



## ORIGINAL ARTICLE OPEN ACCESS

# Impact of Conditioning Intensity on Survival in Adult Patients (< 65 Years) With Acute Myeloid Leukemia Receiving Antithymocyte Globulin and Post-Transplantation Cyclophosphamide Based GVHD Prophylaxis

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## ABSTRACT

**Introduction:** Myeloablative conditioning (MAC) for acute myeloid leukemia (AML) improves disease control by reducing relapse risk but is associated with higher non-relapse mortality (NRM). Reduced-intensity conditioning (RIC) aims to minimize toxicity but raises concerns about higher relapse rates. This study evaluates the impact of RIC versus MAC in AML patients under 65 years receiving GVHD prophylaxis with antithymocyte globulin, post-transplant cyclophosphamide, and cyclosporine.

**Methods:** We retrospectively analyzed 322 AML patients undergoing allogeneic HCT with uniform GVHD prophylaxis. Propensity score matching (PSM) was applied to adjust for baseline differences.

**Results:** In the matched cohort, 2-year overall survival (OS) did not differ significantly between RIC and MAC recipients (64.4% vs. 66.9%,  $p = 0.56$ ). Relapse-free survival (RFS) at 2 years was 65.0% for MAC and 52.7% for RIC ( $p = 0.20$ ). Two-year NRM was 19.4% for MAC and 19.1% for RIC ( $p = 0.84$ ). Improved RFS was associated with non-high-risk DRI (HR: 0.39,  $p = 0.008$ ), whereas conditioning intensity had no significant effect (HR: 0.98,  $p = 0.97$ ). NRM was higher among patients with KPS < 90 (HR: 3.63,  $p = 0.01$ ), with no significant impact observed from conditioning intensity (HR: 1.44,  $p = 0.43$ ).

**Conclusion:** In a relatively younger cohort, conditioning intensity did not significantly impact survival, and MAC was not associated with increased NRM.

## 1 | Introduction

Acute myeloid leukemia (AML) is a predominant indication for allogeneic hematopoietic cell transplantation (HCT), which

remains a cornerstone in the post-remission strategy for treating intermediate- and high-risk AML [1–3]. Historically, myeloablative conditioning (MAC) regimens have been employed to minimize relapse risk through intensive cytoreduction [4]. However,

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the associated toxicity of MAC can limit its applicability, particularly in patients with comorbidities or advanced age [5]. The advent of reduced-intensity conditioning (RIC) regimens aimed to mitigate these toxicities, expanding eligibility by leveraging the graft-versus-leukemia (GVL) effect for disease control [6–8].

Since its introduction, the comparison between RIC and MAC in AML has remained a topic of ongoing debate. Previous studies have reported no clear survival advantage between the two conditioning intensities, with the reduced risk of relapse associated with MAC being offset by the lower non-relapse mortality (NRM) observed with RIC [9–12]. Long-term follow-up data from the pivotal BMT CTN 0901 trial demonstrated a survival advantage for MAC over RIC, primarily driven by a significantly higher risk of relapse in the RIC group, despite the higher transplant-related mortality (TRM) observed with MAC. A significant proportion of the TRM associated with MAC was attributed to mortality related to graft-versus-host disease (GVHD) [13].

Advances in supportive care for allogeneic HCT have been paralleled by significant improvements in GVHD prophylaxis regimens, effectively addressing a major contributor to TRM. Among these strategies, the combination of antithymocyte globulin (ATG) and post-transplant cyclophosphamide (PTCy) has shown superior efficacy in mitigating GVHD risk without increasing the risk of relapse [14–17].

Building on advancements in the field, this study aims to evaluate the outcomes of RIC versus MAC in AML patients under 65 years of age undergoing allogeneic HCT with a unified GVHD prophylaxis regimen incorporating ATG, PTCy, and cyclosporine (CsA). The study seeks to provide insights into the effects of conditioning intensity while enhancing the validity of findings through the application of propensity score matching to address potential confounding factors arising from baseline characteristic imbalances.

## 2 | Materials and Methods

### 2.1 | Study Design and Patient Selection Criteria

This retrospective study involved data from patients diagnosed with AML who underwent allogeneic HCT at Princess Margaret Cancer Centre between October 2015 and October 2023. All patients were under 65 years of age and received a unified GVHD prophylaxis regimen with ATG, PTCy, and CsA. The study was approved by the University Health Network Research Ethics Board and the Cancer Registry Data Access Committee at Princess Margaret Cancer Centre, Toronto, Canada. The study was conducted in accordance with the Declaration of Helsinki.

### 2.2 | Conditioning Regimens and GVHD Prophylaxis

Conditioning regimens used pre-transplantation were categorized as MAC or RIC following internationally accepted definitions, with the majority of patients receiving a combination of (i) fludarabine 35 mg/m<sup>2</sup> daily for 4 days, busulfan 3.2 mg/kg daily for 2 days, and total body irradiation (TBI) 2 Gy and (ii) fludarabine 35 mg/m<sup>2</sup> daily for 4 days and busulfan 3.2 mg/kg daily for 4 days.

The GVHD prophylaxis regimen consisted of ATG (administered at a total dose of either 4.5 mg/kg on Days –3, –2, and –1 or 2 mg/kg on Days –2 and –1), PTCy at 50 mg/kg/day on Days +3 and +4, and CsA at 2.5 mg/kg every 12 h starting on Day +5 post-transplant. Initially, ATG was standardized at 4.5 mg/kg for all donor types in 2015; however, beginning in May 2018, the dose was reduced to 2 mg/kg due to concerns over increased infection rates, except for haploidentical donors [18].

### 2.3 | Statistical Methods, Endpoints, and Analysis

The main outcomes of interest were overall survival (OS; defined from the time of transplant until death or last follow-up), relapse-free survival (RFS), GVHD-free/RFS (GRFS), and the cumulative incidence of acute GVHD, chronic GVHD, cumulative incidence of relapse (CIR), and NRM. Acute and chronic GVHD were graded according to established criteria [19, 20].

Categorical variables were reported as percentages and counts, while continuous variables were reported as means, medians, and ranges. Kaplan–Meier curves were used to report OS, RFS, and GRFS. The log-rank test was used to determine the statistical significance between the two groups for each outcome. Cumulative incidence curves, taking competing events into consideration, were used to present other variables such as NRM, relapse, incidence of GVHD, bloodstream infections (BSI), CMV, and EBV reactivation at 100 days following transplantation. The Gray's test was used to determine the statistical significance between the two groups for each outcome. Univariate and backwards elimination multivariate analyses were performed to identify predictors of outcomes, with a  $p < 0.05$  considered statistically significant.

### 2.4 | Propensity Score Matching (PSM)

PSM was used to balance the MAC and RIC recipients for baseline characteristics such as age (<40 years/≥40 years), HCT-CI, ATG dose (2/4.5), 2017 ELN risk category, DRI, and HLA-mismatch (HLA-MM). To address this limitation, a 1:1 matching strategy was used, resulting in a cut in the total cohort to 120 patients (60 patients in each group).

PSM matching procedure was performed using Statistica software and the extract matched control option. From a total of 322 patients (207 with RIC and 115 with MAC), 60 patient case-control pairs were extracted through PSM within a 0.1 caliper difference. Analysis was performed using TIBCO Statistica 13.5 and EZR software (Kanda).

## 3 | Results

### 3.1 | Baseline Characteristics and Outcomes Prior to PSM

Table 1 summarizes the baseline characteristics of the unmatched cohort. Patients who received RIC were significantly older, had higher HCT-CI scores, poorer performance status, and were more likely to receive frozen grafts and higher ATG doses compared to MAC recipients. No significant differences

**TABLE 1** | Baseline characteristics for the unmatched cohort.

Characteristics	All patients	RIC	MAC	<i>p</i>
No.	322	207	115	
Age	53 (18–64)	57 (18–64)	46 (18–61)	<0.001
Sex				0.85
Male	166 (51.6)	108 (52.2)	58 (50.4)	
Female	156 (48.4)	99 (47.8)	57 (49.6)	
Status				0.48
CR1	266 (82.6)	171 (82.6)	95 (82.6)	
CR2	45 (14)	26 (12.6)	19 (16.5)	
Not in CR	1 (0.3)	1 (0.5)	0	
NA	10 (10)	9 (4.3)	1 (0.87)	
2017 ELN genetic risk				0.38
Favorable	25 (7.8)	16 (7.8)	9 (7.8)	
Intermediate	148 (45.9)	93 (44.9)	55 (47.8)	
Adverse	120 (37.3)	74 (35.7)	46 (40)	
Missing	29 (9)	24 (11.6)	5 (4.3)	
Therapy-related AML	29 (9)	23 (11.1)	6 (5.2)	0.12
DRI				0.03
Low	15 (4.7)	10 (4.8)	5 (4.3)	
Intermediate	255 (79.4)	156 (75.4)	99 (86.1)	
High/very high	51 (15.9)	41 (19.8)	10 (8.7)	
KPS < 90	52 (16.6)	45 (21.7)	7 (6.1)	<0.001
HCT-CI (0/1–2/≥ 3)	79/126/113	36/79/92	43/47/21	<0.001
Donor's age	29 (11–70)	29 (11–70)	29 (17–62)	0.81
CD34 dose (×10 <sup>6</sup> cells/kg)	7.5 (1.8–22.5)	8 (1.8–22.5)	7 (2–12.7)	0.004
Stem cell source				
BM/PBSC	5/317	3/204	2/113	0.79
Donor type				<0.001
MRD	41 (12.7)	36 (17.4)	5 (4.3)	
MUD	173 (53.7)	95 (45.9)	78 (67.8)	
HAPLOIDENTICAL	65 (20.2)	48 (23.2)	17 (14.8)	
MMUD	43 (13.4)	28 (13.5)	15 (13)	
Frozen graft	90 (28)	67 (32.4)	23 (20)	0.025
CMV status				
Recipient				
Positive	277	180	97	0.63
Negative	45	27	18	
Donor				
Positive	149	90	59	0.79

(Continues)

TABLE 1 | (Continued)

Characteristics	All patients	RIC	MAC	<i>p</i>
Negative	173	117	56	
ATG dose				<0.001
2 mg/kg	181 (56.2)	87 (42)	94 (81.7)	
4.5 mg/kg	141 (43.8)	120 (58)	21 (18.3)	
Year of HCT	2019 (2015–23)	2018 (2015–23)	2021 (2015–23)	<0.001
Follow-up (months)	36.5 (0.9–92.9)	57.6 (0.9–89.5)	24 (1.2–92.9)	<0.001

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; CR, complete remission; DRI, disease risk index; HCT-CI, hematopoietic cell transplant comorbidity index; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NA, not available; PBSC, peripheral blood stem cell; RIC, reduced-intensity conditioning.

TABLE 2 | Baseline characteristics for the matched cohort.

Characteristics	All patients	RIC	MAC	<i>p</i>
No.	120	60	60	
Age	49 (18–63)	50 (18–64)	47 (18–61)	0.16
Sex				0.36
Male	63 (52.5)	29 (48.3)	35 (58.3)	
Female	57 (47.5)	31 (51.7)	25 (41.7)	
Status				0.94
CR1	101 (84.2)	51 (85)	52 (86.7)	
CR2	17 (14.2)	7 (11.7)	8 (13.3)	
Not in CR	0	0	0	
NA	2 (1.6)	2 (3.3)	0	
2017 ELN genetic risk				0.58
Favorable	10 (8.3)	4 (6.7)	5 (8.3)	
Intermediate	58 (48.3)	28 (46.7)	30 (50)	
Adverse	43 (35.8)	23 (38.3)	21 (35)	
Missing	9 (7.5)	5 (8.3)	4 (6.7)	
Therapy-related AML	6 (5)	2 (3.3)	4 (6.7)	0.75
DRI				0.37
Low	7 (5.8)	4 (6.7)	3 (5)	
Intermediate	94 (78.3)	44 (73.3)	51 (85)	
High/very high	18 (15)	12 (20)	5 (8.3)	
KPS <90	18 (15)	13 (21.7)	4 (6.7)	0.04
HCT-CI (0/1–2/≥3)	36/52/32	20/23/17	24/21/15	0.51
Donor's age	29 (11–70)	27 (11–70)	30 (17–62)	0.71
CD34 dose (×10 <sup>6</sup> cells/kg)	7.3 (2–17.8)	8.1 (3.1–17.8)	7 (2–12.7)	0.003
Stem cell source				
BM/PBSC	0/120	0/60	0/60	1.0

(Continues)

TABLE 2 | (Continued)

Characteristics	All patients	RIC	MAC	<i>p</i>
Donor type				0.81
MRD	11 (9.2)	7 (11.7)	4 (6.7)	
MUD	62 (51.7)	31 (51.7)	31 (51.7)	
HAPLOIDENTICAL	26 (21.6)	12 (20)	14 (23.3)	
MMUD	21 (17.5)	10 (16.6)	11 (18.3)	
Frozen graft	28 (23.3)	14 (23.3)	12 (20)	0.82
CMV status				
Recipient				
Positive	100	54	46	0.09
Negative	20	6	14	
Donor				
Positive	51	25	26	1.0
Negative	69	35	34	
ATG dose				0.25
2 mg/kg	79 (65.8)	36 (60)	43 (71.7)	
4.5 mg/kg	41 (34.2)	24 (40)	17 (28.3)	
Year of HCT	2020 (2015–23)	2018 (2015–23)	2021 (2015–23)	<0.001
Follow-up (months)	29.9 (4.8–92.9)	48 (5.7–86.8)	24.1 (4.8–92.9)	<0.001

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; CMV, cytomegalovirus; CR, complete remission; DRI, disease risk index; HCT-CI, hematopoietic cell transplant comorbidity index; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; NA, not available; PBSC, peripheral blood stem cell; RIC, reduced-intensity conditioning.

were observed in the incidence of Grade II–IV or III–IV acute GVHD by Day 100, or in chronic and moderate-to-severe chronic GVHD at 2 years. At 2 years, OS (72.5% vs. 63.8%,  $p=0.09$ ) and RFS (67.3% vs. 55.1%,  $p=0.07$ ) were comparable between MAC and RIC recipients. The CIR at 2 years was significantly lower among MAC recipients (18% vs. 29%,  $p=0.04$ ), whereas 2-year NRM did not differ significantly (14.7% vs. 15.9%,  $p=0.96$ ). Graft failure (GF) rates remained low in MAC and RIC recipients, without significant differences (2.6% vs. 1.9%,  $p=0.68$ ). BSI by Day 30 was comparable between recipients. CMV reactivation by Day 100 was significantly more frequent among RIC recipients (50.4% vs. 34.8%,  $p=0.009$ ), while EBV reactivation rates were comparable (58.2% vs. 57.4%,  $p=0.88$ ). (Table S1).

## 3.2 | After Propensity Score Matching (PSM)

### 3.2.1 | Patients' Baseline Characteristics

Table 2 summarizes the baseline characteristics of the matched cohort, comprising 60 RIC and 60 MAC recipients. Median age did not differ significantly between groups (50 vs. 47 years,  $p=0.16$ ), nor did sex distribution. Donor-related variables, including donor age and donor type, were also not significantly different (Table S2).

The CD34+ cell dose was significantly higher among RIC recipients (8.1 vs.  $7.0 \times 10^6$ /kg,  $p=0.003$ ), while the use of frozen

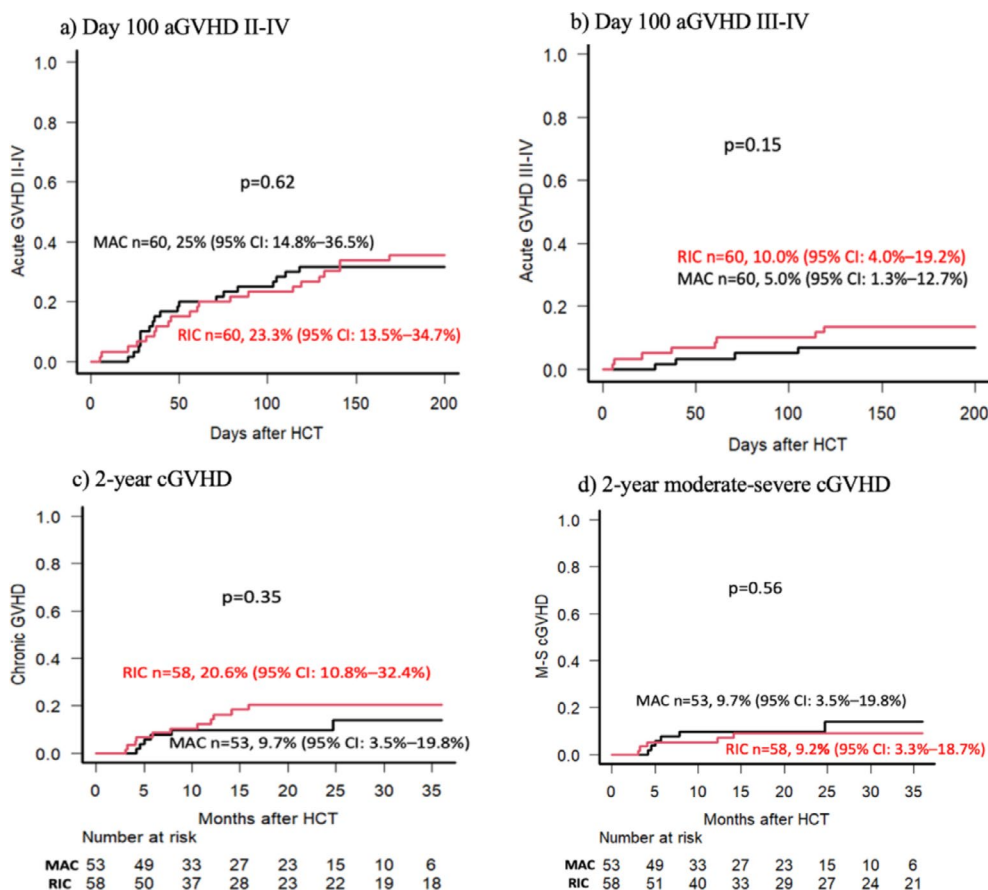
grafts was comparable between RIC and MAC recipients (28.3% vs. 20%,  $p=0.82$ ). HCT-CI scores did not differ significantly ( $p=0.51$ ). Median follow-up duration was significantly longer among RIC recipients (48 vs. 24.1 months,  $p=0.001$ ).

### 3.2.2 | Graft-Versus-Host Disease

After propensity score matching, the incidence of acute GVHD by Day 100 and chronic GVHD at 2 years did not differ significantly between RIC and MAC recipients, as demonstrated in Figure 1a–d.

### 3.2.3 | Main Outcomes

The main outcomes for the matched cohort are shown in Figure 2a–d. At 2 years, OS did not differ significantly between RIC and MAC recipients (64.4% vs. 66.9%,  $p=0.56$ ). The CIR at 2 years was 28.1% among RIC recipients and 15.5% among MAC recipients ( $p=0.07$ ). Two-year RFS and GRFS were 52.7% and 48.1% for RIC recipients, compared to 65.0% and 55.2% for MAC recipients ( $p=0.20$  and  $p=0.47$ , respectively). NRM at 2 years did not differ significantly between RIC and MAC recipients (19.1% vs. 19.4%,  $p=0.84$ ). In multivariable analysis, non-high-risk DRI was associated with improved RFS (HR: 0.39, 95% CI: 0.19–0.78,  $p=0.008$ ). Neither ATG dose (4.5 vs. 2 mg/kg) nor



**FIGURE 1** | Cumulative incidence of acute and chronic GVHD for PSM cohort.

conditioning intensity (MAC vs. RIC) had a significant impact on RFS (HR: 1.66, 95% CI: 0.90–3.03,  $p=0.10$ ; and HR: 0.98, 95% CI: 0.52–1.86,  $p=0.97$ , respectively). For NRM, KPS < 90 was significantly associated with increased risk (HR: 3.63, 95% CI: 1.35–9.81,  $p=0.01$ ), whereas, ATG dose and conditioning intensity were not significantly associated with NRM (HR: 2.20, 95% CI: 0.91–5.34,  $p=0.08$ ; and HR: 1.44, 95% CI: 0.58–3.59,  $p=0.43$ , respectively).

### 3.2.4 | Graft Failure and Post-Transplant Infections

GF occurred in 3.3% of MAC recipients (95% CI: 0.6–10.3) and 1.7% of RIC recipients (95% CI: 0.1–7.9;  $p=0.55$ ). BSI by Day 30 was reported in 55.0% of MAC recipients (95% CI: 41.4–66.7) and 45.0% of RIC recipients (95% CI: 32.0–57.1;  $p=0.37$ ). By Day 100, CMV reactivation was significantly more frequent among RIC recipients at 55.0% (95% CI: 41.4–66.7) compared to 28.3% of MAC recipients (95% CI: 17.5–40.1;  $p=0.004$ ). EBV reactivation during the same period occurred in 61.7% of RIC recipients (95% CI: 48.0–72.8) and 46.7% of MAC recipients (95% CI: 33.6–58.7;  $p=0.15$ ).

## 4 | Discussion

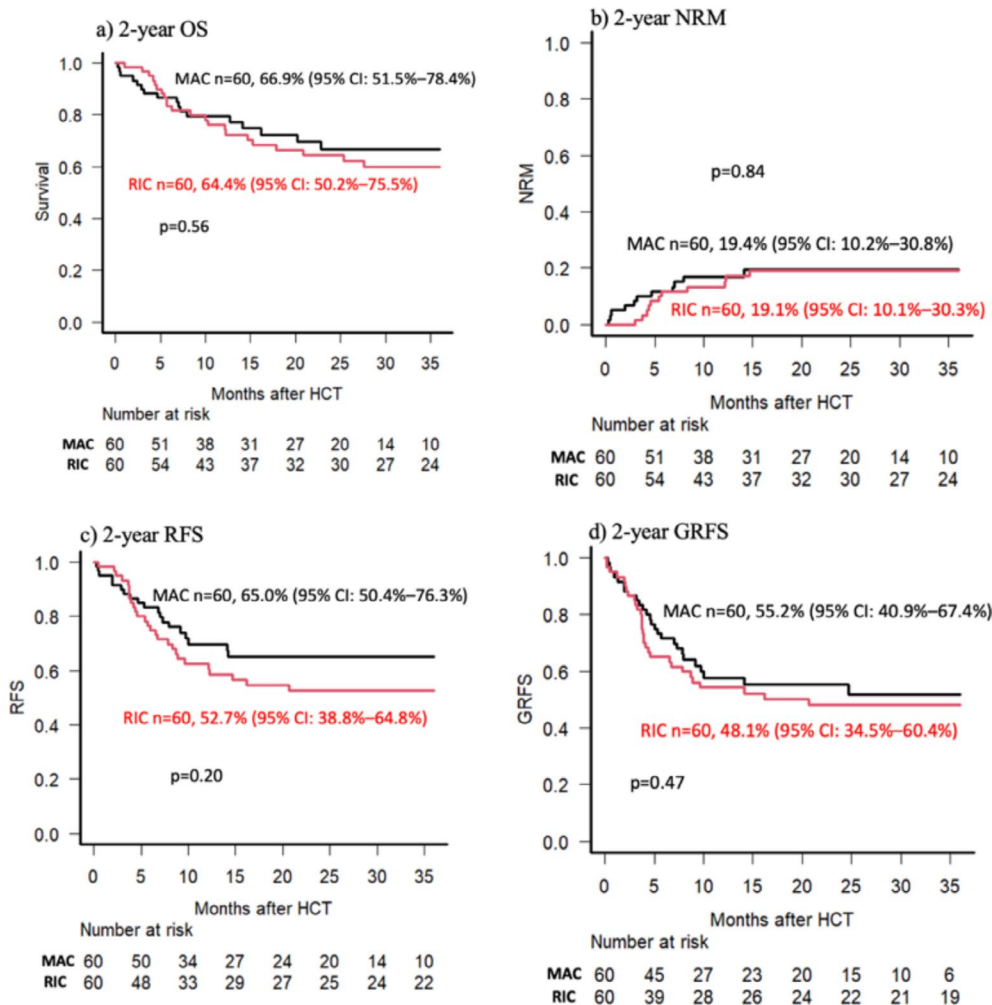
Global access to allogeneic HCT for AML has expanded, with outcomes improving in parallel with advancements in supportive care [21, 22]. Our study aims to provide insights into the optimal conditioning regimen for AML patients receiving a unified

and potent GVHD prophylaxis, specifically in a younger population, and to determine whether conditioning intensity influences outcomes when key contributors to NRM, such as GVHD, are controlled.

In our cohort, conditioning intensity did not impact OS or GRFS. These findings are consistent with previous reports demonstrating comparable survival between MAC and RIC [9, 23–27]. In contrast, long-term data from the BMT CTN 0901 trial showed a survival advantage with MAC over RIC, primarily due to a higher relapse rate (19.8% vs. 60.7%,  $p < 0.001$ ) in the RIC group. However, it is important to note that while conditioning intensity was balanced in that study, the GVHD prophylaxis regimens varied, and PTCy was not utilized [13].

In our PSM cohort, relapse risk was not significantly different between the two conditioning intensities, with incidence rates similar to those observed with MAC and even lower than previously reported rates [10, 28, 29]. Notably, despite the use of combined ATG and PTCy, we did not observe an increased risk of relapse. This finding is consistent with a recent study by Nagler et al., which reported no significant difference in relapse incidence between patients who received PTCy and those who did not (HR: 1.11,  $p=0.31$ ) [30]. Furthermore, a recent review of previously published studies utilizing the combination of ATG and PTCy did not identify any safety signals related to relapse risk [17].

The conditioning regimen in our cohort was homogenous, consisting of a fludarabine/busulfan-based protocol, which has



**FIGURE 2** | Main outcomes for PSM cohort.

previously been associated with lower NRM [31]. A comparative registry-based study of the myeloablative busulfan plus fludarabine (FB4) regimen versus the treosulfan plus fludarabine (FT14) regimen in AML patients in complete remission found that, in patients younger than 55 years, FB4 was associated with superior LFS (HR: 0.77,  $p=0.03$ ) [32]. Conversely, a multicenter retrospective analysis by Sora et al. demonstrated that the thiotepa, busulfan, and fludarabine (TBF) regimen was superior to FB4 in reducing the 5-year CIR (15% vs. 30%,  $p=0.0004$ ) [33]. Considering the limitations of follow-up, the 2-year CIR in our MAC recipients was 15.5% in the PSM cohort.

Bejanyan et al. conducted an observational registry-based study using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) to evaluate the impact of conditioning intensity on outcomes in AML/MDS, stratified by disease risk index (DRI). The study found that RIC was associated with a higher risk of relapse in both the low/intermediate-risk (HR: 1.54,  $p<0.001$ ) and high/very high-risk DRI categories (HR: 1.23,  $p=0.002$ ). Additionally, MAC demonstrated superiority in disease-free survival (DFS) for the low/intermediate-risk group but failed to show the same benefit in the high/very high-risk group, primarily due to the significantly lower NRM observed in RIC recipients in this category [34]. Similarly, a registry-based study from

the European Group for Blood and Marrow Transplantation (EBMT) evaluated conditioning intensity in middle-aged patients (40–60 years) with AML. The study found no clinical benefit of MAC over RIC in terms of LFS and OS for intermediate- and adverse-risk AML, as the reduced relapse rates observed with MAC were counterbalanced by increased NRM [35]. In our cohort, the majority of patients were in the intermediate DRI category, and there were no statistically significant differences between the comparative groups in the high DRI category within the PSM cohort.

Disease status prior to allogeneic HCT is a significant predictor of relapse following transplantation [36, 37]. In our matched cohort, all patients were in complete morphologic remission prior to transplant; however, measurable residual disease (MRD) data were not available. Previous retrospective analyses have highlighted the role of MRD status in conditioning intensity outcomes. One study reported superior survival with MAC compared to RIC in MRD-positive AML, while another found no additional benefit of MAC over RIC in MRD-negative AML [38, 39].

In our study, the higher CMV reactivation rates in RIC recipients compared to MAC likely reflect the increased use of letermovir, which coincided with a shift toward greater MAC utilization. The lower CMV reactivation rates observed in MAC recipients

are likely attributable to broader letermovir adoption rather than the conditioning regimen itself.

The retrospective design of our study inherently introduces certain biases; however, a key strength lies in our efforts to mitigate these biases through the application of propensity score matching. A key limitation of our study is the absence of MRD data, which may have influenced relapse risk stratification and the interpretation of conditioning intensity effects.

This study builds upon our ongoing efforts to optimize transplant outcomes through the implementation of a combined ATG and PTCy-based approach for GVHD prophylaxis [14–16, 18]. Our findings demonstrated no significant differences in outcomes between conditioning intensities, emphasizing that the conditioning regimen is just one component in the multifaceted process of allogeneic HCT. It is not a standalone determinant of success.

With advancements in diagnostic tools for detecting residual disease and the development of post-transplant maintenance strategies, the question of conditioning intensity remains pertinent. This underscores the need for future clinical trials, particularly in the context of PTCy-based GVHD prophylaxis, which is increasingly being utilized as a standard approach across multiple centers.

#### Author Contributions

A.A. and R.A. compiled and summarized the data and wrote the article's first draft. M.R. performed the statistical analysis and contributed to manuscript review and editing. A.V. supervised the project, revised and edited the manuscript. All authors contributed, reviewed, and edited the manuscript.

#### Consent

Informed consent was obtained from all participants.

#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

Data are available upon request from the authors at their discretion.

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### Supporting Information

Additional supporting information can be found online in the Supporting Information section.