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Comparable outcomes for pediatric acute lymphoblastic leukemia patients receiving conditioning with total body irradiation or chemotherapy: A nationwide, Korean registry-based study

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Abstract

Acute lymphoblastic leukemia (ALL) is the predominant malignancy in pediatric patients, and allogeneic hematopoietic stem cell transplantation (HSCT) plays a critical role in high-risk cases. However, real-world nationwide data comparing the outcomes of conditioning regimens are limited. This nationwide registry-based study analyzed data from 270 Korean pediatric patients with high-risk or relapsed ALL who underwent their first allogeneic HSCT with myeloablative conditioning. Among all analyzed patients, 118 received total body irradiation-based conditioning (MAC-TBI) and 152 received chemotherapy-based conditioning (MAC-Chemotherapy), of whom 96.6% underwent busulfan-based regimens. MAC-TBI recipients were older at diagnosis and at HSCT. No significant differences were observed between groups in neutrophil or platelet engraftment times, or infused CD34+ cell doses. Acute graft-versus-host disease (GVHD) incidences (grades II–IV and III–IV) were comparable, although chronic GVHD incidence tended to be lower in the MAC-Chemotherapy group (21.0% vs. 31.1%, P = 0.072). Additionally, the 5-year event-free survival (EFS) rates for MAC-TBI versus MAC-Chemotherapy were 73.7% and 69.8% (P = 0.827), respectively; the 5-year overall survival (OS) rates were 76.3% and 80.2% (P = 0.941), respectively, indicating that conditioning regimen did not significantly impact survival. Pediatric disease risk index, recent HSCT era, haploidentical donor type, and pre-transplant disease status independently influenced EFS and OS, whereas anti-thymocyte globulin administration significantly improved moderate-to-severe chronic GVHD, leukemia-free survival. This nationwide real-world analysis demonstrated comparable outcomes between myeloablative TBI-based and chemotherapy-based conditioning regimens in pediatric patients with ALL. These findings may inform the development of improved treatment strategies for this patient population.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) has the highest incidence among pediatric malignancies.[1] Over the past few decades, outcomes of ALL have dramatically improved with the advent of intensive combination chemotherapy coupled with central nervous system prophylaxis.[2] Nevertheless, to mitigate the risk for relapse of ALL in patients with high-risk features, allogeneic hematopoietic stem cell transplantation (HSCT) plays a crucial role as a consolidative therapy.[3] The indications for treatment of pediatric ALL have continuously evolved, now encompassing factors including unfavorable cytogenetics, notably the *MLL*::*KMT2A* translocation in patients of <6 months of age,[4] induction failure,[5] relapse in cases of T-cell ALL[6] and early relapsed B-cell ALL, and post-consolidation minimal residual disease (MRD) positivity (>0.01% in B-cell ALL[7] and >0.1% in T-cell ALL[6]). Furthermore, regarding the conditioning regimen, a recent pivotal trial reported superior outcomes with total body irradiation (TBI) compared to chemotherapy conditioning in pediatric patients of >4 years of age diagnosed with ALL.[8]

However, the uniform application of indications and conditioning regimens for pediatric ALL poses challenges across different countries and institutions. While TBI conditioning has yielded superior outcomes, its delivery in six fractions over a 3-day period may not be feasible in various institutions. Moreover, its application in younger patients raises concerns, particularly regarding long-term morbidities, such as secondary malignancy.[9,10] Furthermore, recent various immunotherapies, including bispecific T-cell engagers,[11] antibody-drug conjugates,[12] and chimeric antigen receptor (CAR) T-cell therapies,[13,14] have significantly improved the previously dismal outcomes of pediatric patients with relapsed or refractory B-cell precursor ALL. Many clinical trials have applied these immunotherapies to earlier treatment lines to enhance outcomes and mitigate toxicity (NCT03876769, NCT03914625,[15] and NCT03959085). Additionally, the measurement of pretransplant MRD using various techniques has proven valuable for predicting the risk for relapse, enabling a more sophisticated treatment approach.[16,17] Given these advances, the role of allogeneic HSCT in pediatric patients with ALL has recently been reconsidered, taking into account treatment-related toxicities and long-term morbidities associated with HSCT in this patient population.

Therefore, it is crucial to determine the optimal indications and conditioning regimen for allogeneic HSCT, considering leukemic cell characteristics, patient comorbidities, and the availability of the immunotherapies described earlier. Additionally, the 1-year leukemia-free survival rate of pediatric patients with relapsed or refractory B-cell precursor ALL treated with tisagenlecleucel has been reported to be approximately 50%.[14,18] The role of post-CAR-T HSCT in preventing relapse remains controversial.[19,20] Therefore, to improve outcomes, a comprehensive understanding of prognostic factors and outcomes associated with HSCT in the pre-CAR-T era is imperative, which is essential for optimizing the administration of allogeneic HSCT in conjunction with various newly developed immunotherapies for pediatric patients with ALL.

To address these issues, additional nationwide real-world data regarding allogeneic HSCT in pediatric patients with ALL across diverse ethnic groups are needed. In the present study, we retrospectively investigated the outcomes and prognostic factors of allogeneic HSCT in Korean pediatric patients with high-risk or relapsed ALL using data from the nationwide Korean Society of Blood and Marrow Transplantation registry. Furthermore, myeloablative TBI-based conditioning and chemotherapy conditioning were compared.

METHODS

Patients

A comprehensive analysis of data obtained from 368 patients in the Korean Society of Blood and Marrow Transplantation registry was conducted. These patients were diagnosed with ALL, had undergone allogeneic HSCT between 2009 and 2021, and were <19 years of age at the time of HSCT. Indications for HSCT were determined in accordance with guidelines established by each participating institution, which encompassed considerations including relapsed or refractory ALL and high-risk cytogenetic profiles. Of the 368 patients, 11 who lacked follow-up data and 87 who did not undergo HSCT with myeloablative conditioning were excluded. Ultimately, therefore, the final analysis included data from 270 patients who had undergone their first allogeneic HSCT.

Comprehensive data, including sex, age at initial diagnosis and HSCT, date of HSCT, disease status at HSCT, ALL subtype, donor type, stem cell source, conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, engraftment, complications, and disease status at the last follow-up, were collected and analyzed. Unfortunately, the registry dataset did not include data on pre-HSCT MRD status, pre-HSCT performance status, or the rationale for selecting myeloablative conditioning (MAC). However, molecular remission status, obtained using quantitative polymerase chain reaction in patients with Philadelphia chromosome-positive ALL, was included. This study was approved by the Institutional Review Board of our institution, and requirements for consent were waived (H-1808-141-967) due to the retrospective nature of the investigation and the use of anonymized data.

Definitions

Neutrophil engraftment was defined as the first 3 days with a neutrophil count of >0.5 × 10^9/L, while platelet engraftment was defined as the first day with a platelet count of >20 × 10^9/L, without transfusion for at least 7 days. Acute and chronic GVHD were diagnosed and graded according to previously reported criteria.[21,22] The

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pediatric disease risk index (PDRI) was applied as follows.[23] Low risk was defined as age at HSCT ≥ 2 years with first complete remission (CR) status. High risk was characterized by age at HSCT < 2 years with a second or subsequent CR status or any age with persistence before HSCT. Cases that did not fit into either the low- or high-risk categories were classified as intermediate risk. For the conditioning regimen, a myeloablative regimen was defined as a total TBI dose of >800 cGy, a total busulfan dose of >9 mg/kg, or a total treosulfan dose of ≥42 g/m^2.

Statistical analysis

Categorical and continuous variables were compared using the chi-squared test, Student's *t*-test, or one-way analysis of variance, as appropriate. The incidence rates for relapse, non-relapse mortality (NRM), and GVHD were calculated using a cumulative incidence function. The competing risk for relapse or GVHD was NRM, whereas the competing risk for NRM was relapse. Differences in the cumulative incidence curves were examined using Gray's test. Events were defined as death, relapse, or development of a secondary malignancy. Moderate-to-severe chronic GVHD-free, leukemia-free survival (GLFS) was defined as the length of the interval between transplantation and death, relapse, or the development of moderate-to-severe chronic GVHD. Survival was analyzed using the Kaplan–Meier method, and differences in survival rates were assessed using the log-rank test. A Cox proportional hazards regression model was used for multivariate analysis of prognostic factors affecting survival using the backward elimination method (P < 0.05); independent variables (P < 0.1) were included in this model. Differences with P < 0.05 were considered to be statistically significant. Statistical analyses were performed using R version 4.3.1 (R Foundation, Vienna, Austria, www.r-project.org) and SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

Among the 270 patients analyzed, 166 (61.5%) were male. Patients who received TBI-based MAC conditioning (MAC-TBI, *n* = 118) had a significantly older median age at initial diagnosis and HSCT compared to those receiving chemotherapy-based MAC (MAC-Chemotherapy, median age at diagnosis: 11.4 years [range 2.1–18.7] vs. 8.0 years [range 0.6–18.9], P< 0.001; median age at HSCT: 11.4 years [range 2.1–18.7] vs. 8.0 years [range 0.6–18.9], P < 0.001). Regarding immunophenotype, no significant difference was observed between the two groups. Cytogenetic profiles indicated higher *BCR::ABL1* rearrangement incidence in the MAC-TBI group (23.7% vs. 9.2%). Patients who underwent MAC-Chemotherapy had a significantly higher percentage of CR1 status before HSCT compared to MAC-TBI (75.0% vs. 63.6%, P = 0.007). Regarding donor types, haploidentical family donors were more frequently used in the MAC-Chemotherapy group (19.1% vs. 4.2%), while matched sibling donors were slightly more common in the MAC-TBI group.

No significant difference was found in the PDRI distribution. However, MAC-TBI patients received anti-thymocyte globulin less frequently than MAC-Chemotherapy patients (28.8% vs. 68.4%, P < 0.001). Most patients (89.2%) received peripheral blood as the stem cell source. More detailed characteristics are provided in Table 1. In the MAC-TBI group, cyclophosphamide was combined with TBI in more than 89% of patients, whereas in the MAC-Chemotherapy group, 96.6% received busulfan-based conditioning regimens. Regarding TBI delivery, 54.3% of the MAC-TBI group received fractions of 165–200 cGy administered twice daily, whereas the remaining patients received fractions of 300–333 cGy administered once daily (median total dose: 1200 cGy; range: 999–1320 cGy). Further details regarding the specific conditioning combinations are presented in Table 2.

Engraftment

The median infused total nucleated cell and mononuclear cell doses per recipient body weight, excluding cord blood recipients, were significantly lower in the MAC-TBI group compared to the MAC-Chemotherapy group (total nucleated cells: 8.8×10^8/kg [IQR 7.0–11.3] vs. 1.2×10^8/kg [IQR 8.3–16.1], P < 0.001; mononuclear cells: 7.0×10^8/kg [IQR 5.4–9.1] vs. 9.2×10^8/kg [IQR 5.5–10.9], P = 0.015, respectively). However, there was no significant difference between the two groups regarding infused CD34+ cell doses (5.3×10^6/kg [IQR 3.7–8.6] vs. 6.7×10^6/kg [IQR 4.5–9.4], P = 0.091). Among cord blood recipients, the median infused total nucleated cell and mononuclear cell doses per recipient body weight were also significantly lower in the MAC-TBI group compared with the MAC-Chemotherapy group (6.2×10^7/kg [IQR 3.4–9.1] vs. 8.9×10^7/kg [IQR 5.2–14.2], P = 0.034; 2.1×10^7/kg [IQR 1.0–3.6] vs. 5.2×10^7/kg [IQR 2.5–8.1], P = 0.034, respectively), whereas the infused CD34+ cell doses showed no statistically significant difference between groups (2.6×10^5/kg [IQR 1.6–5.6] vs. 5.5×10^5/kg [IQR 2.4–9.2], P = 0.588).

Neutrophil engraftment was achieved at a median of 12 days (IQR 10–15 days) in both groups without significant difference (MAC-TBI vs. MAC-Chemotherapy; 12 days [IQR 10–15] vs. 11 days [IQR 10–14], P = 0.472). Similarly, platelet engraftment occurred within a median of 20 days (IQR 17–30) in the MAC-TBI group and 21 days (IQR 16–35) in the MAC-Chemotherapy group, also without statistical significance (P = 0.383).

GVHD and complications

Post-transplant complications were compared between the MAC-TBI and MAC-Chemotherapy groups. Hepatic veno-occlusive disease occurred significantly more frequently in the MAC-Chemotherapy group than in the MAC-TBI group (11.9% vs. 21.7%; P = 0.034). Epstein–Barr virus reactivation was also significantly higher in the MAC-Chemotherapy group (11.0% vs. 24.3%; P = 0.005). No statistically significant differences were observed in the incidence of hemorrhagic cystitis (18.6% vs. 15.1%; P= 0.442), cytomegalovirus reactivation (48.3% vs. 52.0%; P= 0.550), or cytomegalovirus disease (7.6% vs. 5.3%; P = 0.428) between the two groups. Data regarding post-transplant lymphoproliferative disease were not available from this registry.

The cumulative incidences of grades II–IV acute GVHD (MAC-TBI vs. MAC-Chemotherapy; 45.8% vs. 37.5%, P = 0.147) and grades III–IV acute GVHD (19.5% vs. 14.5%, P = 0.338) were not significantly different between the two groups (Figure 1A,B). There was a trend toward a lower cumulative incidence of overall chronic GVHD (31.1% vs. 21.0%, P = 0.072) and moderate-to-severe chronic GVHD (20.7% vs. 13.5%, P = 0.123) in the MAC-Chemotherapy group; however, these differences were not statistically significant (Figure 1C,D). Among the 44 patients with moderate-to-severe chronic GVHD, 31 (70.5%) had multiorgan involvement, most commonly affecting the skin (71.0%), liver (61.3%), mouth (58.1%), gastrointestinal tract (38.7%), eyes (32.3%), and lungs (29.0%). In contrast, 13 patients (29.5%) had single-organ involvement, with the most frequently affected sites being the skin (36.4%), gastrointestinal tract (36.4%), and lungs (36.4%), followed by the liver (9.1%).

TABLE 1 Characteristics of all patients (*N* = 270).

Variables	TBI-based MAC (*n* = 118)	Chemo MAC (*n* = 152)	P value
Sex			0.810
Male	74 (62.7%)	92 (60.5%)	
Female	44 (37.3%)	60 (39.5%)	
Age at initial diagnosis, year	9.1 (1.7–18.2)	5.6 (0.1–18.6)	<0.001
Age at HSCT, year	11.4 (2.1–18.7)	8.0 (0.6–18.9)	<0.001
Height, cm	147.4 (88.3–187.2)	126.0 (65.2–181.9)	<0.001
Body weight, kg	35.7 (11.8–91.5)	25.7 (6.9–92.5)	<0.001
Time from diagnosis to HSCT, day	188 (99–3858)	210 (88–2347)	0.034
Immunophenotype			0.317
B cell	84 (71.2%)	114 (75.0%)	
BCR::ABL1	28 (23.7%)	14 (9.2%)	
KMT2Ar	2 (1.7%)	19 (12.5%)	
ETV6::RUNX1	5 (4.2%)	6 (3.9%)	
TCF3::PBX1	0 (0.0%)	2 (1.3%)	
Hyperdiploidy	3 (2.5%)	1 (0.7%)	
Hypodiploidy	1 (0.8%)	1 (0.7%)	
Not otherwise specified	45 (38.1%)	71 (46.7%)	
T-cell	32 (27.1%)	32 (21.1%)	
Mixed phenotype	2 (1.7%)	6 (3.9%)	
HSCT era			0.382
2009–2011	32 (27.1%)	51 (33.6%)	
2012–2016	47 (39.8%)	61 (40.1%)	
2017–2021	39 (33.1%)	40 (26.3%)	
Pre-HSCT disease status			0.007
CR1	75 (63.6%)	114 (75.0%)	
CR2	33 (28.0%)	29 (19.1%)	
CR3 or 4	6 (5.1%)	0 (0.0%)	
Persistence	4 (3.4%)	9 (5.9%)	
Donor			0.008
Matched sibling donor	38 (32.2%)	35 (23.0%)	
Matched unrelated donor	41 (34.7%)	52 (34.2%)	
Mismatched unrelated donor	25 (21.2%)	26 (17.1%)	
Haploidentical family donor	5 (4.2%)	29 (19.1%)	
Cord blood donor	9 (7.6%)	10 (6.6%)	
Stem cell source			0.929
Bone marrow	4 (3.4%)	5 (3.3%)	
Peripheral blood	104 (88.1%)	136 (89.5%)	
Cord blood	10 (8.5%)	11 (7.2%)	
Pediatric disease risk index			0.233
Low	75 (63.6%)	84 (55.3%)	
Intermediate	39 (33.1%)	57 (37.5%)	
High	4 (3.4%)	11 (7.2%)	
Anti-thymocyte globulin administration, yes	34 (28.8%)	96 (63.2%)	<0.001
GVHD prophylaxis			<0.001
Tacrolimus-based	29 (24.6%)	89 (58.6%)	
Cyclosporin-based	85 (72.0%)	60 (39.5%)	
Mycophenolate mofetil only	0 (0.0%)	1 (0.7%)	
Not applicable	4 (3.4%)	2 (1.3%)	
Center			0.195
Pediatric	114 (96.6%)	140 (92.1%)	
Internal medicine	4 (3.4%)	12 (7.9%)	
Follow-up period, year	3.3 (0.1–11.5)	2.9 (0.1–11.5)	0.933

Abbreviations: CR, complete remission; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation.

TABLE 2 Details of the conditioning regimen (*N* = 270).

Conditioning regimen	*N* = 270
MAC-TBI (*n* = 118)	
TBI + Cyclophosphamide	66
TBI + Cyclophosphamide + Cytarabine	20
TBI + Cyclophosphamide + Etoposide	7
TBI + Cyclophosphamide + Fludarabine	12
TBI + Fludarabine + Cytarabine	12
TBI + Etoposide	1
MAC-Chemotherapy (*n* = 152)	
Busulfan-based (*n* = 146)	
Busulfan + Cyclophosphamide	38
Busulfan + Cyclophosphamide + Cytarabine	2
Busulfan + Cyclophosphamide + Etoposide	3
Busulfan + Cyclophosphamide + Fludarabine	20
Busulfan + Fludarabine + Etoposide	71
Busulfan + Fludrabine	6
Busulfan + Fludrabine + Melphalan	3
Busulfan + Melphalan	2
Busulfan	1
Treosulfan-based (*n* = 6)	
Treosulfan + Cyclophosphamide + Etoposide	3
Treosulfan + Fludarabine	2
Treosulfan + Fludarabine + Thiotepa	1

Abbreviations: MAC, myeloablative conditioning; TBI, total body irradiation.

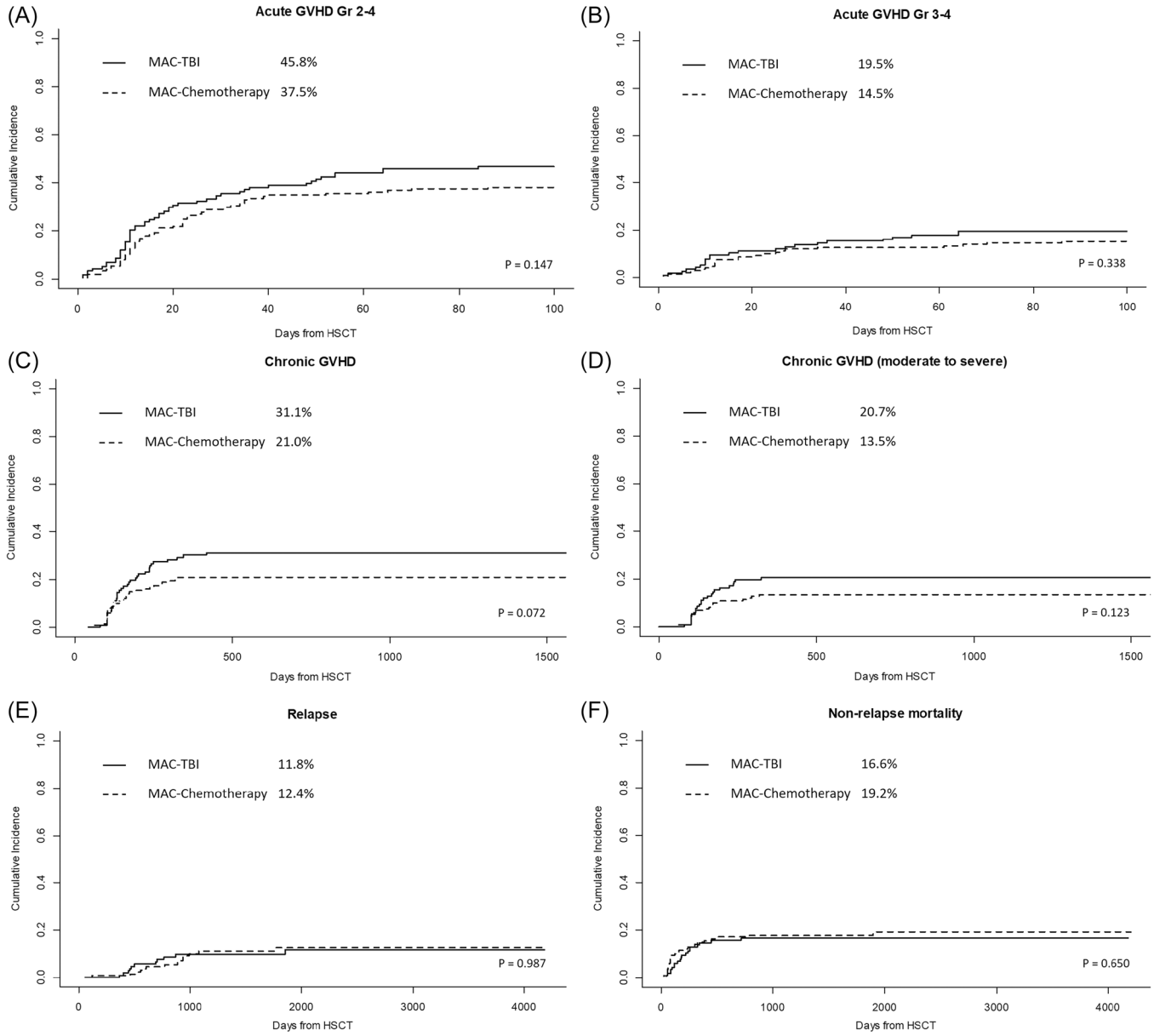

FIGURE 1 The cumulative incidences of **(A)** grades II–IV and **(B)** grades III–IV acute graft-versus-host disease (GVHD) in the MAC-TBI and MAC-Chemotherapy groups were 45.8% vs. 37.5% (P = 0.147) and 19.5% vs. 14.5% (P = 0.338), respectively. Similarly, the cumulative incidences of **(C)** all chronic GVHD and **(D)** moderate-to-severe chronic GVHD were 31.1% vs. 21.0% (P = 0.072) and 20.7% vs. 13.5% (P = 0.123), respectively. The cumulative incidences of **(E)** relapse and **(F)** non-relapse mortality (NRM) were 11.8% vs. 12.4% (P = 0.987) and 16.6% vs. 19.2% (P = 0.650), respectively.

Relapse and survival

The cumulative incidences of relapse between the MAC-TBI and MAC-Chemotherapy groups were comparable (11.8% vs. 12.4%, P = 0.987; Figure 1E). The relapse incidence curve plateaued approximately 3 years after HSCT, although cases of late relapse were reported as late as 5 years post-HSCT. Additionally, NRM did not differ significantly between the two groups (16.6% vs. 19.2%, P = 0.650; Figure 1F), with most cases of NRM occurring within the first year post-HSCT.

Survival outcomes between the MAC-TBI and MAC-Chemotherapy groups were similar. The 5-year rates of GLFS and event-free survival (EFS) were 58.8% (95% confidence interval [CI] 49.6%–68.0%) vs. 59.7% (95% CI 51.1%–68.3%) (P = 0.472) and 73.7% (95% CI 65.5%–81.9%) vs. 69.8% (95% CI 61.8%–77.8%) (P = 0.827), respectively. Additionally, the 5-year overall survival (OS) rates were 76.3% (95% CI 67.5%–85.1%) and 80.2% (95% CI, 73.5%–86.9%) for MAC-TBI and MAC-Chemotherapy groups, respectively (Figures 2 and 3).

In the T-ALL subgroup ($n = 64$; MAC-TBI, $n = 32$ vs. MAC-Chemotherapy, $n = 32$), no significant differences were observed in the 5-year GLFS (64.8% [95% CI 47.9–81.7] vs. 66.1% [95% CI 48.7–83.5]; P = 0.839), 5-year EFS (74.2% [95% CI 58.7–89.7] vs. 78.7% [95% CI, 63.4–94.0]; P = 0.495), or 5-year OS (72.2% [95% CI 55.1–89.3] vs. 82.1% [95% CI, 67.6–96.6]; P = 0.424). Similar findings were noted in the B-ALL subgroup ($n = 198$; MAC-TBI, $n = 84$ vs. MAC-Chemotherapy, $n = 114$), with no significant differences in the 5-year GLFS (56.6% [95% CI 45.6–67.6] vs. 60.2% [95% CI

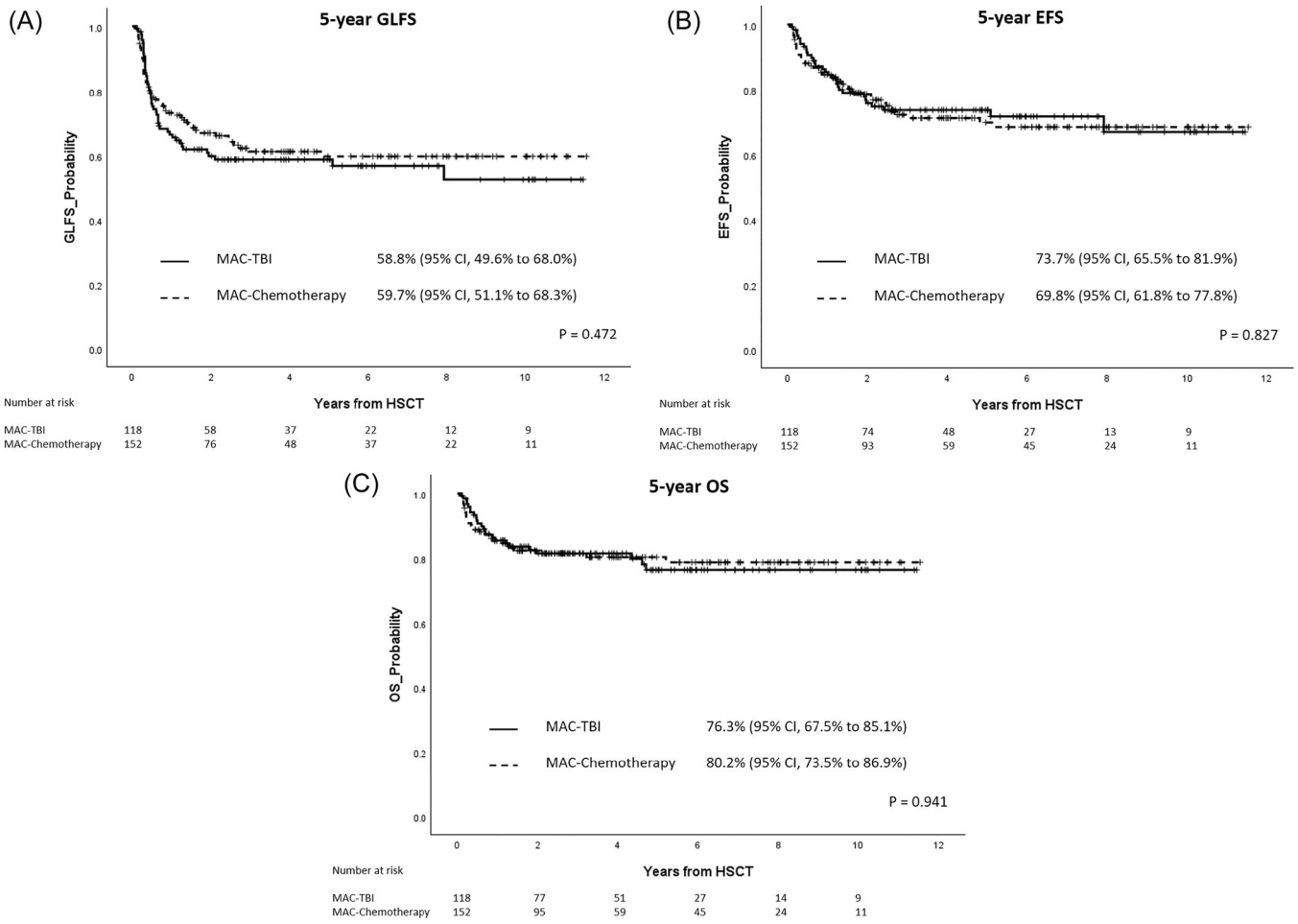

FIGURE 2 The five-year rates of **(A)** moderate-to-severe chronic graft-versus-host disease-free, leukemia-free survival (GLFS), **(B)** event-free survival (EFS), and **(C)** overall survival (OS) were analyzed for the MAC-TBI ($n = 118$) and MAC-Chemotherapy ($n = 152$) groups. No statistically significant differences were observed between the groups.

50.0–70.4]; P = 0.319), 5-year EFS (73.9% [95% CI 63.9–84.0] vs. 69.2% [95% CI 59.6–78.8]; P = 0.770), or 5-year OS (78.5% [95% CI, 68.3–88.7] vs. 82.7% [95% CI, 75.6–89.8]; P = 0.955).

Prognostic factors

In the univariate analysis, significant differences in survival outcomes were observed based on patient age, immunophenotype, disease status at transplant, HSCT era, donor type, anti-thymocyte globulin (ATG) use, and PDRI. Patients older than 15 years exhibited significantly lower 5-year GLFS (27.3%) compared to younger counterparts (64.4%, P = 0.003). Mixed immunophenotype leukemia significantly impacted EFS (P = 0.004) and OS (P < 0.001), and transplantation performed during the recent HSCT era (post-2012) demonstrated improved EFS (P = 0.007). CR status at transplant (CR1) correlated significantly with superior survival outcomes (GLFS, P = 0.033; EFS, P = 0.001; OS, P = 0.016). Haploidentical donor transplantation had a negative impact on EFS (P = 0.024). In contrast, ATG administration positively influenced GLFS (P = 0.010). A higher PDRI was significantly associated with inferior survival across all outcomes (GLFS, P = 0.011; EFS, P < 0.001; OS, P = 0.002).

Multivariate analysis demonstrated that a higher PDRI independently predicted poorer outcomes across all survival measures. ATG administration independently improved GLFS (P = 0.010). Recent HSCT era, disease status at transplant, and haploidentical donor type were independently predictive factors for EFS and OS (Table 3).

DISCUSSION

To our knowledge, this is the first nationwide registry-based study in South Korea reporting outcomes for pediatric patients with ALL undergoing their first allogeneic HSCT with myeloablative conditioning. A comparison between the MAC-TBI and MAC-Chemotherapy groups revealed no significant differences in GLFS, EFS, and OS. Notably, 88.9% of patients received mobilized peripheral blood as the stem cell source. While numerous studies have investigated conditioning regimens for pediatric patients with ALL, the recent For Omitting Radiation Under Majority age (FORUM) trial demonstrated superior outcomes with a TBI plus etoposide regimen compared to various chemotherapy-based regimens.[8] In our study, involving 270 patients who underwent myeloablative conditioning, we did not observe significant differences in outcomes between the TBI-based and chemotherapy-based approaches.

This lack of disparity may, in part, be attributed to variations in TBI delivery methods. In Korea, not all institutions were able to adopt

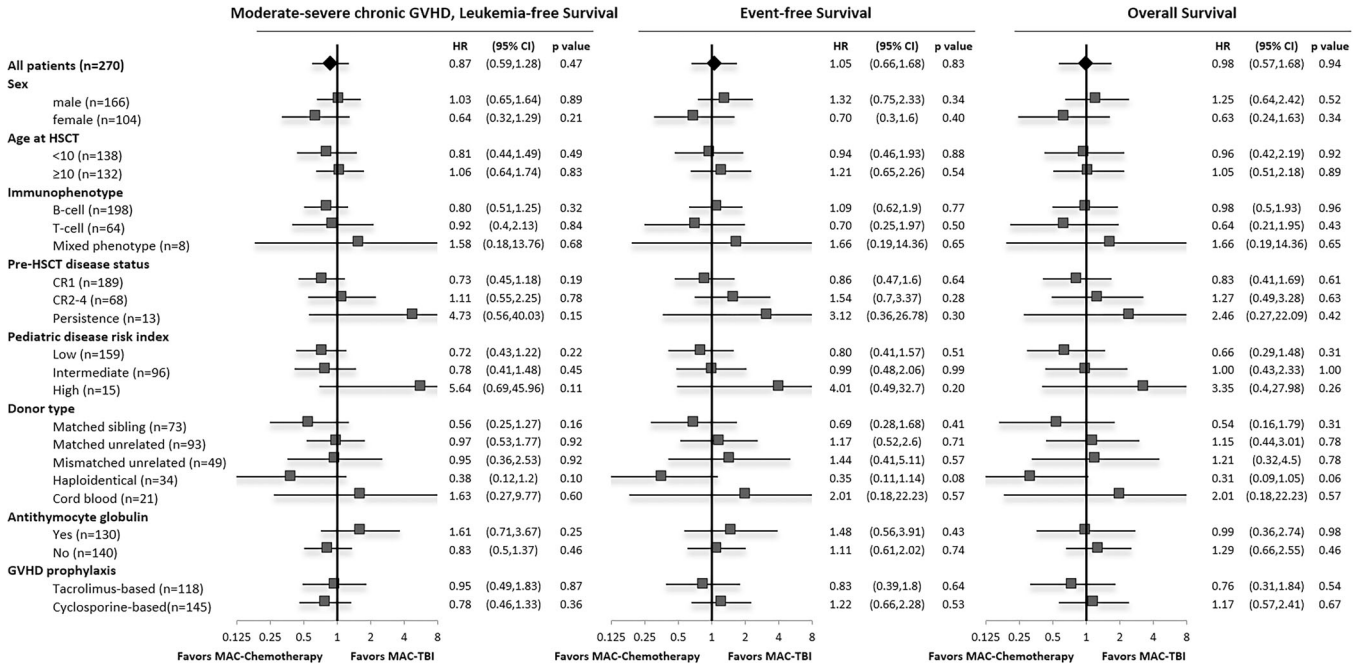

FIGURE 3 Forest plot comparing hazard ratios for moderate-to-severe chronic graft-versus-host disease-free, leukemia-free survival (GLFS), event-free survival (EFS), and overall survival (OS) between the MAC-TBI and MAC-Chemotherapy groups.

the TBI delivery protocol used in the FORUM trial, which involved six fractions over a 3-day period. Approximately 45% of the TBI-MAC group were unable to administer two fractions per day and instead delivered a single daily dose of 300–333 cGy. Furthermore, the selection of chemotherapeutic agents combined with TBI varies across institutions, resulting in lower survival outcomes than those reported in the FORUM trial. However, it is noteworthy that the EFS rate in our MAC-Chemotherapy group was relatively higher than that observed in the FORUM trial. In particular, patients under 4 years of age who underwent MAC-Chemotherapy demonstrated a favorable 5-year EFS rate of 74.5%, in contrast to the 3-year EFS rates of 51%–52% reported in the FORUM trial.[24] Achieving MRD-negative status before HSCT or implementing safer MAC-Chemotherapy regimens through pharmacokinetic monitoring may further improve outcomes.[25–27] In particular, approximately 54% of patients in the MAC-Chemotherapy group received intensive pharmacokinetics-guided busulfan dosing, which has been previously reported to yield feasible outcomes.[28] This suggests that refining busulfan-based conditioning may achieve treatment results comparable to TBI-based regimen. Considering the promising results of MAC-Chemotherapy and the long-term complications associated with TBI,[9,10] it is evident that MAC-Chemotherapy plays a pivotal role in the management of pediatric patients with ALL, especially in younger patients or those who achieve a favorable MRD response.

This study identified several significant prognostic factors influencing survival outcomes in pediatric patients with ALL undergoing HSCT with myeloablative conditioning. We observed that patients with a higher PDRI scores demonstrated significantly inferior GLFS, EFS, and OS rates. Although specific MRD data were not available in our cohort, we adapted the PDRI using age at HSCT and pre-transplant disease status according to previously published criteria.[23] Our findings strongly correlated with the original PDRI developed by the Center for International Blood and Marrow Transplant Research (i.e., "CIBMTR"). Therefore, age between 2 and 10 years and remission status at HSCT may serve as favorable markers for pediatric patients with ALL undergoing allogeneic HSCT.

The use of ATG showed no significant differences in EFS or OS but demonstrated a more favorable impact on GLFS, consistent with previous studies.[29] Notably, nearly 89% of the patients in our study underwent HSCT using mobilized peripheral blood as the stem cell source, primarily due to donor reluctance to undergo bone marrow harvest and logistical constraints within the Korean healthcare system. Recent reports suggest that model-based precision dosing of ATG, rather than fixed dosing, effectively reduces chronic GVHD and graft failure, thereby improving OS.[30] Therefore, optimizing ATG dosing strategies is expected to be particularly beneficial in pediatric patients receiving mobilized peripheral blood HSCT.

However, it is important to note that the majority of patients in our study received transplants before the widespread adoption of post-transplant cyclophosphamide (PTCy) in Korea. Consequently, further research is needed to clarify the role of ATG in the context of increasing PTCy utilization. In particular, haploidentical donor transplants in our study demonstrated inferior outcomes compared to cord blood transplantation, which may be attributable to limited PTCy use during the study period and the relatively small sample size. Nevertheless, a single-center study in Korea has reported comparable outcomes between matched unrelated donors and haploidentical transplants with PTCy in pediatric ALL.[26] Furthermore, retrospective analyses suggest that PTCy-haploidentical transplants achieve outcomes that are at least equivalent to, if not superior to, those of cord blood transplantation.[31] Thus, further large-scale studies are warranted to comprehensively compare long-term transplantation outcomes based on different alternative donor sources. Given the favorable results of PTCy in adults undergoing transplantation with matched donors,[32] similar improvements in prognosis may be anticipated in pediatric populations with evolving GVHD prophylaxis strategies.

TABLE 3 Univariate and multivariate analyses of 5-year GLFS, EFS, and OS. (continued on next page)

	5-year GLFS					5-year EFS					5-year OS				
	Univariates			Multivariates		Univariates			Multivariates		Univariates			Multivariates	
	Total number (case)	Rates ± SE	P value	HR (95% CI)	P value	*n* (case)	Rates ± SE	P value	HR (95% CI)	P value	*n* (case)	Rates ± SE	P value	HR (95% CI)	P value
Sex			0.023					0.098					0.272		
Male	166 (73)	53.5 ± 4.2				166 (50)	67.8 ± 4.0				166 (36)	75.8 ± 3.8			
Female	104 (31)	67.9 ± 5.0				104 (22)	76.7 ± 4.5				104 (17)	82.1 ± 4.1			
Age at initial diagnosis, year			0.003					0.421					0.150		
1–15	197 (68)	64.4 ± 3.6		1		197 (49)	74.4 ± 3.3				197 (34)	81.2 ± 3.1			
≤1	33 (12)	61.1 ± 8.9		0.66 (0.32–1.38)	0.271	33 (10)	67.5 ± 8.5				33 (10)	67.5 ± 8.5			
>15	40 (24)	27.3 ± 10.4		2.42 (1.48–3.95)	<0.001	40 (13)	58.7 ± 9.6				40 (9)	71.5 ± 8.7			
Age at HSCT, year			0.010					0.227					0.388		
<10	138 (42)	67.6 ± 4.2				138 (32)	74.6 ± 3.9				138 (24)	80.9 ± 3.6			
≥10	132 (62)	50.4 ± 4.8				132 (40)	68.1 ± 4.5				132 (29)	75.6 ± 4.2			
Immunophenotype			0.060					0.004					<0.001		
B cell	198 (76)	58.8 ± 3.8				198 (51)	71.3 ± 3.5				198 (34)	80.7 ± 3.1			
T cell	64 (22)	65.4 ± 6.2				64 (15)	76.4 ± 5.6				64 (13)	76.9 ± 5.8			
Mixed phenotype	8 (6)	25.0 ± 15.3				8 (6)	25.0 ± 15.3				8 (6)	25.0 ± 15.3			
Time from diagnosis to HSCT, day			0.191					0.911					0.734		
<200	130 (57)	54.9 ± 4.5		1		130 (36)	71.9 ± 4.1		1		130 (28)	76.4 ± 4.1		1	
≥200	140 (47)	63.7 ± 4.5		0.62 (0.32–0.98)	0.039	140 (36)	71.1 ± 4.3		0.59 (0.33–1.06)	0.076	140 (25)	81.2 ± 3.4		0.54 (0.27–1.07)	0.076
HSCT era			0.704					0.310					0.043		
2009–2011	83 (36)	56.3 ± 5.6				83 (29)	66.0 ± 5.3		1		83 (25)	69.8 ± 5.2		1	
2012–2016	108 (39)	63.6 ± 4.7				108 (25)	76.8 ± 4.2		0.45 (0.25–0.81)	0.007	108 (15)	84.8 ± 3.7		0.30 (0.15–0.60)	0.129
2017–2021	79 (29)	54.9 ± 7.7				79 (18)	69.5 ± 6.8		0.51 (0.27–0.98)	0.042	79 (13)	81.3 ± 4.8		0.14 (0.02–1.06)	0.057
Pre-HSCT disease status			0.033					0.001					0.016		
CR1	189 (66)	64.0 ± 3.7				189 (41)	78.0 ± 3.2		1		189 (31)	82.0 ± 3.1		1	
CR2-4	68 (31)	49.5 ± 6.7				68 (25)	57.1 ± 6.8		2.97 (1.10–7.99)	0.031	68 (17)	72.7 ± 5.8		2.30 (0.79–6.75)	0.129
Persistence	13 (7)	38.9 ± 14.7				13 (6)	45.0 ± 15.6		0.17 (0.02–1.18)	0.073	13 (5)	56.3 ± 14.8		0.14 (0.02–1.06)	0.057
Pediatric disease risk index			0.011					<0.001					0.002		
Low	159 (57)	63.3 ± 4.0		1		159 (34)	78.5 ± 3.5		1		159 (24)	83.3 ± 3.3		1	
Intermediate	96 (38)	56.4 ± 5.5		1.94 (1.15–3.28)	0.013	96 (30)	64.2 ± 5.4		0.98 (0.43–2.25)	0.964	96 (22)	74.9 ± 4.7		1.22 (0.51–2.89)	0.653
High	15 (9)	33.3 ± 13.1		3.18 (1.52–6.66)	0.002	15 (8)	38.6 ± 14.0		19.43 (3.01–122.29)	<0.001	15 (7)	48.2 ± 13.8		25.89 (3.95–169.86)	<0.001
Conditioning			0.472					0.827					0.941		

TABLE 3 (Continued)

	5-year GLFS					5-year EFS					5-year OS				
	Univariates			Multivariates		Univariates			Multivariates		Univariates			Multivariates	
	Total number (case)	Rates ± SE	P value	HR (95% CI)	P value	*n* (case)	Rates ± SE	P value	HR (95% CI)	P value	*n* (case)	Rates ± SE	P value	HR (95% CI)	P value
MAC-TBI	118 (49)	58.8 ± 4.7				118 (31)	73.7 ± 4.2				118 (24)	76.3 ± 4.5			
MAC-Chemotherapy	152 (55)	59.7 ± 4.4				152 (41)	69.8 ± 4.1				152 (29)	80.2 ± 3.4			
Donor			0.208					0.064					0.081		
Matched sibling donor	73 (25)	63.9 ± 6.1				73 (20)	70.5 ± 5.9		1		73 (12)	77.1 ± 6.6		1	
Matched unrelated donor	93 (43)	51.7 ± 5.5				93 (25)	71.2 ± 5.1		1.26 (0.68–2.31)	0.465	93 (17)	79.9 ± 4.5		1.49 (0.69–3.18)	0.318
Mismatched unrelated donor	49 (15)	67.2 ± 7.1				49 (9)	81.9 ± 6.0		0.74 (0.34–1.65)	0.465	49 (8)	85.1 ± 5.2		1.13 (0.46–2.82)	0.788
Haploidentical family donor	34 (15)	49.7 ± 9.7				34 (14)	51.2 ± 9.9		2.34 (1.12–4.88)	0.024	34 (12)	60.4 ± 9.3		3.64 (1.54–8.70)	0.004
Cord Blood	21 (6)	71.4 ± 9.9				21 (4)	81.0 ± 8.6		0.60 (0.20–1.84)	0.372	21 (4)	81.0 ± 8.6		0.96 (0.29–3.17)	0.948
Stem cell source			0.686					0.437					0.103		
Bone marrow	9 (4)	55.6 ± 16.6				9 (4)	55.6 ± 16.6				9 (3)	66.7 ± 15.7			
Peripheral blood	240 (94)	58.1 ± 3.5				240 (64)	71.1 ± 3.2				240 (46)	83.5 ± 3.6			
Cord blood	21 (6)	71.4 ± 9.9				21 (4)	81.0 ± 8.6				21 (4)	81.0 ± 8.6			
Anti-thymocyte globulin administration, yes			0.010					0.174					0.103		
Yes	130 (38)	65.7 ± 4.8		1		130 (28)	73.0 ± 4.6				130 (19)	80.4 ± 3.2			
No	140 (66)	53.0 ± 4.3		1.94 (1.29–2.93)	0.001	140 (44)	69.6 ± 4.0				140 (34)	74.2 ± 4.0			
GVHD prophylaxis			0.206					0.409					0.500		
Tacrolimus-based	118 (46)	58.4 ± 4.9				118 (32)	71.6 ± 4.5				118 (23)	80.6 ± 3.7			
Cyclosporin-based	145 (58)	58.4 ± 4.3				145 (40)	70.4 ± 4.1				145 (30)	75.9 ± 4.1			

Abbreviations: CR, complete remission; EFS, event-free survival; GLFS, moderate-severe chronic GVHD, leukemia-free survival; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; OS, overall survival; SE, standard error.

Although our study included a large and homogeneous cohort of pediatric patients with ALL, it had several limitations. First, its retrospective design introduced inherent constraints. The choice of conditioning regimen could have influenced patient outcomes, as lower-risk patients may have been more likely to receive MAC-Chemotherapy rather than MAC-TBI. Additionally, the absence of data on the genetic characteristics of leukemic cells, MRD status, and causes of death limited the ability to perform a more comprehensive analysis. Third, as a multicenter study, center effects should be considered due to variations in clinical practice among institutions. Fourth, the small number of patients in certain subgroups may limit the interpretation of outcomes. For example, survival outcomes in patients with mixed phenotype acute leukemia (MPAL, $n = 8$) were unexpectedly lower than previously reported.[33,34] Similarly, caution is warranted when interpreting outcomes in patients with persistent disease before HSCT ($n = 13$).

In conclusion, our study provides real-world data from a nationwide registry of 270 Korean pediatric patients with ALL who underwent their first allogeneic HSCT with myeloablative conditioning. Survival outcomes, including GLFS, EFS, and OS, were comparable between the MAC-TBI and MAC-Chemotherapy groups. The PDRI and pre-HSCT disease status were identified as significant prognostic factors for survival. With the growing availability of novel immunotherapies and advancements in disease monitoring, careful consideration of these prognostic factors and their impact on long-term outcomes is essential in optimizing the role of HSCT in pediatric ALL treatment.

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AUTHOR CONTRIBUTIONS

Kyung Taek Hong: Writing—original draft; writing—review and editing; investigation; methodology; formal analysis; validation; conceptualization; software; data curation; project administration; visualization. **Jung Yoon Choi**: Data curation; validation. **Hyery Kim**: Data curation; validation. **Ho Joon Im**: Data curation; validation; methodology; supervision. **Seung Min Hahn**: Data curation; validation. **Chuhl Joo Lyu**: Data curation; validation; methodology; supervision. **Hee Young Ju**: Data curation; validation. **Keon Hee Yoo**: Data curation; validation; methodology; supervision. **Eu Jeen Yang**: Data curation; validation; methodology; supervision. **Sung-Soo Yoon**: Data curation; validation; methodology; supervision. **Hyeon Jin Park**: Data curation; validation; methodology; supervision. **Hyoung Soo Choi**: Data curation; validation; methodology; supervision. **Hee Won Chueh**: Data curation; validation; methodology; supervision. **Deok-Hwan Yang**: Data curation; validation; methodology; supervision. **Joon Ho Moon**: Data curation; validation; methodology; supervision. **Jae Min Lee**: Data curation; validation; methodology; supervision. **Jung-Hee Lee**: Data curation; validation; methodology; supervision. **Jeong-A Kim**: Data curation; validation; methodology; supervision. **Jong-Ho Won**: Data curation; validation; methodology; supervision. **Hyoung Jin Kang**: Conceptualization; investigation; writing—review and editing; validation; supervision; resources; methodology; project administration.

CONSENT

Requirements for consent were waived due to the retrospective nature of the investigation and the use of anonymized data.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of Seoul National University Hospital (Seoul, Korea) (H-1808-141-967).

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