Impact of minimal residual disease on the outcome of hematopoietic stem cell transplantation for childhood acute lymphoblastic leukemia within the FORUM trial

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Abstract

In the randomized cohort of the international phase-III FORUM trial, which showed the superiority of total-body irradiation (TBI) over chemotherapy-based conditioning prior to hematopoietic stem cell transplantation (HSCT) for pediatric acute lymphoblastic leukemia (ALL), type of conditioning and remission phase, but not pre-HSCT minimal residual disease (MRD), were associated with outcome. We report the impact of MRD within the extended FORUM cohort. Patients (N=1,014) aged 4-21 years old, transplanted from a matched donor who had ≥1 MRD measurement prior to and/or 100 days and/or one year after HSCT were eligible. A threshold of 0.01% defined MRD positivity *versus* negativity. Prior to HSCT, 21% of patients were MRD_{pos}. Three-year event-free survival (EFS) was 0.73 and 0.59 (P<0.001), and 3-year cumulative incidence of relapse (CIR) was 0.20 and 0.33 (P<0.001) in MRD_{neg} and MRD_{pos} patients, respectively. The level of MRD positivity pre-HSCT (<0.1% *vs*. ≥0.1%) did not significantly affect outcome. Pre-HSCT MRD_{neg} and TBI/etoposide conditioning were associated with a 2-fold lower risk of relapse, whereas MRD_{pos} had a 2-fold higher risk of any failure and/or death. No detrimental effect of MRD_{pos} pre-HSCT could be demonstrated in patients with T-cell ALL. MRD_{pos} *versus* MRD_{neg} patients at day 100 had an EFS of 0.47 *versus* 0.77 (P<0.001) and a CIR of 0.51 *versus* 0.17 (P<0.001), respectively, but post-HSCT MRD_{pos} did not necessarily imply relapse. In conclusion, the MRD status pre-HSCT and at day 100 post-HSCT was a strong prognostic factor for children transplanted for ALL in the extended FORUM cohort.

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is considered beneficial in first complete remission (CR1) for approximately 5% of children, adolescents and young adults (CAYA) with very high-risk acute lymphoblastic leukemia (ALL) and for the majority experiencing disease recurrence.[1-6] ALL relapse is the primary cause of treatment failure after HSCT, since transplant-related mortality (TRM) in CAYA has been significantly reduced to <10%, mainly due to refined HLA-typing, improved graft-*versus*-host disease (GvHD) management, and better infection prophylaxis and treatment.[6-9]

The prognostic role of minimal residual disease (MRD) for patients with acute leukemia has been consistently demonstrated in the HSCT setting across studies of multiple co-operative groups or single institutions.[3,6,10-14]

The randomized, open-label, international, multicenter, phase III trial ALL SCTped 2012 FORUM - Allogeneic Stem Cell Transplantation in Children and Adolescents with Acute Lymphoblastic Leukaemia - was designed to test for the non-inferiority of chemotherapy-based regimens *versus* total body irradiation plus etoposide (TBI/VP16) in patients ≥4 years old and <21 years old at the time of HSCT with an indication for transplantation for ALL in morphological CR from a compatible donor. A futility stopping rule was breached and random assignment halted because patients receiving chemo-conditioning with fludarabine, thiotepa, and either busulfan or treosulfan had inferior overall survival (OS) compared with those who received TBI/VP16 due to a higher cumulative incidence of relapse (CIR) (0.33; 95% Confidence Interval [CI]: 0.25-0.40 *vs*. 0.12; 95% CI: 0.08-0.17; P<0.0001).[15] In the randomized cohort, conditioning and remission phase were the only variables associated with risk of relapse whereas, unexpectedly, no association between pre-HSCT MRD and CIR or event-free survival (EFS) was detected.[15]

The primary aim of this analysis was to assess the impact of MRD status before and after HSCT in the extended FORUM cohort, which included patients enrolled prior to and after randomization was stopped.

Methods

Eligibility criteria

Patients ≥4 years old in the FORUM trial (EudraCT: 2012-003032-22; EU CT: 2024-512657-24-00; clinicaltrials.gov: NCT01949129) enrolled between April 2013 and February 1st, 2024, and transplanted from an HLA-identical sibling or a 10/10 or a 9/10 HLA-matched related or unrelated donor were eligible, as long as they had at least one MRD measurement either prior to HSCT and/or 100 days after and/or one year after HSCT (±45 days), assessed by polymerase chain reaction (PCR) or flow cytometry in the bone marrow, recorded in the study database (Marvin).

The cohort included patients from 97 centers in 21 countries where the randomization took place (randomizing countries) and 8 countries in which the randomization was not planned that could provide MRD data. Within the randomizing countries, non-randomized patients were also included (i.e., those considered ineligible for randomization due to patient-related factors or family/physician's decision, or because they were enrolled after March 2019, when the randomization was stopped). Thus, the cohort of this analysis comprises a much broader population of patients than the previously reported FORUM analysis.[15]

Transplant procedure

Details regarding transplant procedures have been published previously[15] and are outlined in the *Online Supplementary Appendix*. (See *Online Supplementary Figure S1* for conditioning regimens.)

Changes in immunosuppression or administration of donor lymphocyte infusion (DLI) due to MRD levels were beyond the scope of this investigation.

Minimal residual disease analysis

Minimal residual disease status reported within the 45 days prior to HSCT and at day +100 and day +365 (±45 days) was analyzed (see *Online Supplementary Appendix*). A threshold of $1x10^{-4}$ was selected to stratify patients according to their MRD level. Patients with undetectable MRD, detectable but unquantifiable MRD, and those who were MRD positive but $<1x10^{-4}$ by PCR or <0.01% by flow cytometry were defined as MRD_{neg} whereas patients with positive MRD $\geq 1x10^{-4}$ by PCR or ≥0.01% by flow cytometry were defined as MRD_{pos} consistent with previous reports.[3,13,16] For additional sub-analyses, patients with positive MRD were further divided in subgroups of patients with MRD $\geq 1x10^{-4}$ but $<1x10^{-3}$ ($MRD_{pos\text{-}low}$), and $\geq 1x10^{-3}$ ($MRD_{pos\text{-}high}$).

The protocol and statistical analysis plan were approved by the Vienna Investigational Review Board (IRB) and Ethics Committee (EC), as well as the IRB and EC for each center. The trial was performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from each participant or each participant's guardian. Statistical methods are detailed in the *Online Supplementary Appendix*.

Results

Enrollment

Of the 1,619 patients enrolled up to February 1st, 2024, the first was transplanted in April 2013 and the last in November 2023. Of 1,247 patients aged four years or older and transplanted from a compatible donor, 1,014 (81%) met the inclusion criteria regarding MRD data as shown in the Consort diagram (Figure 1). (MRD levels were recorded for at least one timepoint, namely for 852 before HSCT, 714 at 100 days and 504 at one year after HSCT). Of 2,070 MRD assessments, 1,385 (67%) were by PCR and 685 (33%) by flow cytometry.

Patient outcomes were last updated on January 1st, 2024, resulting in a median follow-up of 3.0 years (range: 0.03-9.35).

Patient characteristics are listed in *Online Supplementary Table S1*. In brief, median age was 10.5 years (1st and 3rd

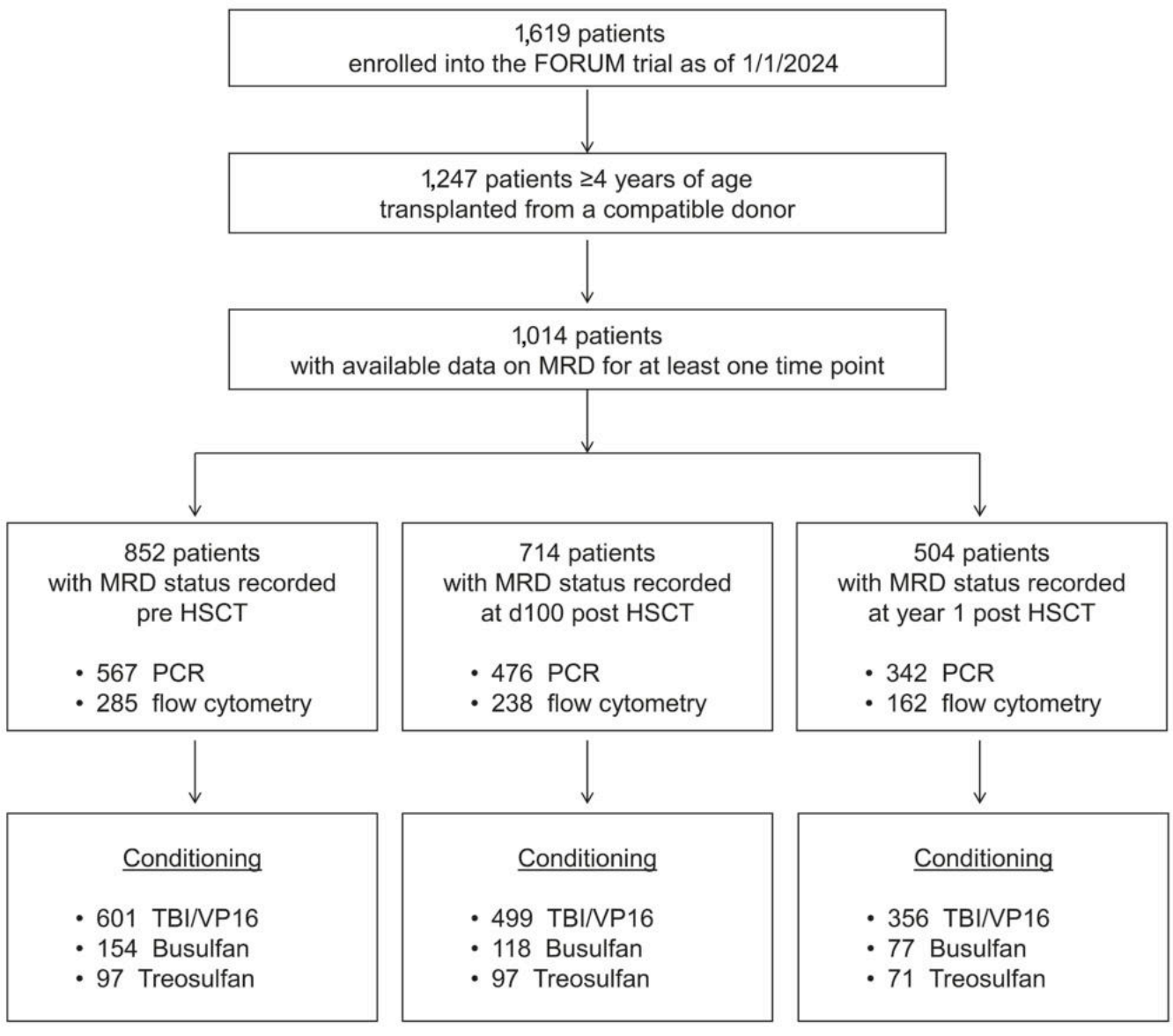

Figure 1. CONsolidated Standards Of Reporting Trials diagram. CONSORT: CONsolidated Standards Of Reporting Trials. HSCT: hematopoietic stem cell transplantation; MRD: minimal residual disease; PCR: polymerase chain reaction; TBI: total body irradiation; VP16: etoposide.

interquartile: 7.7 and 14.1 years). The conditioning regimen consisted of TBI/VP16 in 719 (71%) and chemo-conditioning in 295 (29%) patients (busulfan-based, 16%; treosulfan-based 13%). ALL immunophenotype was B lineage in 76% and T lineage in 23%. In terms of disease risk, 47% were transplanted in CR1, 45% in CR2, and 7% ≥CR3; 29% were higher risk (see *Online Supplementary Appendix*). Grafts were from matched donors (MD) in 71% and from matched sibling donor (MSD) in 29%; 71% received BM stem cells.

Minimal residual disease status pre-hematopoietic stem cell transplantation

Patient distribution - Of the 852 patients with pre-HSCT MRD status reported, 79% were MRD_{neg} and 21% were MRD_{pos}. The proportion of MRD_{pos} patients was higher among recipients conditioned with TBI/VP16 (81%) or busulfan-based chemo-conditioning (82%) *versus* treosulfan-based chemo-conditioning (65%) (Table 1).

Engraftment - 832 of 852 patients with pre-HSCT MRD status achieved myeloid engraftment (absolute neutrophil count >0.5x10^9/L) at a median of 21 days after HSCT, 821 achieved platelet engraftment (unsupported platelet count >50x10^9/L) at a median of 32 days after HSCT, and 20 patients did not achieve myeloid engraftment by day 100. Cumulative incidence of myeloid and platelet engraftment at 30 days was 0.93 (Standard Error [SE]: 0.01) and 0.86 (SE: 0.01), respectively. Engraftment kinetics did not differ by MRD status pre-HSCT (*Online Supplementary Figure S2*).

Outcomes - 3-year OS were 0.82 (SE: 0.02) and 0.71 (SE: 0.04) for the MRD_{neg} and MRD_{pos} patients pre-HSCT, respectively (*P*=0.003), and 3-year EFS was 0.73 (SE: 0.02) and 0.59 (SE: 0.04), respectively (*P*<0.001) (Figure 2A, B, *Online Supplementary Table S2*).

Three-year CIR was 0.20 (SE: 0.02) and 0.33 (SE: 0.04) for the pre-HSCT MRD_{neg} and MRD_{pos} groups, respectively (*P*<0.001), whereas 3-year TRM was 0.06 (SE: 0.01) and 0.07 (SE: 0.02), respectively (*P*=0.53) (Figure 2C, D, *Online Supplementary Table S2*).

According to disease risk profile, 3-year CIR was 0.17 (SE: 0.02) and 0.27 (SE: 0.04) for the lower risk patients who had pre-HSCT MRD_{neg} and MRD_{pos}, respectively (*P*=0.020), and 0.26 (SE: 0.03) and 0.57 (SE: 0.09) for the higher risk patients who had pre-HSCT MRD_{neg} and MRD_{pos}, respectively (*P*=0.036) (*Online Supplementary Table S2*).

Differentiated outcomes for MRD positive patients according to level of positivity are detailed in *Online Supplementary Figure S4* and no differences could be detected between pre-HSCT $MRD_{pos\text{-}low}$ and $MRD_{pos\text{-}high}$ patients.

Detailed outcomes for pre-HSCT MRD_{neg} and MRD_{pos} patients receiving TBI/VP16 *versus* those receiving chemo-conditioning are shown in Figure 2G, H, and *Online Supplementary Table S2*.

For patients with B-ALL, 3-year EFS was 0.73 (SE: 0.02) and 0.54 (SE: 0.05) (*P*<0.001) and 3-year CIR was 0.20 (SE: 0.02) and 0.38 (SE: 0.05) (*P*<0.001), for the pre-HSCT MRD_{neg} and MRD_{pos} groups, respectively. For patients with T-ALL, 3-year EFS was 0.75 (SE: 0.04) and 0.73 (SE: 0.07) (*P*=0.747) and 3-year CIR was 0.18 (SE: 0.03) and 0.21 (SE: 0.07) (*P*=0.796) for pre-HSCT MRD_{neg} and MRD_{pos} groups, respectively (Figure 3, *Online Supplementary Table S2*). The test for interaction between immunophenotype and MRD for the purpose of EFS was not significant (*P*=0.349).

The impact of MRD within B- and T-lineage ALL, according to disease risk profile and conditioning regimen, is shown in Table 2.

Outcome results by univariable analyses are summarized in *Online Supplementary Table S2*.

Acute and chronic graft-versus-host disease - acute GvHD (aGvHD) grade and incidence overall and by pre-HSCT MRD status and by conditioning regimen were reported for 799 patients (94%) with MRD status reported pre-HSCT (Table 3). The test for interaction between aGvHD and MRD for the purpose of EFS was not significant (*P*=0.914).

Cumulative incidence (CI) of chronic GvHD (cGvHD) was 0.12 (SE: 0.01) for MRD_{neg} and 0.20 (SE: 0.03) for MRD_{pos} patients pre-HSCT (*P*=0.017) (*Online Supplementary Figure S3A*). The CI of limited and extensive cGVHD are also reported in *Online Supplementary Figure S3B* and *C*.

In patients with MRD status pre-HSCT, 3-year EFS was 0.74 (SE: 0.02), 0.82 (SE: 0.03), and 0.61 (SE: 0.06) for those with no or grade I aGvHD, grade II aGvHD, or grade III-IV aGvHD, respectively (*P*=0.027). Three-year CIR was 0.23 (SE: 0.02), 0.15 (SE: 0.03), and 0.21 (SE: 0.06) in patients with no or grade I aGvHD, grade II aGvHD or grade III-IV aGvHD, respectively (*P*=0.105). Three-year TRM was 0.03 (SE: 0.01), 0.02 (SE: 0.01), and 0.14 (SE: 0.05) in patients with no or grade I aGvHD, grade II aGvHD or grade III-IV aaGvHD, respectively (*P*=0.002) (*Online Supplementary Figure S5*).

Multivariable analyses - the Hazard Ratio (HR) of relapse in the pre-HSCT MRD_{pos} *versus* MRD_{neg} groups was 2.039 (*P*<0.0001) in the multivariable analysis, adjusting for type of donor (MD *vs*. MSD; not significant [n.s.]), remission phase and risk profile (higher risk *vs*. lower risk, HR: 2.209; *P*<0.0001), type of conditioning (chemo-conditioning *vs*. TBI/VP16, HR: 2.291; *P*<0.0001), age (>10 years *vs*. ≤10 years; n.s.), and immunophenotype (B lineage *vs*. others; n.s.). Results of multivariable analyses are reported in Table 4, in which the HR of failure from any cause (1-EFS), associated with MRD status, risk profile and type of conditioning; the HR of death (1-OS) are also shown.

The HR of non-leukemic death was not significantly associated with pre-HSCT MRD status or conditioning regimen, but was associated with remission phase (higher *vs*. lower risk, HR: 2.026; *P*=0.035) and older age (>10 years *vs*. ≤10 year, HR: 2.793; *P*=0.002), and there was a trend for an association with donor type (MD *vs*. MSD, HR; 2.041; *P*=0.059).

In the model accounting for aGvHD and cGvHD, as time-dependent co-variates, the occurrence of aGvHD grade II compared with grade 0 (absent) or I, was associated with

Table 1. Patient distribution by minimal residual disease status pre-hematopoietic stem cell transplantation and by conditioning regimen in patients for whom minimal residual disease status was available pre-hematopoietic stem cell transplantation.

	Total		MRD_{neg} (neg, NQ, <10^{-4})		MRD_{pos} (pos ≥10^{-4})		*P*
	N	%	N	%	N	%	
Total	852	100	674	79	178	21	
Sex							
Male	552	65	436	65	116	65	0.930
Female	300	35	238	35	62	35	
Age, years							
4-10	415	49	327	49	88	49	0.926
10-14	241	28	190	28	51	29	
14-18	166	19	134	20	32	18	
>18	30	4	23	3	7	4	
Median age, years (Q1, Q3)	10.4 (7.7-14.0)	-	10.7 (7.9-14.0)	-	9.8 (7.4-13.5)	-	0.409
Donor							
MSD	241	28	190	28	51	29	0.926
MD	611	72	484	72	127	71	
Remission status							
CR1	412	48	318	47	94	53	0.236
CR2	376	44	305	45	71	40	
CR3	60	7	48	7	12	7	
>CR3	3	0	3	0	0	0	
Missing	1	-	0	-	1	-	
Risk							
CR1, CR2 late relapse	602	71	466	70	136	77	0.076
CR2 early relapse, ≥CR3	243	29	202	30	41	23	
Missing	7	-	6	-	1	-	
Stem cell source							
BM	595	70	465	69	130	73	0.059
PB	231	27	192	29	39	22	
CB	23	3	15	2	8	5	
Missing	3	-	2	-	1	-	
Conditioning regimen							
TBI/VP16	601	71	485	72	116	65	0.002
FLU/THIO/BU	154	18	126	19	28	16	
FLU/THIO/TREO	97	11	63	9	34	19	
Immunophenotype							
BCP	651	77	526	79	125	70	0.049
T-ALL	195	23	142	21	53	30	
Other	2	0	2	0	0	0	
Missing	4	-	4	-	0	-	
BCR-ABL or *t*(9,22)							
Negative	741	91	585	91	156	91	1.000
Positive	73	9	58	9	15	9	
Missing	38	-	31	-	7	-	
TEL-AML or *t*(12,21)							
Negative	693	89	545	88	148	92	0.254
Positive	84	11	71	12	13	8	
Missing	75	-	58	-	17	-	
aff1(aff4)mll or *t*(4,11)							
Negative	755	97	595	97	160	97	0.787
Positive	21	3	16	3	5	3	
Missing	76	-	63	-	13	-	

BCP: B-cell precursor; BM: bone marrow; BU: busulfan; CB: cord blood; CR: complete remission; FLU: fludarabine; HSCT: hematopoietic stem cell transplantation; MD: matched donor; MRD: minimal residual disease; MSD: matched sibling donor; neg: negative; NQ: non-quantifiable; pos: positive; PB: peripheral blood; T-ALL: T-cell acute lymphoblastic leukemia; TBI: total body irradiation; THIO: thiotepa; TREO: treosulfan; VP16: etoposide.

a lower risk of death from any cause (HR: 0. 587; *P*=0.031), of any failure (HR: 0.613; *P*=0.010), and of relapse (HR: 0.574; *P*=0.011). The occurrence of grade III-IV compared with grade 0-I aGvHD was associated with a higher risk of

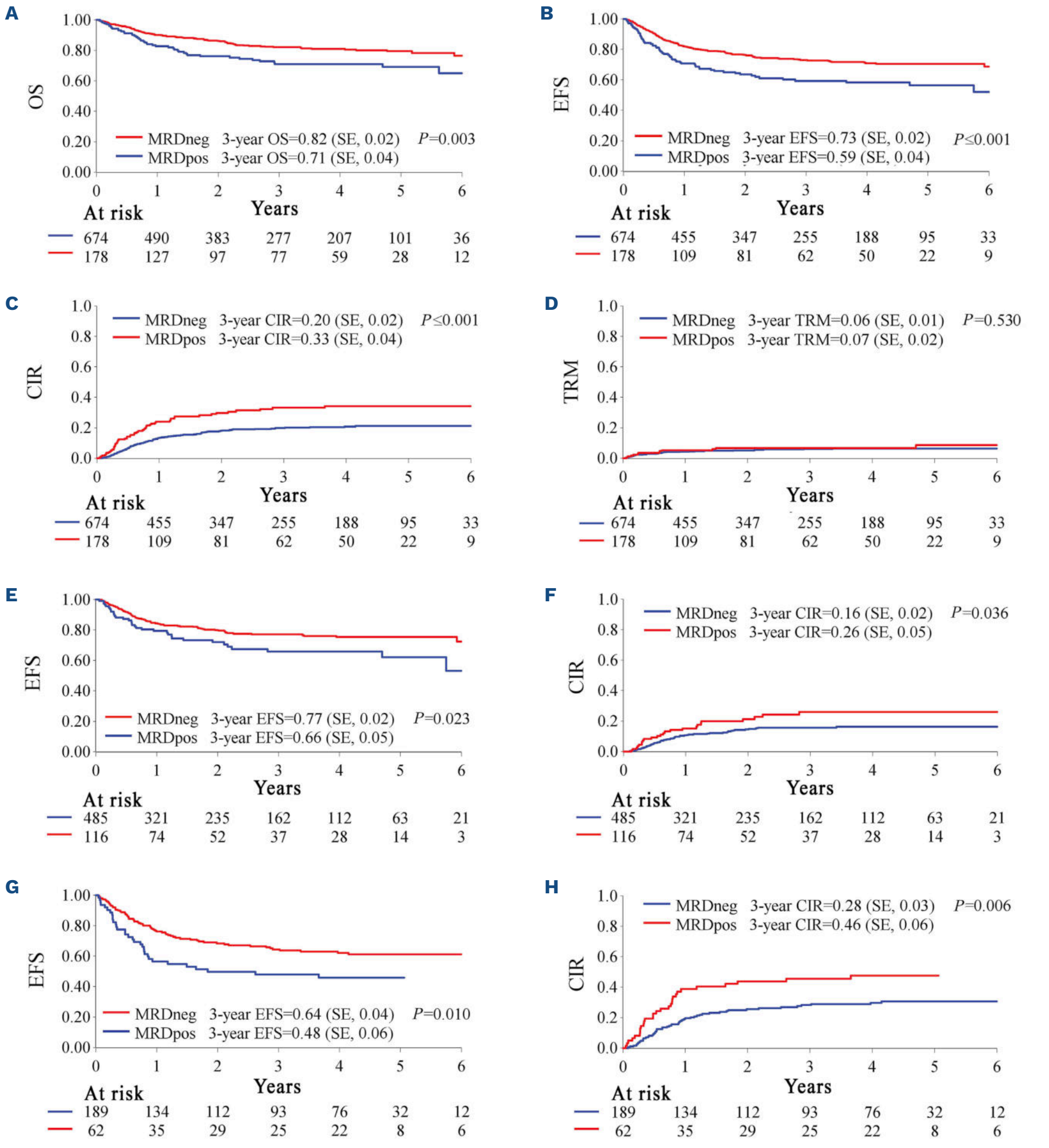

Figure 2. Outcome according to minimal residual disease status at the time of hematopoietic stem cell transplantation. Overall survival (OS) (A), event-free survival (EFS) (B), cumulative incidence of relapse (CIR) (C), and transplant-related mortality (TRM) (D). EFS (E) and CIR (F) for the total body irradiation/etoposide (TBI/VP16) subgroup. EFS (G) and CIR (H) for the chemo-conditioning subgroup. HSCT: hematopoietic stem cell transplantation; MRD: minimal residual disease; PCR: polymerase chain reaction; pos: positive; SE: Standard Error; TBI: total body irradiation; VP16: etoposide.

death from any cause (HR: 1. 741; *P*=0.026) and of TRM (HR: 3.543; *P*=0.001) (Table 4). Extensive cGvHD was associated with a significantly higher risk of TRM (HR: 4.913; *P*=0.001).

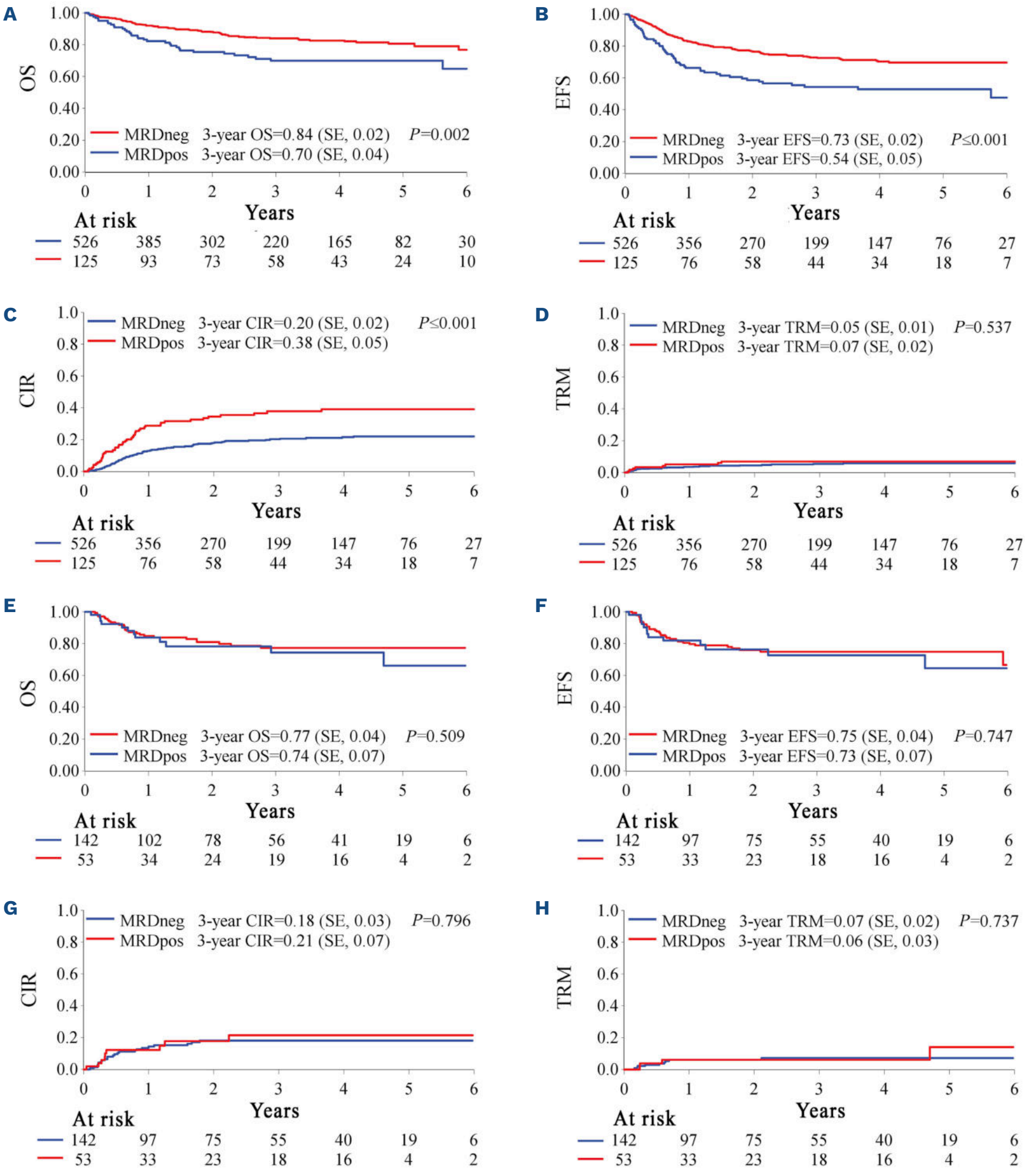

Figure 3. Outcome by minimal residual disease status at the time of hematopoietic stem cell transplantation according to immunophenotype. Overall survival (OS) (A), event-free survival (EFS) (B), cumulative incidence of relapse (CIR) (C), and transplant-related mortality (TRM) (D) for patients affected with B-lineage acute lymphoblastic leukemia (ALL). OS (E), EFS (F), CIR (G), and TRM (H) for those affected with T-lineage ALL. HSCT: hematopoietic stem cell transplantation; MRD: minimal residual disease; PCR: polymerase chain reaction; pos: positive; SE: Standard Error; TBI: total body irradiation; VP16: etoposide.

Table 2. Univariable analysis: outcomes overall and by minimal residual disease status pre-hematopoietic stem cell transplantation for the subgroups of patients defined by immunophenotype.

A. Overall survival (OS) and event-free survival (EFS) are reported for patients affected with B- and T-lineage ALL according to conditioning regimen and risk profile.

Risk factor	OS									EFS								
	MRD_{neg} (neg, NQ, <10^{-4})			MRD_{pos} (≥10^{-4})			*P*	3-year pOS	*P*	MRD_{neg} (neg, NQ, <10^{-4})			MRD_{pos} (≥10^{-4})			*P*	3-year pEFS	*P*
	N	events	3-year pOS	N	events	3-year pOS				N	events	3-year pEFS	N	events	3-year pEFS			
TBI																		
B-lineage	379	38	0.88±0.02	76	17	0.75±0.05	0.007	0.85±0.02	0.055	379	69	0.81±0.02	76	26	0.68±0.06	0.003	0.75±0.02	0.892
T- lineage	102	18	0.77±0.05	40	8	0.75±0.09	0.689	0.76±0.04		102	22	0.76±0.05	40	8	0.75±0.09	0.903	0.76±0.04	
Chemo-conditioning																		
B-lineage	147	35	0.77±0.04	49	17	0.64±0.07	0.203	0.74±0.03	0.905	147	56	0.62±0.04	49	28	0.45±0.07	0.016	0.58±0.04	0.172
T- lineage	40	9	0.77±0.07	13	4	0.69±0.13	0.493	0.75±0.06		40	11	0.72±0.07	13	5	0.62±0.13	0.340	0.70±0.06	
CR1+CR2 late relapse																		
B-lineage	348	41	0.87±0.02	88	17	0.78±0.05	0.150	0.85±0.02	0.062	348	75	0.76±0.03	88	31	0.65±0.05	0.028	0.74±0.02	0.633
T- lineage	114	19	0.79±0.04	48	10	0.76±0.07	0.600	0.78±0.04		114	22	0.78±0.04	48	11	0.75±0.07	0.634	0.77±0.04	
CR2 early relapse + ≥CR3																		
B-lineage	173	30	0.79±0.04	37	17	0.51±0.09	<0.001	0.73±0.04	0.746	173	47	0.67±0.04	37	23	0.27±0.09	<0.001	0.60±0.04	0.998
T- lineage	27	7	0.74±0.09	4	2	0.50±0.25	0.053	0.70±0.08		27	10	0.67±0.09	4	2	0.50±0.25	0.150	0.64±0.09	

B. Cumulative incidence (CI) of relapse (CIR) and CI of treatment-related mortality (TRM) are reported for patients affected with B- and T-lineage acute lymphoblastic leukemia (ALL) according to conditioning regimen and risk profile.

Risk factor	CIR									CI of TRM								
	MRD_{neg} (neg, NQ, <10^{-4})			MRD_{pos} (≥10^{-4})			*P*	3-year CIR	*P*	MRD_{neg} (neg, NQ, <10^{-4})			MRD_{pos} (≥10^{-4})			*P*	3-year CI of TRM	*P*
	N	events	3-year CIR	N	events	3-year CIR				N	events	3-year CI of TRM	N	events	3-year CI of TRM			
TBI																		
B-lineage	379	47	0.15±0.02	76	20	0.30±0.06	0.008	0.18±0.02	0.956	379	14	0.04±0.01	76	5	0.07±0.03	0.283	0.05±0.01	0.297
T- lineage	102	15	0.17±0.04	40	5	0.19±0.08	0.787	0.18±0.04		102	6	0.07±0.03	40	3	0.05±0.04	0.697	0.07±0.02	
Chemo-conditioning																		
B-lineage	147	44	0.30±0.04	49	25	0.49±0.07	0.009	0.35±0.04	0.137	147	11	0.07±0.02	49	3	0.06±0.03	0.693	0.07±0.02	0.936
T- lineage	40	8	0.20±0.06	13	4	0.31±0.13	0.357	0.23±0.06		40			13				0.08±0.04	
CR1+CR2 late relapse																		
B-lineage	348	51	0.17±0.02	88	26	0.30±0.05	0.004	0.20±0.02	0.646	348	15	0.05±0.01	88	4	0.05±0.02	0.945	0.05±0.01	0.460
T- lineage	114	17	0.17±0.04	48	7	0.19±0.07	0.937	0.18±0.03		114	5	0.05±0.02	48	4	0.07±0.04	0.324	0.06±0.02	
CR2 early relapse + ≥CR3																		
B-lineage	173	38	0.27±0.04	37	19	0.57±0.09	<0.001	0.33±0.04	0.667	173	9	0.05±0.02	37	4	0.12±0.06	0.201	0.07±0.02	0.591
T- lineage	27	6	0.22±0.08	4	2	0.50±0.25	0.084	0.26±0.08		27	3	0.11±0.06	4	0	0.00±0.00	0.997	0.10±0.05	

CR: complete remission; MRD: minimal residual disease; N: number; neg: negative; NQ: non-quantifiable; pos: positive; TBI: total body irradiation.

Minimal residual disease status after hematopoietic stem cell transplantation

Of the 714 patients alive and in continuous morphological CR who were assessed for MRD 100 days after HSCT, 92% were MRD_{neg} and 8% MRD_{pos}.

Three-year OS was 0.88 (SE: 0.01) for MRD_{neg} and 0.63 (SE: 0.07) for MRD_{pos} 100 days after HSCT (*P*<0.001), whereas 3-year EFS was 0.77 (SE: 0.02) and 0.47 (SE: 0.07) (*P*<0.001), respectively (*Online Supplementary Figure S6A, B*). Three-year CIR was 0.17 (SE: 0.02) and 0.51 (SE: 0.07) for MRD_{neg} and MRD_{pos} 100 days after HSCT, respectively (*P*<0.001), whereas 3-year TRM was 0.04 (SE: 0.01) and 0.02 (SE: 0.02), respectively (*P*=0.370) (*Online Supplementary Figure S6A*). Similarly, the outcome of the 504 patients alive and in continuous CR whose MRD status was assessed one year after HSCT and was shown with 95% being MRD_{neg} and 5% being MRD_{pos} (*Online Supplementary Figure S7*).

Discussion

This study demonstrated the impact of MRD pre-HSCT on outcome in the extended FORUM cohort of CAYA with ALL in CR aged 4-21 years receiving an HSCT from a compatible donor after myeloablative conditioning. According to previous reports,[3,13,16] the MRD_{neg} group included patients with MRD positivity that was either unquantifiable or $<1x10^{-4}$. The majority of the patients (79%) were MRD_{neg} pre-HSCT, i.e., negative/non-quantifiable / $<1x10^{-4}$, as assessed by either PCR or flow cytometry. MRD status pre-HSCT was highly predictive of outcome. The finding of higher 3-year EFS (0.73 *vs*. 0.59; *P*<0.001) and OS (0.82 *vs*. 0.71; *P*=0.003), and lower CIR (0.20 *vs*. 0.33; *P*<0.001) in MRD_{neg} *versus* MRD_{pos} patients is consistent with previous reports in CAYA patients.[3,6,10-14]

There are many reasons which may explain the discrepancy between the present analysis and the randomized FORUM cohort published in 2021, in which no significant association between MRD pre-HSCT and outcome was detected.[15] Namely: i) the sample size of the current analysis is greater (852 *vs*. 336 patients); ii) a different cut-off was used to define MRD positivity by flow cytometry (0.01%, consistent with $1x10^{-4}$ used in PCR analyses, instead of the 0.1% adopted in the previous analysis; and iii) median follow-up was longer (3.0 *vs*. 2.1 years).[15] The proportion of MRD_{neg} patients in the current analysis was 79% *versus* 57% in the previous analysis, which may reflect better disease control pre-HSCT, although the proportion of patients who had received further intensified treatment is unknown.

There was no difference in prognostic value of MRD status

Table 3. Incidence of acute graft-*versus*-host disease by minimal residual disease status pre-hematopoietic stem cell transplantation and by conditioning regimen in patients for whom minimal residual disease status was available pre-hematopoietic stem cell transplantation.

	Total							TBI/VP16						FLU/THIO/BU or FLU/THIO/TREO					
	Total		MRD_{neg} (neg, NQ, $<10^{-4}$)		MRD_{pos} ($\geq10^{-4}$)		*P*	Total	MRD_{neg} (neg, NQ, $<10^{-4}$)		MRD_{pos} ($\geq10^{-4}$)		*P*	Total	MRD_{neg} (neg, NQ, $<10^{-4}$)		MRD_{pos} ($\geq10^{-4}$)		*P*
	N	%	N	%	N	%		N	N	%	N	%		N	N	%	N	%	
Total	852	100	674	100	178	100		601	485	100	116	100		251	189	100	62	100	
aGvHD grade													-						
Absent	334	42	261	39	73	41	-	205	163	34	42	36	-	129	98	52	31	50	-
I	202	25	169	25	33	19	-	159	136	28	23	20	-	43	33	17	10	16	-
II	193	24	151	22	42	24	-	145	116	24	29	25	-	48	35	19	13	21	-
III	52	6	35	5	17	10	-	38	25	5	13	11	-	14	10	5	4	6	-
IV	18	2	12	2	6	3	-	14	11	2	3	3	-	4	1	1	3	5	-
Unknown	49	-	42	6	7	4	-	38	32	7	6	5	-	11	10	5	1	2	-
Death prior to d100 (without aGvHD)	4	0.5	4	1	0	0	-	2	2	0	0	0	-	2	2	1	0	0	-
Grade 0-I/II	733	91	585	87	148	83	0.021	511	417	86	94	81	0.042	222	168	89	54	87	0.172
Grade III-IV	70	9	47	7	23	13	-	52	36	7	16	14	-	18	11	6	7	11	-
Unknown	49	-	42	6	7	4	-	38	32	7	6	5	-	11	10	5	1	2	-
Grade 0-I	540	67	434	64	106	60	0.045	366	301	62	65	56	0.090	174	133	70	41	66	0.337
Grade II	193	24	151	22	42	24	-	145	116	24	29	25	-	48	35	19	13	21	-
Grade III-IV	70	9	47	7	23	13	-	52	36	7	16	14	-	18	11	6	7	11	-
Unknown	49	-	42	6	7	4	-	38	32	7	6	5	-	11	10	5	1	2	-

aGvHD: acute graft-*versus*-host disease; BU: busulfan; d: day; FLU: fludarabine; HSCT: hematopoietic stem cell transplantation; MRD: minimal residual disease; N: number; NQ: non-quantifiable; TBI: total body irradiation; THIO: thiotepa; TREO: treosulfan; VP16: etoposide.

Table 4. Multivariable analyses for any failure, death from any cause, relapse, and treatment-related mortality for the cohort according to the minimal residual disease status pre-hematopoietic stem cell transplantation and by the conditioning regimen after adjusting for age, disease risk profile and immunophenotype, accounting for acute and chronic graft-*versus*-host disease.

	Any event (relapse or death)				Death from any cause				Relapse				TRM			
	HR	HR Conf.Lim.		*P*	HR	HR Conf.Lim.		*P*	HR	HR Conf.Lim.		*P*	HR	HR Conf.Lim.		*P*
MRD_{pos} *vs.* MRD_{neg}	1.950	1.447	2.628	<0.0001	1.855	1.288	2.670	0.001	2.182	1.561	3.051	<0.0001	1.315	0.658	2.629	0.438
MD *vs.* MSD	1.103	0.812	1.500	0.530	0.941	0.651	1.360	0746	0.949	0.677	1.329	0.758	2.565	1.166	5.643	0.019
CR2 early relapse, ≥CR3 *vs.* CR1, CR2 late relapse	2.355	1.759	3.153	<0.0001	2.512	1.759	3.588	<0.0001	2.467	1.775	3.431	<0.0001	2.436	1.281	4.631	0.007
FLU/THIO/BU or FLU/THIO/TREO *vs.* TBI	1.909	1.447	2.517	<0.0001	1.792	1.270	2.528	0.001	2.304	1.687	3.148	<0.0001	1.484	0.803	2.745	0.208
>10 years *vs.* ≤10 years	1.229	0.937	1.613	0.137	1.549	1.101	2.179	0.012	1.028	0.755	1.398	0.862	2.864	1.484	5.526	0.002
Immunophnotype BCP *vs.* no BCP	1.102	0.783	1.551	0.579	0.734	0.497	1.085	0.121	0.839	0.566	1.242	0.381	0.572	0.291	1.124	0.105
aGvHD grade II *vs.* grade 0/I	0.613	0.423	0.889	0.010	0.587	0.362	0.951	0.031	0.574	0.374	0.882	0.011	0.900	0.395	2.050	0.801
aGvHD grade III/IV *vs.* grade 0/I	1.444	0.949	2.198	0.086	1.741	1.070	2.835	0.026	1.177	0.702	1.973	0.536	3.543	1.645	7.633	0.001
cGvHD limited *vs.* no cGvHD	1.303	0.658	2.581	0.448	1.081	0.467	2.501	0.856	0.842	0.367	1.933	0.686	3.444	0.967	12.269	0.056
cGvHD extensive *vs.* no cGvHD	1.038	0.549	1.961	0.909	1.233	0.604	2.517	0.565	0.354	0.111	1.129	0.079	4.913	1.907	12.656	0.001

1-EFS: any failure; 1-OS: death from any cause; aGvHD: acute graft-*versus*-host disease; BCP: B-cell precursor; BU: busulfan; Conf.Lim: confidence limit; cGvHD: chronic graft-*versus*-host disease; CR: complete remission; EFS: event-free survival; FLU: fludarabine; HR: Hazard Ratio; HSCT: hematopoietic stem cell transplantation; MD: matched donor; MRD: minimal residual disease; MSD: matched sibling donor; OS: overall survival; TBI: total body irradiation; THIO: thiotepa; TREO: treosulfan; TRM: treatment-related mortality; VP16: etoposide.

according to method of determination (PCR *vs*. flow cytometry) (*data not shown*).

The level of MRD positivity pre-HSCT, i.e., $MRD_{pos\text{-}low}$ <1x10^{-3} and $MRD_{pos\text{-}high}$ ≥1x10^{-3}, was not relevant to outcome; in particular, it did not significantly affect EFS (0.60 *vs*. 0.58; *P*=0.780) or CIR (0.31 *vs*. 0.37; *P*=0.468), even after stratification by conditioning regimen.

In the multivariable analysis, MRD negativity pre-HSCT, conditioning with TBI/VP16, and lower risk profile (CR1 and CR2 after late relapse) were associated with approximately half the risk of relapse, whereas pre-HSCT MRD positivity was associated with twice the risk of any failure (1-EFS) and death (1-OS). Observations regarding the conditioning regimen should be interpreted in consideration of the low rate of randomization (32%); non-randomized patients were assigned to a regimen based on physician preference. Prior to the stopping rule which was breached in March 2019, regimen assignment might have been based on disease risk, with patients with more refractory disease more likely to receive TBI/VP16 and patients with comorbidities more likely to receive chemo-conditioning. After this, the vast majority of the patients were conditioned with TBI/VP16. Furthermore, no differences in outcome were detected between the randomized and the non-randomized patients assigned to TBI/VP16.

The disparity in the outcome between MRD_{pos} and MRD_{neg} patients pre-HSCT was apparently greater among recipients receiving chemo-conditioning *versus* TBI/VP16, suggesting that TBI/VP16 could partially compensate for poorer disease control, thus rescuing some MRD_{pos} patients. In fact, the 3-year CIR of 0.26 in MRD_{pos} patients given TBI/VP16 is remarkable, suggesting that TBI/VP16 can be effective in CAYA patients with MRD_{pos}. This compares favorably with a 2-year CIR of 0.54 (±0.14) reported in a recent pediatric series conditioned without TBI in the Netherlands.[17]

Treatment-related mortality in our overall cohort was 0.06 and was similar across MRD groups, which is remarkably low in the context of previous reports, especially given the international setting. Besides a trend for higher mortality in MD *versus* MSD recipients, as expected, older age (>10 years) was associated with an almost 3-fold higher risk of TRM compared with younger age.

Despite the fact that immunophenotype was not associated with outcome, the impact of the MRD status pre-HSCT was striking for B-cell precursor ALL, whereas it was virtually absent for patients with T-ALL, in whom EFS, OS, and CIR were superimposable for MRD_{neg} and MRD_{pos} patients. This suggests that the graft-*versus*-leukemia effect may be stronger in T-ALL than B-cell precursor ALL. Based on these findings, intensifying treatment and postponing transplant in patients with T-ALL who are MRD_{pos} pre-HSCT, in the attempt to reduce MRD levels, might be unwarranted.

Furthermore, the relatively large gap between OS and EFS in B-lineage ALL, both overall (0.81 *vs*. 0.69) and according to pre-HSCT-MRD status (0.84 *vs*. 0.77 in pre-HSCT MRD_{neg} patients; 0.70 *vs*. 0.59 in pre-HSCT MRD_{pos} patients), reflects the availability of further treatments, such as immunotherapy, after post-HSCT relapse. In contrast, in T-lineage ALL, EFS is very similar to OS (0.77 *vs*. 0.74), as very few chances would be available to treat a post-HSCT relapse. The only option could be a subsequent HSCT, possibly with the additional value of TBI (if not used previously) or the alloreactive effect of a partially incompatible donor.

The overall risk of aGvHD was low in our cohort (69% grade 0-I aGvHD, and 9% grade III-IV aGvHD). Cumulative incidence of overall cGvHD was higher in pre-HSCT MRD_{pos} compared with MRD_{neg} patients (0.20 *vs*. 0.12; *P*=0.017), but extensive cGvHD was similar. aGvHD grade II *versus* 0-I was associated with lower risk of relapse (HR: 0.57; *P*=0.008), whereas grade III-IV aGvHD was associated with a 4-fold higher risk of TRM. Nevertheless, there was no evidence of interactions between MRD and aGvHD; therefore, whether the occurrence of mild GvHD could have been protective against the risk of any failure with a different pattern in MRD_{pos} compared with MRD_{neg} patients could not be demonstrated. This finding is in line with those from pooled data of several consortia, as reported by Bader *et al*.,[13] but is in contrast to those of Pulsipher *et al*., who described that pre-HSCT MRD_{pos} patients who developed no degree of GvHD had higher rates of relapse *versus* MRD_{pos} patients with mild aGvHD.[18]

Positive MRD at day 100 post-HSCT, seen in 8% of the evaluable patients, was associated with dismal outcome, even though MRD detection did not necessarily imply relapse: MRD_{pos} at 100 days post HSCT had an EFS of 0.47 and a CIR of 0.51 at three years, compared with 0.77 and 0.17 of MRD_{neg} patients, respectively.

At one year, 5% of patients were MRD_{pos} and this resulted in overt relapse in approximately half. EFS in MRD_{pos} patients at 1-year post-HSCT was relatively high.

The intrinsic limitations of this study include the fact that MRD analyses are standardized within most European countries, but not worldwide, and that the range of 45 days for the timing of MRD assessments may affect the pre-HSCT analyses more than analyses at 100 days or one year. Moreover, treatment prior to HSCT was performed according to local policies and was not accounted for in the study. However, no significant differences in outcome were observed among countries, even when accounting for center size (*data not shown*). Furthermore, MRD levels were not recorded for one-third of the FORUM cohort and assessment of the impact of interventions to manage MRD positivity (including early immunosuppression discontinuation, DLI, infusion of immune effector cells or second HSCT) was beyond the scope of this study.

The high proportion of MRD_{neg} patients pre-HSCT (79%) provides only partial clues regarding the responsiveness or refractoriness of disease, as MRD recorded pre-HSCT may have been achieved by treatment per protocol or treatment intensification. Unfortunately, exploring the role of additional

pre-HSCT chemo- or immune-therapy, to achieve deeper remission in patients who otherwise would have received HSCT with higher MRD levels, was beyond the scope of this study and could not be assessed. Moreover, the predictive value of pre-HSCT MRD achieved with immunotherapy *versus* conventional chemotherapy is still to be assessed. Specific recommendations might be provided by a panel of experts involved in prospective studies dealing with HSCT in ALL. Based on our data, confirming the crucial role of the MRD status at HSCT on outcome, we conclude that a pre-HSCT MRD level $<1x10^{-4}$ is recommended overall and, as demonstrated, in B-lineage ALL. Such a finding would suggest intensifying treatment and/or adding immunotherapy to achieve MRD negativity prior to HSCT in patients who would otherwise still be MRD positive prior to HSCT. Nevertheless, we were unable to determine whether achieving MRD negativity before HSCT was attributable to the disease response to standard treatment or was achieved by treatment intensification, possibly with immunotherapy. Whether a MRD negative status achieved by means of immunotherapy had the same favorable prognostic impact of MRD negativity achieved with standard treatment could not be assessed by this study, but multiple reports would confirm it.

In this study, MRD data analyzed before transplantation and subsequently at 100 days and one year (±45 days) are reported. In terms of potential interventions, a graft-*versus*-leukemia effect could be enhanced by an early tapering of immunosuppression, based on either pre- or post-HSCT MRD positivity. In this regard, an additional timepoint of assessment, approximately in the second month, could drive the decision-making process of immunotapering, at least in patients who do not experience GvHD. Additional timepoints should be considered in case of MRD positivity. Furthermore, more frequent assessments could drive post-HSCT immunotherapy, based on the detection of post-HSCT MRD positivity. The prescription of monoclonal antibodies or chimeric antigen receptor (CAR) T-cell therapy are beyond the scope of this study and are also limited by regulatory/contract restrictions, which vary between countries.

A subsequent analysis assessing the role of immunotherapy pre- and post-HSCT is ongoing and recommendations might follow based on those findings.

In conclusion, in a large, prospective, international trial of CAYA undergoing HSCT for ALL, we can demonstrate that: i) pre-HSCT MRD level $\geq 10^{-4}$ was associated with worse outcome, due to higher incidence of relapse; ii) the detrimental effect of pre-HSCT MRD positivity could not be demonstrated in T-ALL; iii) the level of positivity did not significantly affect outcome; and iv) post-HSCT MRD positivity has a dismal prognosis but does not necessarily imply relapse. Furthermore, the superiority of TBI over chemo-conditioning was confirmed, grade II aGvHD was associated with better OS and EFS, and lower CIR, patients >10 years of age or developing grade III-IV aGvHD had higher risk of any failure and experienced higher mortality.

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Contributions

All authors contributed to study conception and design, collection and assembly of data, data analysis, manuscript writing, and final approval of the manuscript, and are accountable for all aspects of the work. KK contributed to this work on behalf of the PD WP EBMT. All authors except for EG provided study materials and/or recruited patients.

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Data-sharing statement

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References

1. Schrappe M, Hunger SP, Pui CH, et al. Outcomes after induction failure in childhood acute lymphoblastic leukemia. N Engl J Med. 2012;366(15):1371-1381.
2. Pulsipher MA, Peters C, Pui CH. High-risk pediatric acute lymphoblastic leukemia: to transplant or not to transplant? Biol Blood Marrow Transplant. 2011;17(1 Suppl):S137-148.
3. Balduzzi A, Di Maio L, Silvestri D, 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(3):396-408.
4. Conter V, Valsecchi MG, Parasole R, et al. Childhood high-risk acute lymphoblastic leukemia in first remission: results after chemotherapy or transplant from the AIEOP ALL 2000 study. Blood. 2014;123(10):1470-1478.
5. Pui CH, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012;120(6):1165-1174.
6. Balduzzi A, Dalle JH, Wachowiak J, et al. Transplantation in children and adolescents with acute lymphoblastic leukemia from a matched donor versus an HLA-identical sibling: is the outcome comparable? Results from the International BFM ALL SCT 2007 study. Biol Blood Marrow Transplant. 2019;25(11):2197-2210.
7. Peters C, Schrappe M, von Stackelberg A, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: a prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. J Clin Oncol. 2015;33(11):1265-1274.
8. Majhail NS, Chitphakdithai P, Logan B, et al. Significant improvement in survival after unrelated donor hematopoietic cell transplantation in the recent era. Biol Blood Marrow Transplant. 2015;21(1):142-150.
9. Bader P, Pötschger U, Dalle JH, et al. Low rate of nonrelapse mortality in under-4-year-olds with ALL given chemotherapeutic conditioning for HSCT: a phase 3 FORUM study. Blood Adv. 2024;8(2):416-428.
10. Bader P, Kreyenberg H, Henze GH, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. J Clin Oncol. 2009;27(3):377-384.
11. Bader P, Kreyenberg H, von Stackelberg A, et al. Monitoring of minimal residual disease after allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia allows for the identification of impending relapse: results of the ALL-BFM-SCT 2003 trial. J Clin Oncol. 2015;33(11):1275-1284.
12. Sutton R, Shaw PJ, Venn NC, et al. Persistent MRD before and after allogeneic BMT predicts relapse in children with acute lymphoblastic leukaemia. Br J Haematol. 2015;168(3):395-404.
13. Bader P, Salzmann-Manrique E, Balduzzi A, et al. More precisely defining risk peri-HCT in pediatric ALL: pre- versus post-MRD measures, serial positivity, and risk modeling. Blood Adv. 2019;3(21):3393-3405.
14. Ifversen M, Turkiewicz D, Marquart HV, et al. Low burden of minimal residual disease prior to transplantation in children with very high risk acute lymphoblastic leukaemia: the NOPHO ALL2008 experience. Br J Haematol. 2019;184(6):982-993.
15. Peters C, Dalle JH, Locatelli F, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: a multinational, randomized, noninferiority phase III study. J Clin Oncol. 2021;39(4):295-307.
16. Modvig S, Hallböök H, Madsen HO, et al. Value of flow cytometry for MRD-based relapse prediction in B-cell precursor ALL in a multicenter setting. Leukemia. 2021;35(7):1894-1906.
17. Versluijs AB, de Koning CCH, Lankester AC, et al. Clofarabine-fludarabine-busulfan in HCT for pediatric leukemia: an effective, low toxicity, TBI-free conditioning regimen. Blood Adv. 2022;6(6):1719-1730.
18. Pulsipher MA, Carlson C, Langholz B, 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(22):3501-3508.