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Original Article

Post-Transplant Relapse in Acute Leukemia: Comparative Value of MRD and Chimerism

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Abstract. ***Background*: Relapse remains the principal cause of treatment failure after allogeneic hematopoietic stem cell transplantation (AHSCT) in acute leukemia. Post-transplant surveillance commonly relies on measurable residual disease (MRD) and donor chimerism monitoring; however, their relative predictive value and optimal timing remain uncertain.**
Aims: To compare the prognostic performance of MRD and donor chimerism in predicting relapse after AHSCT in adult patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL).
Methods: This retrospective cohort included 264 adults (186 AML, 78 ALL) who underwent AHSCT. MRD was assessed by multiparametric flow cytometry on day 28 and at months 3 and 12, and chimerism by short tandem repeat PCR. Cox regression identified independent relapse predictors.
Results: Relapse occurred in 95 patients (68 AML, 27 ALL). In AML, MRD positivity at month 3 (HR 3.69, p<0.001) and mixed total chimerism at month 3 (HR 2.47, p=0.029) independently predicted relapse and were associated with inferior overall and disease-free survival. MRD detected relapse earlier and with greater sensitivity than chimerism. In ALL, total mixed chimerism at month 3 was associated with relapse in univariate analysis, whereas MRD showed limited statistical power due to small sample size.
Conclusion: Post-transplant MRD monitoring at month 3 provides superior risk stratification compared with chimerism in AML. In ALL, both approaches appear complementary, but conclusions are limited by cohort size. Disease-specific, risk-adapted surveillance strategies are warranted.

Keywords: Acute leukemias; Allogeneic hematopoietic stem cell transplantation; Multiparametric flow cytometry; Measurable residual disease; Chimerism.

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Introduction. Allogeneic hematopoietic stem cell transplantation (AHSCT) is a life-saving treatment for acute leukemia. Although treatment-related mortality has decreased in recent years, relapse remains the leading cause of mortality after AHSCT. While salvage therapies after hematologic relapse often result in mortality, studies have shown that early intervention when the leukemia burden is low may be effective.

The two primary methods for early detection of recurrence are donor chimerism monitoring and

measurable residual disease (MRD) assessment. Chimerism detection relies on analyzing genetic and phenotypic differences between donor and recipient cells using molecular and cellular biology techniques. PCR-based short tandem repeat (STR) analysis is the most commonly used method in clinical laboratories.[1] MRD analysis by multiparametric flow cytometry (MFC) or RT-qPCR can detect low-level leukemia after AHSCT, even in the absence of morphologic relapse.[1-3] While MRD identifies residual or re-emerging leukemia clones, chimerism reflects residual or re-emerging recipient hematopoiesis. In patients with specific MRD markers, recurrence detection primarily relies on MRD; however, these markers may be lost. Declining donor chimerism may then serve as the earliest sign of relapse. Literature increasingly supports an association between post-transplant MRD positivity or mixed chimerism and higher relapse risk and poorer survival.[4-7]

In clinical practice, both chimerism and MRD are used to monitor patients with acute leukemia after AHSCT. However, few studies have directly compared their performance in relapse detection, and no standard reference method exists. In this study, we aimed to compare the effectiveness of chimerism and MFC-based MRD monitoring in predicting relapse in patients with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) following transplantation.

Materials and Methods

Study Design and Patients. Patients who underwent AHSCT for acute leukemia between 2014 and 2021, at the Bone Marrow Transplant Unit at the Department of Hematology, Ankara University Faculty of Medicine, were retrospectively analyzed. This study was approved by the Ethics Committee of Ankara University Faculty of Medicine (Approval No: 2021/161). The study was conducted in accordance with the principles of the Declaration of Helsinki. Since this was a retrospective study based on anonymized data, the ethics committee waived the requirement for informed consent.

Inclusion criteria were: diagnosis of AML or ALL, first-time AHSCT, morphological complete remission on day 28 post-transplantation, and age ≥18 years. Patients who died before day 28 post-transplantation were excluded.

Data were collected from patient files and the hospital information system (AVICENNA) and included: age, sex, blood type, histopathological diagnosis, cytogenetic features of the disease, date and preparative regimen of AHSCT, disease status at transplant, chimerism rates (total and T-cell) at day 28, months 2, 3, 6, and 12 post-transplant, MFC and molecular based MRD results at days 28, months 3 and 12, occurrence of acute or chronic graft-versus-host disease (GVHD) and steroid use, relapse status and date, chimerism and MRD findings at relapse, histopathology results of bone marrow or extramedullary tissues at relapse, date of last visit, and date of death. The study aimed to evaluate the predictive value of chimerism and MRD results for post-transplant relapse.

Definitions and Classifications. Complete remission (CR) was defined as <5% blasts in the bone marrow, no blasts in peripheral blood or extramedullary sites, and normalization of peripheral blood counts. Relapse was defined as loss of morphological remission. The second and third CRs (CR2 and CR3, respectively) were defined as achieving remission after salvage chemotherapy following the first and second relapses, respectively. Active disease refers to failure to achieve remission after initial or salvage induction therapy.

Risk stratification for acute leukemias was performed in accordance with the 2017 European LeukemiaNet and 2021 National Comprehensive Cancer Network (NCCN) guidelines.[8-10]

Chimerism and Measurable Residual Disease Analysis. Chimerism status was determined by PCR-based analysis of STR microsatellites using GeneMapper v3.2 software (Applied Biosystems, USA) on day +28 and at months 2, 3, 6, and 12 following AHSCT. Chimerism analysis was performed using PCR-based STR microsatellite analysis. Full donor chimerism was defined as ≥99% donor-derived cells, whereas values below this threshold were classified as mixed chimerism. This cutoff was chosen to allow a conservative definition of complete donor engraftment and to minimize the impact of low-level recipient DNA detection, which may be observed due to assay sensitivity or biological variability.

MRD was assessed using ten-color MFC at the pre-transplant period, on day +28, and at months 3 and 12 following AHSCT. MRD was determined by visual identification of cell populations exhibiting immunophenotypic deviations. The MFC approach relied on detecting leukemia-associated immunophenotypes (LAIPs) that differed from those of normal hematopoietic cells, as well as on recognizing patterns that were different from normal. For LAIP evaluation, CD13, CD33, CD117, CD34, and HLA-DR expression levels were analyzed, along with CD38 expression on $CD34^+$ cells and aberrant expression of markers such as CD7, CD56, and CD123 to enhance the sensitivity of aberrant antigen detection. Core markers forming the backbone of the panel were used to identify blast populations and were complemented by additional markers from lymphoid and myelomonocytic maturation pathways to establish the MRD panel. For AML, the antibody combination included CD45, CD34, CD117, CD38, HLA-DR, CD123, CD33, CD19, CD7, and CD56; for B-ALL, CD45, CD10, CD19, CD34, CD38, CD20, and CD58; and for T-ALL, CD2, CD5, CD7,

cytoplasmic CD3, surface CD3, CD45, CD1a, CD4, and CD8. A total of 100,000 to 500,000 nucleated cells were examined. Cell acquisition was performed on Navios flow cytometer (3L10C; Beckman Coulter, USA), and data were analyzed using Kaluza software (Beckman Coulter, USA). When an abnormal cell population was identified, it was quantified as a percentage of total $CD45^+$ white cell events. Any measurable MRD level was considered positive.

Molecular assessments were performed at the pre-transplant period, on day +28, and at months 3 and 12 following AHSCT. The presence of recurrent translocations, including (8;21), t(9;22), t(15;17) and inv(16), was qualitatively assessed at diagnosis using RT-qPCR with the HemaVision®-7Q kit (DNA Diagnostic A/S, Risskov, Denmark). In cases where a translocation was detected, quantitative assessment was performed using the Ipsogen RT-qPCR Kit (Qiagen, Germany). *NPM1* mutations were evaluated quantitatively by RT-qPCR at diagnosis and during follow-up. *FLT3* mutations (ITD and TKD) were qualitatively assessed at diagnosis and in subsequent samples using the LeukoStrat® CDx FLT3 Mutation Assay (Invivoscribe, Inc., San Diego, CA, USA), an FDA-approved companion diagnostic test with CE-IVD certification in Europe. The chromosomal translocations t(1;19), t(4;11), and t(12;21) were analyzed using fluorescence in situ hybridization (FISH) with locus-specific probes.

Statistical Analysis. All statistical analyses were conducted using IBM SPSS Statistics version 30 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed both visually (via histograms and Q–Q plots) and analytically using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Descriptive statistics were expressed as mean ± standard deviation (SD or median (minimum–maximum) according to distribution of normality, and frequency (percentage) for categorical variables. For comparisons between groups, the Student-T test or Mann–Whitney U test was applied for continuous variables, while the Chi-square or Fisher's exact test was used for categorical variables.

For time-dependent variables (MRD and chimerism status), landmark analyses were performed at predefined time points. In a landmark analysis, only patients alive, in remission, and relapse-free at the landmark time point were included for that time point. This approach was chosen to avoid immortal-time bias and to assess the prognostic value of MRD and chimerism at clinically relevant time points.

To identify independent predictors of relapse, variables with p-values <0.25 in the univariate analysis were included in the multivariate model. Variables were excluded if they demonstrated non-proportional hazards (as indicated by a log-rank $p > 0.25$ or non-parallel log-minus-log survival curves). In cases of multicollinearity (defined as a correlation coefficient >0.6), the variable with the higher log-rank p-value or lower clinical relevance was omitted. The remaining variables were entered into a Cox proportional hazards regression model to estimate hazard ratios (HRs) and 95% confidence intervals for independent risk factors. The proportional hazards assumption and overall model fit were evaluated using residual analysis. To directly compare the predictive power of MRD and chimerism, univariate and multivariate regression analyses used the month 3 landmark, during which both biomarkers were assessed synchronously. Chimerism assessments at additional timepoints (months 2 and 6) were included only in descriptive analyses to maintain temporal synchrony in comparative modeling. For the ALL cohort, multivariate analysis was not performed due to the limited number of relapse events (n=27), which would result in an inadequate events-per-variable ratio and risk model overfitting. Therefore, only univariate results are reported for ALL patients

Overall survival (OS) and disease-free survival (DFS) were analyzed using the Kaplan–Meier method, and comparisons between groups were performed using the log-rank test. A two-sided p-value <0.05 was considered statistically significant.

Results

Patient Baseline Characteristics. This study included 264 patients with acute leukemia who underwent AHSCT. The mean age was 40.4 ± 13.8 years, and the median follow-up was 18.8 (1.1–137.9) months. Of the patients, 186 (70.5%) had AML and 78 (29.5%) had ALL. Among ALL cases, 52 (66%) had B-ALL and 26 (34%) had T-ALL. The descriptive characteristics of AML and ALL patients are summarized in **Table 1**.

Relapse Following AHSCT. Relapse occurred in 95 patients (35%): 68 with AML and 27 with ALL. Median time to relapse was 5 months (1.7 – 67.8).

The relapse rate among AML patients was 36.5%, and most (73.5%) occurred within the first year. Relapsed AML patients were more often male (63.2% vs 44.1%, p=0.012). Pre-transplant active disease and CR2/3 were more common in relapsed AML. High-risk cytogenetics were more frequent in relapsed AML cases (p=0.049). Development of chronic GVHD (p=0.117) did not differ between the relapsed and non-relapsed groups. However, the proportion of patients with steroid-requiring chronic GVHD was significantly lower in the relapsed group (9 patients, 69.2%) compared to the non-relapsed group (34 patients, 97.1%; p=0.015). (Table 2)

ALL relapse rate was 34.6%, with most relapses (81.4%) occurring in the first year. A male predominance was observed among relapsed patients (77.2% vs 56.1%; p=0.062). Pre-transplant active disease was more

Table 1. Baseline characteristics of the patients.

	Total (n=264)	AML (n=186)		ALL (n=78)	
Age, y (mean ± SD)	40.4 ± 13.8	43.6 ± 13.6		32.7 ± 11.2	
Gender, female, n.	119 (45.1%)	91 (48.9%)		28 (35.9%)	
Follow-up duration, m.	18.8 (1.1–137.9)	18.7 (1.1–137.9)		21.9 (1.4–135.2)	
Sex mismatch, n.	123 (46.6%)	91 (48.9%)		32 (41.0%)	
ABO incompatibility, n.	142 (53.8%)	100 (53.8%)		42 (53.8%)	
HLA Match, n.					
– 10/10 matched related donor	112 (42.4%)	83 (44.6%)		29 (37.2%)	
– 10/10 matched unrelated donor	61 (23.1%)	40 (21.5%)		21 (26.9%)	
– 9/10 matched related donor	2 (0.7%)	2 (1.1%)		–	
– 9/10 matched unrelated donor	65 (24.6%)	43 (23.1%)		22 (28.2%)	
– Haploidentical transplant	24 (9.0%)	18 (9.7%)		6 (7.7%)	
Disease status, n.					
– CR1	124 (46.9%)	84 (45.2%)		40 (51.3%)	
– CR2/CR3	79 (29.9%)	58 (31.2%)		21 (26.9%)	
– Active disease	61 (23.2%)	44 (23.7%)		17 (21.8%)	
MRD positivity at transplant, n.	80 (30.2%)	58 (31.2%)		22 (28.2%)	
Risk classification, n.		Low risk	24 (12.9%)	(n=76)	
		Standard risk	92 (49.5%)	Standard risk	15 (19.7%)
		High risk	70 (37.6%)	High risk	61 (80.3%)
Stem cell source, n.					
– Peripheral blood	248 (93.9%)	173 (93.0%)		75 (96.2%)	
– Bone marrow	14 (5.3%)	11 (5.9%)		3 (3.8%)	
– Peripheral + Bone marrow	2 (0.8%)	2 (1.1%)		–	
Conditioning regimen, n					
– Myeloablative	219 (83.0%)	147 (79.0%)		72 (92.3%)	
– Reduced-intensity	45 (17.0%)	39 (21.0%)		6 (7.7%)	
Use of ATG, n.	123 (46.6%)	79 (42.5%)		44 (56.4%)	
CD34+ cell dose, ×10⁶/kg (mean ± SD)	5.83 ± 1.53	5.78 ± 1.46		5.94 ± 1.69	
Neutrophil engraftment day	17 (10–53)	16 (10–53)		17 (10–29)	
Platelet engraftment day	14 (5–57)	14 (5–57)		15.5 (7–54)	

HLA: Human leukocyte antigen, CR: Complete remission MRD: Measurable residual disease, ATG: Anti-thymocyte-globulin.

common in relapsed ALL patients, but this was not significantly different (p=0.070). The rates of acute GVHD, chronic GVHD, and steroid-requiring chronic GVHD did not differ significantly between the relapsed and non-relapsed groups. However, the proportion of patients who received steroids for acute GVHD was significantly higher among relapsed patients (9 patients, 81.8%) compared to non-relapsed patients (12 patients, 40%; p=0.018) (**Table 2**).

Chimerism Assessment Following AHSCT. Among the 68 AML patients who developed overt relapse, MC detected via routine chimerism monitoring predicted relapse in 36 patients (52.9%, 95% CI: 40.2%–65.3%). The median interval between first detection of MC and clinical relapse was 90 days (range: 3–1944 days). At day 28, no significant differences were observed between relapsed and non-relapsed patients in either total chimerism (13.8% vs 12.4%, p = 0.784) or T-cell chimerism (37.8% vs 25.7%, p = 0.191). However, at month 3, both total MC (33.3% vs 8.8%, p < 0.001) and T-cell MC (36.1% vs 17.6%, p = 0.036) were significantly more frequent in relapsed patients (**Table 3**).

Among the 27 ALL patients who developed overt relapse, MC detected through chimerism monitoring predicted relapse in 10 patients (37.04%, 95% CI: 19.40%–57.63%). The median time from MC detection to clinical relapse was 34 days (range: 6–108 days). No significant differences were observed in total chimerism at day 28 (p = 0.162) or month 3 (p = 0.181). However, T-cell MC at month 3 was markedly higher in relapsed patients (50.0% vs 3.8%, p = 0.001) (**Table 3**).

Extended time-point data, including months 2 and 6 for chimerism, are provided in **Supplementary Table S1**.

Table 2. Comparison of relapsed and nonrelapsed patients with AML and ALL after AHSCT.

	AML (n=186)			ALL (n=78)		
	Relapsed (n=68)	**Non-relapsed (n=118)**	**p value**	**Relapsed (n=27)**	**Non-relapsed (n=51)**	**p value**
Age, y (mean ± SD)	41.9±13.3	44.5±13.8	0.323	33.1±10.9	32.5±11.4	0.671
Gender, female, n.	25 (36.8%)	66 (55.9%)	0.012	6 (22.8%)	22 (43.1%)	0.062
Follow-up duration, m. (median, min-max)	14.1 (2.7–134.3)	24.9 (1.1–137.9)	0.062	10.1 (2.2–73.7)	38.3 (1.4–135.2)	**0.016**
Sex mismatch, n.	30 (44.1%)	61 (51.7%)	0.322	11 (40.7%)	21 (41.2%)	0.976
ABO incompatibility, n.	40 (58.8%)	60 (50.8%)	0.292	15 (55.6%)	27 (52.9%)	0.837
HLA Match, n.			0.593			0.678
– 10/10 matched related donor	32 (47.1%)	51 (43.2%)		10 (37.0%)	19 (37.3%)	
– 10/10 matched unrelated donor	17 (25.0%)	23 (19.5%)		9 (33.3%)	12 (23.5%)	
– 9/10 matched related donor	1 (1.5%)	1 (0.8%)		-	-	
– 9/10 matched unrelated donor	14 (20.6%)	29 (24.6%)		7 (25.9%)	15 (29.4%)	
– Haploidentical transplant	4 (5.9%)	14 (11.9%)		1 (3.7%)	5 (9.8%)	
Disease status, n.			**0.001**			0.070
– CR1	19 (27.9%)	65 (55.1%)		9 (33.3%)	31 (60.8%)	
– CR2/CR3	25 (36.8%)	33 (28.0%)		10 (37.0%)	11 (21.6%)	
– Active disease	24 (35.3%)	20 (16.9%)		8 (29.6%)	9 (17.6%)	
MRD positivity before transplant, n.	23 (33.8%)	35 (29.6%)	0.798	7 (25.9%)	13 (25.4%)	0.995
Risk classification, n.			**0.049**			0.981
AML - Low risk	9 (13.2%)	15 (12.7%)				
AML - Standard risk	41 (60.3%)	51 (43.2%)				
AML - High risk	18 (26.5%)	52 (44.1%)				
ALL - Standard risk				5 (18.5%)	10 (21.4%)	
ALL - High risk				22 (81.5%)	39 (79.6%)	
Stem cell source, n.			0.496			0.272
– Peripheral blood	63 (92.6%)	110 (93.2%)		25 (92.6%)	50 (98%)	
– Bone marrow	5 (7.4%)	6 (5.1%)		2 (7.4%)	1 (2%)	
– Peripheral + Bone marrow	0 (0%)	2 (1.7%)		-	-	
Conditioning regimen, n.			0.641			0.412
– Myeloablative	55 (80.9%)	92 (78.0%)		24 (88.9%)	48 (94.1%)	
– Reduced-intensity	13 (19.1%)	26 (22.0%)		3 (11.1%)	3 (5.9%)	
Use of ATG, n.	34 (50.0%)	45 (38.1%)	0.121	18 (66.7%)	26 (51.0%)	0.182
Acute GVHD (%)	27 (39.7%)	47 (39.8%)	0.992	11 (40.7%)	30 (58.8%)	0.135
Steroid for acute GVHD (n=115)	15 (55.6%)	30 (63.8%)	0.486	9 (81.8%)	12 (40.0%)	**0.018**
Chronic GVHD, n.	13 (19.1%)	35 (29.7%)	0.117	6 (22.2%)	10 (19.6%)	0.797
Steroid for chronic GVHD (n=64)	9 (69.2%)	34 (97.1%)	**0.015**	4 (66.7%)	10 (100.0%)	0.130
Death (n=139)	57 (83.8%)	42 (35.6%)	**<0.001**	22 (81.5%)	18 (35.3%)	**<0.001**

AHSCT: Allogeneic hematopoietic stem cell transplantation, ATG: Anti-thymocyte-globulin CR: Complete remission, GVHD: Graft-versus-host disease, HLA: Human leukocyte antigen, MRD: Measurable residual disease,

MRD Monitoring by MFC Following AHSCT. Considering pre-transplant disease status, 44 AML patients (23.7%) underwent AHSCT with active disease, and 58 patients (31.2%) underwent transplantation in morphological remission but with MRD positivity. Among the 44 patients with active disease, 31 (70.4%) achieved MRD-negative CR by day 28 post-transplant. Similarly, among the 58 MRD-positive patients, 46 (79.3%) achieved MRD-negative CR at day 28. In total, 30 of the 68 relapsed AML patients (44.1%, 95% CI: 32.3%–56.6%) had MRD positivity detected prior to overt relapse. The median time from MRD detection to clinical relapse was 177 days (range: 6–819 days). MRD was detected at or near the time of clinical relapse in 8

Table 3. Comparison of chimerism status of relapsed and non-relapsed patients with AML and ALL.

Total Chimerism	Relapsed	Non-relapsed	p-value	T- cell Chimerism	Relapsed	Non-relapsed	p-value
AML Patients							
Day 28, n=178	**n=65**	**n=113**	0.784	**Day 28, n=107**	**n=37**	**n=70**	0.191
MC	9 (13.8%)	14 (12.4%)		**MC**	14 (37.8%)	18 (25.7%)	
CC	56 (86.2%)	99 (87.6%)		**CC**	23 (62.2%)	52 (74.3%)	
Month 3, n=151	**n=60**	**n=91**	**<0.001**	**Month 3, n=104**	**n=46**	**n=68**	**0.036**
MC	20 (33.3%)	8 (8.8%)		**MC**	13 (36.1%)	12 (17.6%)	
CC	40 (66.7%)	83 (91.2%)		**CC**	23 (63.9%)	56 (82.4%)	
Month 12, n=104	**n=36**	**n=68**	**<0.001**	**Month 12, n=70**	**n=20**	**n=50**	**<0.001**
MC	13 (36.1%)	2 (2.9%)		**MC**	8 (40.0%)	2 (4.0%)	
CC	23 (63.9%)	66 (97.1%)		**CC**	12 (60.0%)	48 (96.0%)	
ALL Patients							
Day 28, n=69	**n=24**	**n=45**	0.162	**Day 28, n=44**	**n=14**	**n=30**	0.662
MC	0 (0.0%)	5 (11.1%)		**MC**	3 (21.4%)	4 (13.3%)	
CC	24 (100.0%)	40 (88.9%)		**CC**	11 (78.6%)	26 (86.7%)	
Month 3, n=61	**n=23**	**n=38**	0.181	**Month 3, n=40**	**n=14**	**n=26**	**0.001**
MC	7 (30.4%)	5 (13.2%)		**MC**	7 (50.0%)	1 (3.8%)	
CC	16 (69.6%)	33 (86.8%)		**CC**	7 (50.0%)	25 (96.2%)	
Month 12, n=45	**n=12**	**n=33**	0.996	**Month 12, n=32**	**n=7**	**n=25**	0.992
MC	1 (8.3%)	2 (6.1%)		**MC**	1 (14.3%)	4 (16.0%)	
CC	11 (91.7%)	31 (93.9%)		**CC**	6 (85.7%)	21 (84.0%)	

AHSCT: Allogeneic hematopoietic stem cell transplantation, CC: Complete chimerism, MC: Mixed chimerism.

patients (11.8%) who had been MRD-negative at earlier monitoring timepoints, bringing the total MRD detection rate to 38 patients (55.9%). No significant difference in MRD positivity at day 28 was observed between the relapsed and non-relapsed groups (28.4% vs 19.8%; p = 0.192). However, at month 3, MRD positivity was significantly higher in relapsed patients (55.2% vs 22.0%, p < 0.001).

Regarding ALL patients, 17 (21.8%) underwent AHSCT with active disease, and 22 (28.2%) were in morphological remission but MRD-positive. By day 28 post-transplant, 10 of the 17 patients with active disease (58.8%) and 11 of the 22 MRD-positive patients (50%) had achieved MRD-negative complete remission.

Among the 27 ALL patients who relapsed, MRD positivity detected before overt relapse predicted relapse in 13 cases (48.1%; 95% CI: 28.7%–67.6%), with a median interval of 93 days from MRD detection to relapse (range: 18–951 days). MRD was detected at relapse in an additional 2 patients (7.4%), bringing the total MRD detection rate to 15 patients (55.6%). No significant difference was observed at day 28 (p = 0.582), while month 3 MRD positivity showed a trend toward significance (66.7% vs 41.5%, p = 0.050).

The MFC-based MRD results of patients with AML and ALL are summarized in **Table 4**.

MRD Monitoring by Molecular Analysis Following AHSCT. Molecular MRD markers were available for 83 patients. Among the subset with available molecular markers (54 AML, 29 ALL), molecular MRD predicted relapse in 73.7% of AML and 71.4% of ALL cases with evaluable markers. Molecular MRD positivity showed concordant predictive patterns, with a statistically significant association observed at month 12 for AML (p=0.010) and at month 3 for ALL (p=0.032) (detailed data in **Supplementary Table S2**).

Extramedullary Relapse Following AHSCT. Among relapsed patients, isolated extramedullary relapse occurred in 6 AML (8.8%) and 9 ALL (33.3%) cases, while simultaneous extramedullary and marrow relapse was observed in 2 AML (2.9%) and 1 ALL (3.7%) case. In isolated extramedullary relapse, both MRD positivity and MC preceded relapse in 3 AML patients (50%), whereas mixed chimerism alone and MRD positivity alone were each detected in 1 AML patient (16.6%). In ALL, MRD positivity preceded relapse in 5 patients (55.5%) and mixed chimerism in 3 patients (33.3%); all mixed chimerism–positive cases also showed MRD positivity.

Comparison of Risk Factors for Predicting Relapse AHSCT. In the univariate analysis, male sex (HR: 1.86, 95% CI: 1.14–3.05, p=0.014), pre-transplant active disease (HR: 2.48, 95% CI: 1.51–4.09, p<0.001), mixed

Table 4. Comparison of MFC based MRD status of relapsed and nonrelapsed patients with AML and ALL after AHSCT.

MRD status	AML (n=186)		p value	ALL (n=78)		p value
	Relapsed	Non-relapsed		Relapsed	Non-relapsed	
Day 28, n=257	n=67	n=116		n=26	n=48	
MRD positive	19 (28.4%)	23 (19.8%)	0.192	12 (46.2%)	19 (39.6%)	0.582
MRD negative	48 (71.6%)	93 (80.2%)		14 (53.8%)	29 (60.4%)	
Month 3, n=223	n=58	n=100		n=24	n=41	
MRD positive	32 (55.2%)	22 (22.0%)	**<0.001**	16 (66.7%)	17 (41.5%)	**0.050**
MRD negative	26 (44.8%)	78 (78.0%)		8 (33.3%)	24 (58.5%)	
Month 12, n=122	n=35	n=51		n=11	n=25	
MRD positive	19 (54.3%).	5 (9.8%)	**<0.001**	5 (45.5%)	6 (24.0%)	0.254
MRD negative	16 (45.7%)	46 (90.2%)		6 (54.5%)	19 (76.0%)	

AHSCT: Allogeneic hematopoietic stem cell transplantation MFC: Multiparametric flow cytometry MRD: Measurable residual disease.

Table 5. Evaluation of factors associated with relapse after AHSCT in AML patients.

Variables	Univariate Analysis HR (95% CI)	p-value	Multivariate Analysis HR (95% CI)	p-value
Male sex	1.86 (1.14–3.05)	**0.014**	1.81 (0.89–3.69)	0.102
Age	1.00 (0.98–1.01)	0.672	0.99 (0.97–1.01)	0.357
ABO incompatibility	1.37 (0.84–2.21)	0.211	1.68 (0.79–3.55)	0.181
Active disease at transplant	2.48 (1.51–4.09)	**<0.001**	3.47 (1.53–7.83)	**0.003**
High - risk classification	0.61 (0.36–1.05)	0.075	0.68 (0.31–1.49)	0.334
ATG use	1.39 (0.86–2.24)	0.186	1.74 (0.79–3.82)	0.172
Presence of chronic GVHD	0.51 (0.28–0.93)	**0.028**	0.72 (0.32–1.65)	0.446
Total MC at month 3	3.78 (2.20–6.48)	**<0.001**	2.47 (1.10–5.56)	**0.029**
MFC based - MRD positivity at month 3	2.69 (1.43–5.04)	**0.002**	3.69 (1.84–7.41)	**<0.001**

AHSCT: Allogeneic hematopoietic stem cell transplantation ATG: Anti-thymocyte globulin, GVHD: Graft-versus-host disease MC: Mixed chimerism MFC: Multiparametric flow cytometry MRD: Measurable residual disease.

Table 6. Univariate evaluation of factors associated with relapse after AHSCT in ALL patients.

Variables	Univariate Analysis HR (95% CI)	p-value
T-ALL	1.67 (0.78–3.55)	0.196
Male sex	1.93 (0.78–4.78)	0.162
Age	1.01 (0.98–1.05)	0.524
Active disease at transplant	3.24 (1.37–7.68)	**0.008**
Reduced-intensity conditioning	2.30 (0.68–7.74)	0.186
Total – MC at month 3	2.61 (1.07–6.38)	**0.036**
MFC based- MRD positivity at month 3	1.73 (0.68–4.40)	0.253

AHSCT: Allogeneic hematopoietic stem cell transplantation MC: Mixed chimerism MFC: Multiparametric flow cytometry MRD: Measurable residual disease.

total chimerism at month 3 (HR: 3.78, 95% CI: 2.20–6.48, p<0.001), and MRD positivity by MFC at month 3 (HR: 2.69, 95% CI: 1.43–5.04, p=0.002) were found to be significantly associated with increased risk of relapse in AML patients. Conversely, the presence of chronic GVHD was found to be negatively associated with relapse (HR: 0.51, 95% CI: 0.28–0.93, p=0.028). In the multivariate analysis, pre-transplant active disease (HR: 3.47, 95% CI: 1.53–7.83, p=0.003), mixed total chimerism at month 3 (HR: 2.47, 95% CI: 1.10–5.56, p=0.029), and MRD positivity by MFC at month 3 (HR: 3.69, 95% CI: 1.84–7.41, p<0.001) remained independently associated with relapse (**Table 5**).

In the univariate analysis of factors associated with relapse in ALL patients after AHSCT, pre-transplant active disease (HR: 3.24, 95% CI: 1.37–7.68, p = 0.008)

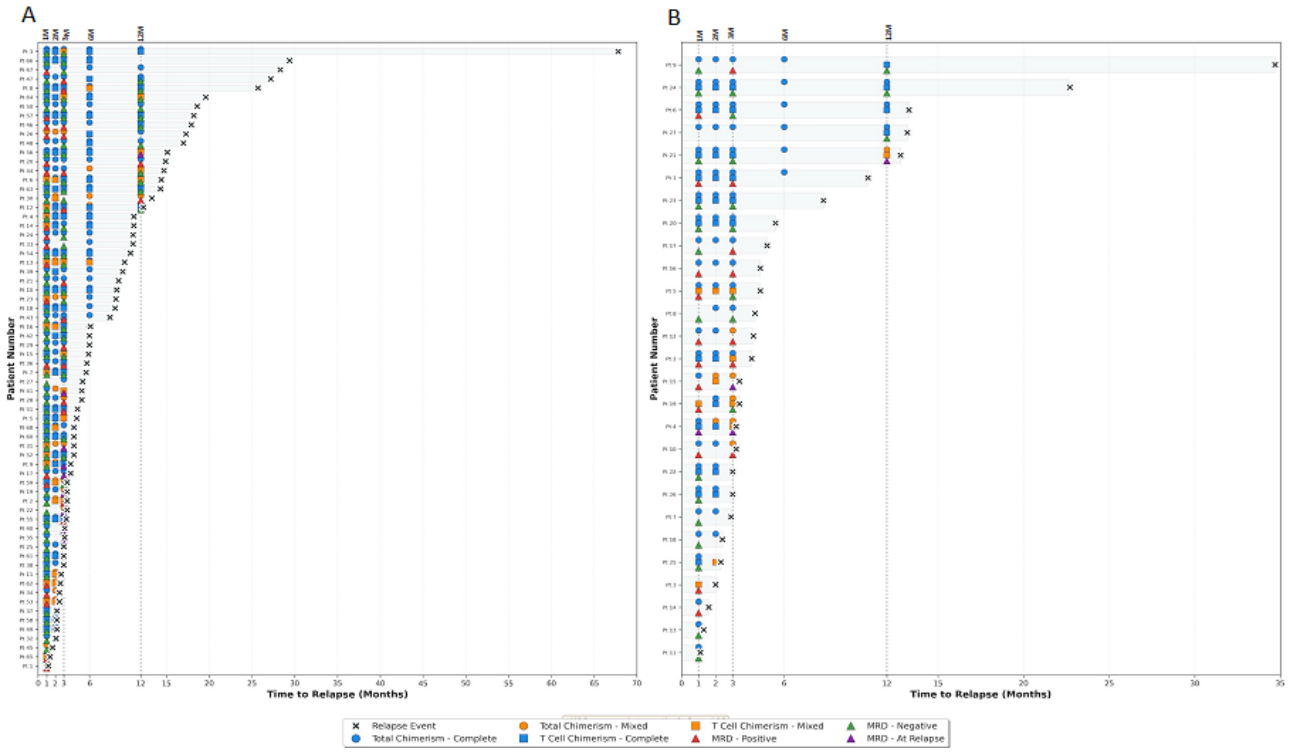

Figure 1. Swimmer plot depicting longitudinal chimerism and MRD monitoring in relation to time to relapse following allogeneic hematopoietic stem cell transplantation. Left panel (A): AML patients (n=68); Right panel (B): ALL patients (n=27). Each horizontal bar represents an individual patient, with length corresponding to time from HSCT to overt hematologic relapse. Patients are ordered by time to relapse (shortest at bottom, longest at top). Markers indicate chimerism and MRD status at routine monitoring timepoints: month 1 (1M), month 2 (2M), month 3 (3M), month 6 (6M), and month 12 (12M) post-HSCT. Circles represent total chimerism status (blue = complete donor chimerism orange = mixed chimerism); squares represent T-cell chimerism status (blue = complete, orange = mixed); triangles represent MRD status by multiparameter flow cytometry (red = positive, green = negative, purple = detected at time of relapse). Black X marks indicate overt relapse events. Vertical dashed lines indicate assessment timepoints. MRD was assessed at months 1, 3, and 12 (*), whereas chimerism was assessed at all five time points.

and mixed total chimerism at month 3 (HR: 2.61, 95% CI: 1.07–6.38, p = 0.036) were significantly associated with relapse (**Table 6**).

Impact of Chimerism and MFC - MRD on Survival Outcomes Following AHSCT. The longitudinal patterns of chimerism and MRD status in relation to time to relapse are illustrated in **Figure 1** for AML and ALL patients. In AML patients, both total - MC and MRD positivity by MFC, when detected at month 3 post-AHSCT, were found to have a significant negative impact on overall survival (OS) (p = 0.044 and p = 0.001, respectively) and disease-free survival (DFS) (p < 0.001 for both) (**Figure 2**). In contrast, among ALL patients, the presence of total-MC and MRD positivity at month 3 did not reach statistical significance for OS (p = 0.090 and p = 0.071, respectively) or DFS (p = 0.120 and p = 0.211, respectively) (**Figure 3**).

Discussion. One of the key measures to improve treatment response and survival after AHSCT in acute leukemia is to identify patient subgroups at high risk of relapse. Patients with increasing levels of recipient chimerism post-transplant are reported to have a higher relapse risk.[11,12] MRD positivity detected by MFC after induction or consolidation chemotherapy and before transplantation has been associated with poor outcomes. Evidence is growing that MFC is also a useful post-transplant MRD detection technique.[13-15] However, it remains unclear which of these two methods provides better predictive information for relapse and how and when they should be assessed.

We found that MRD positivity by MFC at months 3 and 12, and the presence of total-MC and T-cell-MC, were significantly more frequent among patients with relapsed AML. In multivariate analysis, MRD positivity at month 3 emerged as an independent predictor of relapse. Moreover, MRD positivity at month 3 was associated with decreased OS and DFS. Our results confirm previous studies showing a strong link between post-transplant MRD and relapse risk and inferior survival.[16-19] Additionally, total-MC at month 3 was also found to be an independent predictor of relapse and associated with worse survival. When entered in the same model, month-3 MRD retained a higher HR than MC. While chimerism monitoring has shown predictive potential,[20,21] its sensitivity and specificity have been questioned.[5] A study by Bernal T et al. found that MRD positivity at day 100 was the strongest prognostic factor for relapse and survival, whereas mixed CD3 chimerism

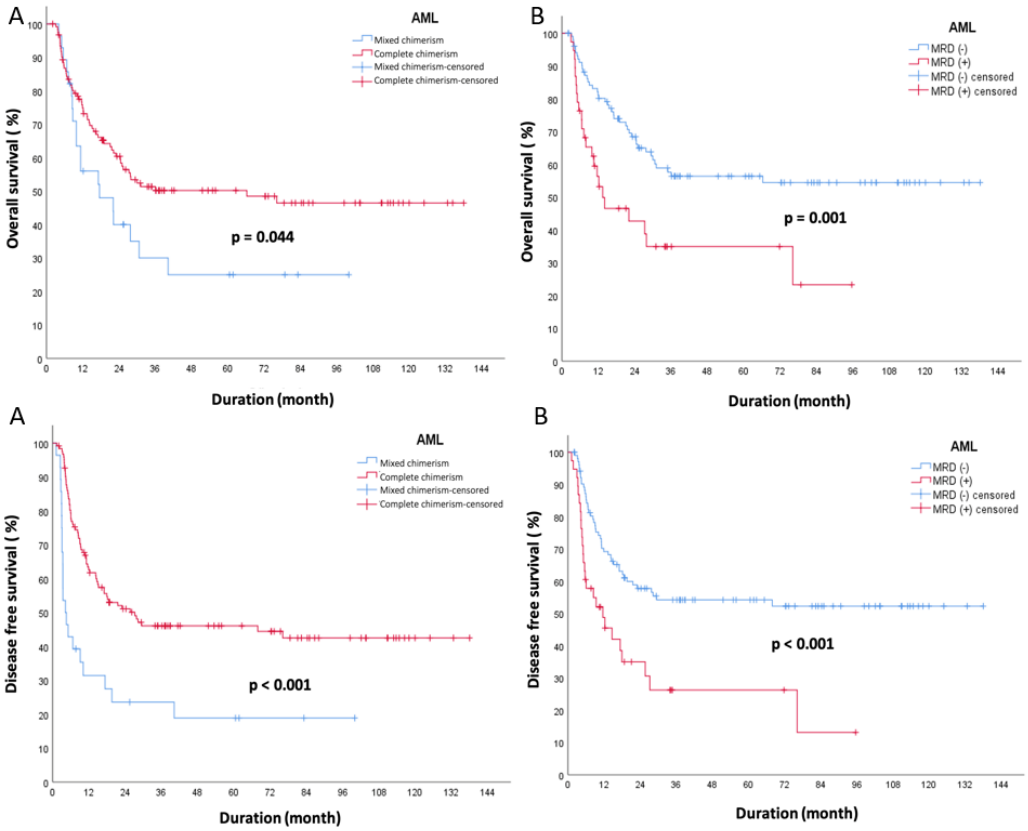

Figure 2. Median overall survival (OS) and disease-free survival (DFS) according to chimerism and MRD status in AML patients. Patients with mixed chimerism had significantly shorter median OS (17.5 months, 95% CI: 0.4–34.6; p = 0.044) and DFS (4.2 months, 95% CI: 2–6.5; p < 0.001) compared with those with complete chimerism (OS = 66.2 months; DFS = 27.2 months, 95% CI: 0–68.5). Similarly, MRD-positive patients showed significantly reduced survival outcomes (median OS = 13.4 months, 95% CI: 0.6–26.2; median DFS = 11.6 months, 95% CI: 2.7–20.5; p < 0.001), while median survival was not reached in the MRD-negative group.

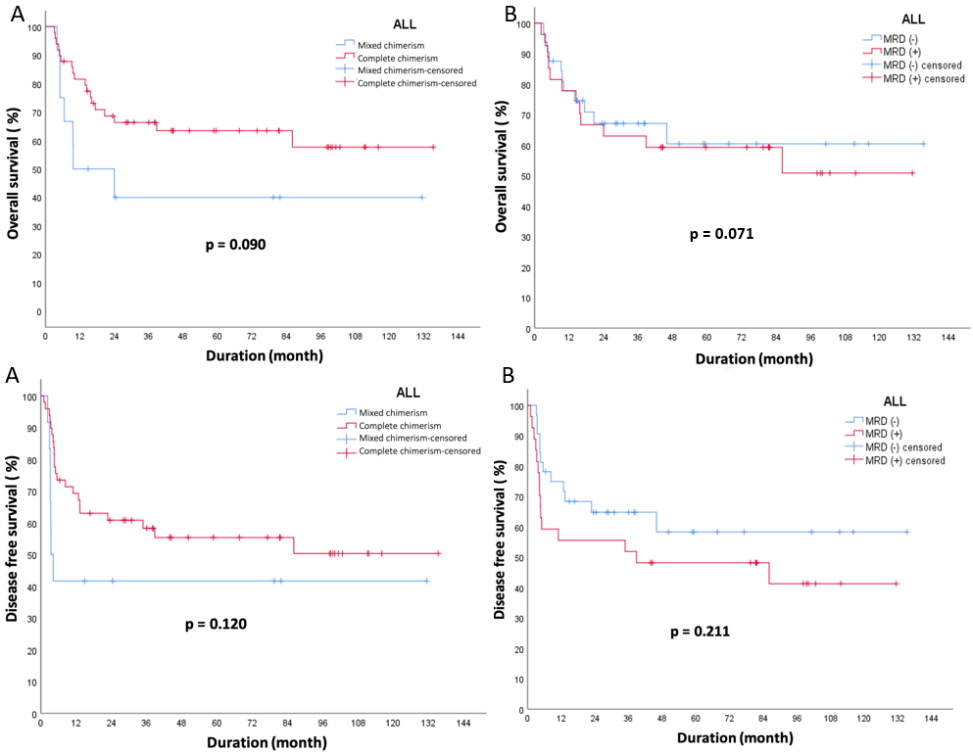

Figure 3. Median overall survival (OS) and disease-free survival (DFS) according to chimerism and MRD status in ALL patients. Patients with mixed chimerism showed a trend toward shorter survival compared with those with complete chimerism (median OS: 9.6 months, 95% CI: 0–31.9 vs. not reached, p = 0.090; median DFS: 3.5 months, 95% CI: 2–4.9 vs. not reached, p = 0.120). No statistically significant differences were observed between MRD-positive and MRD-negative groups (median OS and DFS not reached; p = 0.071 and p = 0.211, respectively).

showed only borderline significance.[22] Similarly, Loke et al. demonstrated that MRD positivity after transplant conferred more than twice the hazard of death (HR ~2.2) and remained significant in multivariate analysis regardless of pre-transplant MRD status.[23] These concordant findings solidify post-HSCT MRD as a more robust and clinically relevant predictor of relapse than chimerism analysis.

The superior predictive value of MRD over donor chimerism in AML can be explained by their distinct biological mechanisms. MRD assays directly detect residual leukemic cells, whereas chimerism measures the proportion of donor vs. recipient hematopoiesis.[24] MC does not distinguish between benign residual host cells and malignant blasts. Thus, a patient may have low recipient cells without harboring leukemia – a scenario where MRD tests are negative, and relapse risk appears low.[19] In our study, MRD positivity detected prior to overt relapse predicted relapse in 44.1% of AML patients (30/68) and 48.1% of ALL patients (13/27). An additional 11.8% of AML patients (8/68) and 7.4% of ALL patients (2/27) became MRD-positive at or near relapse despite prior MRD negativity, resulting in overall MRD detection rates of 55.9% in AML and 55.6% in ALL. Pincez et al. found similar results in pediatric leukemia: MRD by MFC alone predicted 40% of relapses, while combining MFC and RT-qPCR detected 89%. Chimerism loss occurred in 27%, never preceding MRD positivity.[25] These findings confirm that MC alone did not predict relapse. Although chimerism applies to all leukemia subtypes, its sensitivity — especially with STR-PCR — is limited.[5] Advanced methods such as single-nucleotide polymorphism (SNP)- or insertion/deletion (INDEL)-based qPCR offer improved sensitivity but are technically complex and costly.[1] MRD-positive patients (even with full donor chimerism) are at high risk, since any detectable leukemia indicates failing graft-versus-leukemia mechanisms. While our MRD findings were primarily MFC-based, molecular MRD data were available in a subset where RT-qPCR predicted relapse in 73% of AML and 71.4% of ALL cases. Although MFC remains broadly applicable, RT-qPCR may offer higher sensitivity,[26-28] though its clinical utility is constrained by limited standardization and accessibility.

In our study, univariate analysis showed associations for active disease and MC at month 3 in ALL. The limited prognostic value of MRD in ALL patients is likely due to the small sample size and consequent limitations in statistical power. Thus, we caution against dismissing MRD monitoring in ALL. MRD remains clinically validated in ALL and is recommended for routine surveillance.[28] Extensive literature supports MRD as a key prognostic marker in ALL, with meta-analyses demonstrating strong associations between MRD positivity and relapse as well as inferior survival.[15,29] In adult ALL, flow cytometry–based MRD has shown independent prognostic value,[14] although post-transplant data remain limited by small cohort sizes. Studies comparing MRD and chimerism suggest that these approaches are complementary, particularly in the setting of extramedullary relapse.[30]

Post-HSCT MRD and chimerism monitoring should enable early intervention before overt relapse. In our study, MRD positivity detected before clinical relapse had a median of 177 days in AML and 93 days in ALL. MC provided a median of 90 days and 34 days, respectively. Similar intervals have been reported in the literature.[25,27]

Isolated extramedullary relapse was infrequent in AML (8.8%) but more common in ALL (33%), and was preceded by MRD positivity in 50% of AML and 55.5% of ALL cases and by mixed chimerism in 50% of AML and 33.3% of ALL cases; however, the small sample size precluded reliable statistical analysis. Terwey TH et al. reported extramedullary relapse in 9 of 29 relapsed ALL cases, with all showing chimerism loss but lacking MRD data.[30]

Known AML relapse risk factors post-HSCT include non-CR status, high-risk genetics, RIC regimens, intensive GVHD prophylaxis, and absence of GVHD.[31] In our univariate analysis, male sex, active disease at transplant, MRD positivity at month 3, and unseparated MC were associated with relapse, while chronic GVHD was protective. In multivariate analysis, active disease at transplant, MRD positivity, and MC at month 3 remained independent risk factors. Unlike some prior studies, our data did not show an association between relapse and pre-transplant MRD positivity or high-risk classification, possibly due to exclusion of early-death patients or those with active disease on day-28 marrow biopsy. In ALL, risk factors include pre-transplant MRD, non-CR status, and absence of GVHD.[29,32] In our ALL cohort, univariate analyses identified active disease at transplantation and MC at month 3 as factors associated with post-transplant relapse. These findings are consistent with prior reports indicating that higher disease burden at the time of transplant and early loss of donor hematopoiesis reflect an increased risk of relapse in ALL.

The main limitations of our study include its retrospective and single-center nature, potential missing data, and the absence of intervention data (e.g., Donor lymphocyte infusion, immunosuppression withdrawal) following MRD or MC detection. The relatively small ALL cohort (n = 78) represents a major limitation, as the study was sufficiently powered to detect associations in AML but not in ALL subgroups. With only 27 relapse events, the ability to detect modest associations — particularly for post-transplant monitoring parameters — was limited. Additionally, the heterogeneity of ALL (B-ALL vs T-ALL, Philadelphia chromosome-positive vs negative) and the relatively small numbers in each

subgroup further limit the ability to draw definitive conclusions. Future multicenter collaborative studies with larger sample sizes are needed to clarify the optimal monitoring strategy for adult patients with ALL after AHSCT.

Conclusions. Our data suggest that MRD-based monitoring is superior for risk stratification in AML and should be prioritized post-transplant. Chimerism analysis still has value — especially when MRD markers are unavailable — but is more predictive when used selectively in ALL. However, the limited sample size prevents definitive conclusions about the comparative utility of MRD versus chimerism in this population. While our ALL cohort showed trends consistent with published literature, larger multicenter studies are needed to validate optimal monitoring strategies for adult ALL patients after AHSCT. Overall, post-transplant surveillance strategies should be disease-specific, with MFC-based MRD monitoring emphasized in AML. These findings support personalized, risk-adapted surveillance approaches and highlight areas requiring further investigation to improve transplant outcomes across acute leukemia subtypes.

Data Availability Statement. The dataset generated and analyzed during the current study contains identifiable patient information and is therefore not publicly available in accordance with institutional ethics regulations and data privacy laws. De-identified summary data are available from the corresponding author upon reasonable request.

Declaration of Generative AI and AI-Assisted Technologies in the Manuscript Preparation Process. During the preparation of this work, the authors used ChatGPT (OpenAI) solely for language editing and grammar correction. After using this tool, the authors reviewed and revised the text as needed and take full responsibility for the content of the manuscript.

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