recent years, a handful of therapeutic strategies, such as CAR-T therapy,[21,40] blinatumomab,[41] TKIs,[19] DLI,[20] and IFN-α,[22] have been successfully applied for leukemia cell elimination for ALL patients with positive post-HSCT MRD. However, in our study, the primary endpoint was the cumulative incidence of post-HSCT MRD, which could not be affected by post-HSCT MRD-directed preemptive therapy. In addition, the effects of improved supportive care, and evolving transplantation techniques on post-HSCT MRD outcomes should be investigated further.

Based on this large-scale clinical cohort, our results demonstrated that pre-HSCT MRD was the most significant risk factor for positive post-HSCT MRD in the total ALL population as well as different subgroups. Moreover, disease status at transplant was crucial in predicting post-HSCT MRD in most ALL patients. The risk score system based on pre-HSCT MRD and disease status could be used to predict post-HSCT MRD and refine the risk stratification. These risk factors and the risk score for post-HSCT MRD positivity can be used to identify a specific population that could be considered for prophylaxis or early preemptive therapy.

Acknowledgement

The authors thank American Journal Experts for their assistance in editing this manuscript.

Funding

This work was partly supported by grants from the Beijing Municipal Science and Technology Commission (No. Z221100007422008) and the National Natural Science Foundation of China (No. 81930004).

Conflicts of interest

None.

References

1. Chang YJ, Pei XY, Huang XJ. Haematopoietic stem-cell transplantation in China in the era of targeted therapies: Current advances, challenges, and future directions. Lancet Haematol 2022;9:e919–e929. doi: 10.1016/S2352-3026(22)00293-9.
2. Short NJ, Jabbour E, Albitar M, de Lima M, Gore L, Jorgensen J, *et al*. Recommendations for the assessment and management of measurable residual disease in adults with acute lymphoblastic leukemia: A consensus of North American experts. Am J Hematol 2019;94:257–265. doi: 10.1002/ajh.25338.
3. Snowden JA, Sánchez-Ortega I, Corbacioglu S, Basak GW, Chabannon C, de la Camara R, *et al*. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: Current practice in Europe, 2022. Bone Marrow Transplant 2022;57:1217–1239. doi: 10.1038/s41409-022-01691-w.
4. Marks DI, Clifton-Hadley L, Copland M, Hussain J, Menne TF, McMillan A, *et al*. In-vivo T-cell depleted reduced-intensity conditioned allogeneic haematopoietic stem-cell transplantation for patients with acute lymphoblastic leukaemia in first remission: Results from the prospective, single-arm evaluation of the UKALL14 trial. Lancet Haematol 2022;9:e276–e288. doi: 10.1016/S2352-3026(22)00036-9.
5. Zhang Y, Bai L, Cheng Y, Lu A, Wang Y, Wu J, *et al*. Haploidentical hematopoietic stem cell transplantation may improve long-term survival for children with high-risk T-cell acute lymphoblastic leukemia in first complete remission. Chin Med J 2022;135:940–949. doi: 10.1097/CM9.0000000000001999.
6. Zhao X, Wu H, Cheng Y, Xu Z, Chen Y, Chang Y, *et al*. Bridging chimeric antigen receptor T-cell before transplantation improves prognosis of relapsed/refractory B-cell acute lymphoblastic leukemia. Chin Med J 2023;136:2011–2013. doi: 10.1097/CM9.0000000000002764.

7. Wang Y, Liu QF, Xu LP, Liu KY, Zhang XH, Ma X, *et al*. Haploidentical versus matched-sibling transplant in adults with Philadelphia-negative high-risk acute lymphoblastic leukemia: A biologically phase iii randomized study. Clin Cancer Res 2016;22:3467–3476. doi: 10.1158/1078-0432.CCR-15-2335.
8. Bazarbachi A, Labopin M, Aljurf M, Niittyvuopio R, Balsat M, Blaise D, *et al*. 20-year steady increase in survival of adult patients with relapsed Philadelphia-positive acute lymphoblastic leukemia post allogeneic hematopoietic cell transplantation. Clin Cancer Res 2022;28:1004–1012. doi: 10.1158/1078-0432.CCR-21-2675.
9. Sun YQ, Li SQ, Zhao XS, Chang YJ. Measurable residual disease of acute lymphoblastic leukemia in allograft settings: How to evaluate and intervene. Expert Rev Anticancer Ther 2020;20:453–464. doi: 10.1080/14737140.2020.1766973.
10. Bassan R, Brüggemann M, Radcliffe HS, Hartfield E, Kreuzbauer G, Wetten S. A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. Haematologica 2019;104:2028–2039. doi: 10.3324/haematol.2018.201053.
11. Campbell M, Kiss C, Zimmermann M, Riccheri C, Kowalczyk J, Felice MS, *et al*. Childhood acute lymphoblastic leukemia: Results of the randomized acute lymphoblastic leukemia intercontinental-Berlin-Frankfurt-Munster 2009 trial. J Clin Oncol 2023;41:3499–3511. doi: 10.1200/JCO.22.01760.
12. Kotrová M, Koopmann J, Trautmann H, Alakel N, Beck J, Nachtkamp K, *et al*. Prognostic value of low-level MRD in adult acute lymphoblastic leukemia detected by low- and high-throughput methods. Blood Adv 2022;6:3006–3010. doi: 10.1182/bloodadvances.2021006727.
13. Fan M, Wang Y, Lin R, Lin T, Huang F, Fan Z, *et al*. Haploidentical transplantation has a superior graft-versus-leukemia effect than HLA-matched sibling transplantation for Ph- high-risk B-cell acute lymphoblastic leukemia. Chin Med J 2022;135:930–939. doi: 10.1097/CM9.0000000000001852.
14. Liu J, Wu D, Liu Q, Chang Y, Xu Y, Huang F, *et al*. More than two courses of pre-transplant consolidation therapy benefits patients with acute myeloid leukemia in the first complete remission who underwent human leukocyte antigen-matched sibling allografts: A multicenter study. Chin Med J 2023;136:1855–1863. doi: 10.1097/CM9.0000000000002347.
15. Pulsipher MA, Carlson C, Langholz B, Wall DA, Schultz KR, Bunin N, *et al*. IgH-V(D)J NGS-MRD measurement pre- and early post-allotransplant defines very low- and very high-risk ALL patients. Blood 2015;125:3501–3508. doi: 10.1182/blood-2014-12-615757.
16. Wang XY, Fan QZ, Xu LP, Wang Y, Zhang XH, Chen H, *et al*. The quantification of minimal residual disease pre- and post-unmanipulated haploidentical allograft by multiparameter flow cytometry in pediatric acute lymphoblastic leukemia. Cytometry B Clin Cytom 2020;98:75–87. doi: 10.1002/cyto.b.21840.
17. Bader P, Salzmann-Manrique E, Balduzzi A, Dalle JH, Woolfrey AE, Bar M, *et al*. More precisely defining risk peri-HCT in pediatric ALL: Pre- vs post-MRD measures, serial positivity, and risk modeling. Blood Adv 2019;3:3393–3405. doi: 10.1182/bloodadvances.2019000449.
18. Jabbour EJ, Short NJ, Jain N, Jammal N, Jorgensen J, Wang S, *et al*. Blinatumomab is associated with favorable outcomes in patients with B-cell lineage acute lymphoblastic leukemia and positive measurable residual disease at a threshold of 10(-4) and higher. Am J Hematol 2022;97:1135–1141. doi: 10.1002/ajh.26634.
19. Liu H, Xuan L, Lin R, Deng L, Fan Z, Nie D, *et al*. A new pre-emptive TKIs strategy for preventing relapse based on BCR/ABL monitoring for Ph+ALL undergoing allo-HCT: A prospective clinical cohort study. Leukemia 2021;35:2054–2063. doi: 10.1038/s41375-020-01090-4.
20. Yan CH, Liu DH, Liu KY, Xu LP, Liu YR, Chen H, *et al*. Risk stratification-directed donor lymphocyte infusion could reduce relapse of standard-risk acute leukemia patients after allogeneic hematopoietic stem cell transplantation. Blood 2012;119:3256–3262. doi: 10.1182/blood-2011-09-380386.
21. Zhao XY, Xu ZL, Mo XD, Chen YH, Lv M, Cheng YF, *et al*. Preemptive donor-derived anti-CD19 CAR T-cell infusion showed a promising anti-leukemia effect against relapse in MRD-positive B-ALL after allogeneic hematopoietic stem cell transplantation.Leukemia2022;36:267–270.doi:10.1038/s41375-021-01351-w.
22. Mo XD, Zhang XH, Xu LP, Wang Y, Yan CH, Chen H, *et al*. IFN-alpha is effective for treatment of minimal residual disease in patients with acute leukemia after allogeneic hematopoietic stem cell transplantation: Results of a registry study. Biol Blood Marrow Transplant 2017;23:1303–1310. doi: 10.1016/j.bbmt.2017.04.023.
23. Balduzzi A, Di Maio L, Silvestri D, Songia S, Bonanomi S, Rovelli A, *et al*. Minimal residual disease before and after transplantation for childhood acute lymphoblastic leukaemia: Is there any room for intervention? Br J Haematol 2014;164:396–408. doi: 10.1111/bjh.12639.
24. Chang YJ, Wang Y, Xu LP, Zhang XH, Chen H, Chen YH, *et al*. Haploidentical donor is preferred over matched sibling donor for pre-transplantation MRD positive ALL: A phase 3 genetically randomized study. J Hematol Oncol 2020;13:27. doi: 10.1186/s13045-020-00860-y.
25. Zhao XS, Liu YR, Xu LP, Wang Y, Zhang XH, Chen H, *et al*. Minimal residual disease status determined by multiparametric flow cytometry pretransplantation predicts the outcome of patients with ALL receiving unmanipulated haploidentical allografts. Am J Hematol 2019;94:512–521. doi: 10.1002/ajh.25417.
26. Laboratory Diagnosis Group, Chinese Society of Hematology, Chinese Medical Association. Chinese consensus on minimal residual disease detection and interpretation of patients with acute lymphoblastic leukemia (2023) (in Chinese). Chinese Journal of Hematology 2023;44:267–275. doi: 10.3760/cma.j.issn.0253-2727.2023.04.002.
27. Brown PA, Shah B, Advani A, Aoun P, Boyer MW, Burke PW, *et al*. Acute lymphoblastic leukemia, version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:1079–1109. doi: 10.6004/jnccn.2021.0042.
28. Malard F, Mohty M. Acute lymphoblastic leukaemia. Lancet 2020;395:1146–1162. doi: 10.1016/S0140-6736(19)33018-1.
29. Masic D, Fee K, Bell H, Case M, Witherington G, Lansbury S, *et al*. Hyperactive CREB subpopulations increase during therapy in pediatric B-lineage acute lymphoblastic leukemia. Haematologica 2023;108:981–992. doi: 10.3324/haematol.2022.281177.
30. Pagliuca S, Gurnari C, Hercus C, Hergalant S, Hong S, Dhuyser A, *et al*. Leukemia relapse via genetic immune escape after allogeneic hematopoietic cell transplantation. Nat Commun 2023;14:3153. doi: 10.1038/s41467-023-38113-4.
31. Forman SJ, Rowe JM. The myth of the second remission of acute leukemia in the adult. Blood 2013;121:1077–1082. doi: 10.1182/blood-2012-08-234492.
32. Kaito S, Kurosawa S, Najima Y, Sakaida E, Shingai N, Fukuda T, *et al*. Allogeneic hematopoietic stem cell transplantation for adult Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia in second complete remission. Transplant Cell Ther 2022;28:326.e1–326.e10. doi: 10.1016/j.jtct.2022.03.017.
33. Nagler A, Labopin M, Houhou M, Aljurf M, Mousavi A, Hamladji RM, *et al*. Outcome of haploidentical versus matched sibling donors in hematopoietic stem cell transplantation for adult patients with acute lymphoblastic leukemia: A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. J Hematol Oncol 2021;14:53. doi: 10.1186/s13045-021-01065-7.
34. Xu ZL, Huang XJ, Liu KY, Chen H, Zhang XH, Han W, *et al*. Haploidentical hematopoietic stem cell transplantation for paediatric high-risk T-cell acute lymphoblastic leukaemia. Pediatr Transplant 2016;20:572–580. doi: 10.1111/petr.12704.
35. Bakr M, Rasheed W, Mohamed SY, Al-Mohareb F, Chaudhri N, Al-Sharif F, *et al*. Allogeneic hematopoietic stem cell transplantation in adolescent and adult patients with high-risk T cell acute lymphoblastic leukemia. Biol Blood Marrow Transplant 2012;18:1897–1904. doi: 10.1016/j.bbmt.2012.07.011.
36. Gleissner B, Gökbuget N, Bartram CR, Janssen B, Rieder H, Janssen JW, *et al*. Leading prognostic relevance of the BCR-ABL translocation in adult acute B-lineage lymphoblastic leukemia: A prospective study of the German Multicenter Trial Group and confirmed polymerase chain reaction analysis. Blood 2002;99:1536–1543. doi: 10.1182/blood.v99.5.1536.
37. Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M, *et al*. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): Analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group

(ECOG) 2993 trial. Blood 2007;109:3189–3197. doi: 10.1182/blood-2006-10-051912.
38. Liang EC, Craig J, Torelli S, Cunanan K, Iglesias M, Arai S, *et al*. Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia in the modern era. Transplant Cell Ther 2022;28:490–495. doi: 10.1016/j.jtct.2022.05.010.
39. Wieduwilt MJ, Metheny L, Zhang MJ, Wang HL, Estrada-Merly N, Marks DI, *et al*. Haploidentical vs sibling, unrelated, or cord blood hematopoietic cell transplantation for acute lymphoblastic leukemia. Blood Adv 2022;6:339–357. doi: 10.1182/bloodadvances.2021004916.
40. Lin M, Zhao X, Chang Y, Zhao X. Current assessment and management of measurable residual disease in patients with acute lymphoblastic leukemia in the setting of CAR-T-cell therapy. Chin Med J 2023;137:140–151. doi: 10.1097/CM9.0000000000002945.
41. Keating AK, Gossai N, Phillips CL, Maloney K, Campbell K, Doan A, *et al*. Reducing minimal residual disease with blinatumomab prior to HCT for pediatric patients with acute lymphoblastic leukemia. Blood Adv 2019;3:1926–1929. doi: 10.1182/bloodadvances.2018025726.

How to cite this article: Wang YW, Fu GM, Xu LP, Wang Y, Cheng YF, Zhang YY, Zhang XH, Liu YR, Liu KY, Huang XJ, Chang YJ. Risk factors for positive post-transplantation measurable residual disease in patients with acute lymphoblastic leukemia. Chin Med J 2025;138:1084–1093. doi: 10.1097/CM9.0000000000003150