



# Long-term outcome of 2-year survivors after allogeneic hematopoietic cell transplantation for acute leukemia

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## Abstract

Information on late complications in patients with acute leukemia who have undergone allogeneic hematopoietic cell transplantation (HCT) is limited. We performed a left-truncated analysis of long-term survival in patients with acute leukemia who were alive and disease-free 2 years after HCT. We included 2701 patients with acute lymphoblastic leukemia (ALL) and 9027 patients with acute myeloid leukemia (AML) who underwent HCT between 2005 and 2012. The 10-year overall survival (OS) rate was 81.3% for ALL and 76.2% for AML, with the main causes of late mortality being relapse (ALL-33.9%, AML-44.9%) and chronic graft-versus-host disease (ALL-29%, AML-18%). At 10 years, HCT-related mortality was 16.8% and 20.4%, respectively. Older age and unrelated donor transplantation were associated with a worse prognosis for both types of leukemia. In addition, transplantation in the second or third complete remission and peripheral blood HSC for ALL are associated with worse outcomes. Similarly, adverse cytogenetics, female donor to male patient combination, and reduced intensity conditioning in AML contribute to poor prognosis. We conclude that 2-year survival in remission after HCT for acute leukemia is encouraging, with OS of nearly 80% at 10 years. However, the long-term mortality risk of HCT survivors remains significantly higher than that of the age-matched general population. These findings underscore the importance of tailoring transplantation strategies to improve long-term outcomes in patients with acute leukemia undergoing HCT.

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## INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a curative therapy for patients with acute leukemia. Advances in transplantation techniques and supportive care have allowed a much larger population to be considered for transplantation and have resulted in significantly improved long-term survival for HCT recipients.<sup>1,2</sup> In the early years of HCT, only younger patients were considered eligible due to the toxicity of conventional myeloablative conditioning (MAC) regimens. Reduced intensity conditioning (RIC) is now widely used to allow transplantation in the elderly and in patients with multiple comorbidities. Several studies have shown similar survival outcomes in both acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) patients following HCT with RIC or MAC.<sup>3–7</sup> Over the past two decades, there has also been a significant increase in the number of human leukocyte antigen (HLA)-matched unrelated donor (MUD), mismatched unrelated donor (MMUD), and haploidentical (haplo) transplants for patients without an HLA-matched sibling donor (MSD). A number of retrospective studies have shown similar overall survival (OS) and leukemia-free survival (LFS) between haplo-HCT with high-dose posttransplant cyclophosphamide and MUD-HCT.<sup>8–13</sup> Most deaths after HCT occur in the first 2 years post transplantation due to disease relapse, infection, graft-versus-host disease (GVHD), or organ toxicity from conditioning regimens.<sup>14</sup> Within the first 2 years after transplantation, advances in GVHD prophylaxis have led to improvements in mortality.<sup>15–21</sup> However, long-term survivors of HCT remain at risk of late complications resulting in higher morbidity and mortality compared to the general population.<sup>22,23</sup> The largest study of long-term survivors reported by the Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) showed that the probability of survival at 10 years for patients who were alive and disease-free 2 years after HCT was 84% in AML or ALL.<sup>24</sup> A major limitation was that the majority of patients transplanted for ALL were in the pediatric or adolescent and young adult (AYA) population, with only 1% of patients older than 50 years. In a more recent long-term survivors study comparing RIC to MAC in MSD-HCT for AML, the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) group showed that the 10-year OS of patients alive and disease-free at the 2-year time point approached 75% in both groups.<sup>25</sup> The most common cause of late mortality was relapse, but chronic GVHD (cGVHD), infection, transplant-related organ toxicity, and secondary malignancies were also important causes of late death.<sup>26–28</sup> Given the major advances in transplantation practices, there is likely to be a larger number of survivors with similar long-term outcomes as reported in previous studies, despite the increased incidence of high-risk transplantation. In addition, previous studies did not consider current cytogenetic risk categories and measurable residual disease (MRD) status, which are important prognostic factors for transplantation outcomes.<sup>29–33</sup> Long-term survival after HCT needs to be re-evaluated and updated. We thus conducted an analysis of long-term survival and prognostic factors of late relapse in patients with acute leukemia who are alive and disease-free at 2 years after HCT, reported to the ALWP of the EBMT.

## MATERIALS AND METHODS

### Study design and data collection

This is a retrospective, multicenter, registry-based analysis. Data were provided by the EBMT registry, to which >600 transplant centers annually submit anonymized data on all their consecutive HCTs

according to specific guidelines and audited quality measures, after informed consent of the patients and according to local regulations in place at the time of transplantation. The ALWP of the EBMT approved the study according to the tenets of the Declaration of Helsinki. Adult patients aged  $\geq 18$  years who received an HCT for AML or ALL, who were alive and relapse-free 2 years after their first allogeneic HCT, and who were reported to the EBMT between 2005 and 2012, were included. Patients with ex vivo T cell depletion (TCD) or cord blood transplantation were excluded from the study.

### Endpoints and statistical analysis

The primary objective of the study was to estimate 10-year OS after HCT for patients with ALL or AML who were disease-free at 2 years. OS was defined as the time from HCT to death, regardless of the cause. All surviving patients were censored at the time of last documented contact. Secondary endpoints included non-relapse mortality (NRM), relapse incidence (RI), leukemia-free survival (LFS), cGVHD and the composite of cGVHD-free and relapse-free survival (cGRFS). LFS was defined as survival without evidence of relapse or progression. RI was defined as leukemia recurrence at any site. NRM was defined as death without evidence of relapse or progression. cGRFS was defined as the time being alive with neither severe cGVHD nor disease relapse at any time point. Probabilities of OS, LFS, and cGRFS were calculated using the Kaplan–Meier method. Cumulative incidence was used to estimate the endpoints of RI and NRM, and cGVHD to accommodate for competing risks. When assessing the cumulative incidence of cGVHD, we considered relapse and death as competing events. The follow-up time was calculated using the reverse Kaplan–Meier method.

Univariate analyses were performed using the Log-rank test for OS, LFS, and cGRFS and Gray's test for cumulative incidence functions. Multivariate analysis was performed using the Cox proportional-hazards model including variables known to potentially influence posttransplant outcomes. Covariates were not statistically selected. Patients with missing information were excluded from the Cox model, except missing cytogenetics which was included as a separate category. Results were expressed as the hazard ratio (HR) with a 95% confidence interval (95% CI). All tests were two-sided with a type 1 error rate fixed at 0.05. HCT-related crude mortality was estimated using common methods in relative survival<sup>34,35</sup> in which patients were matched by age, sex, and country in the year of HCT, to a cohort from the general population for whom survival information was available in the Human Mortality Database population tables ([www.mortality.org](http://www.mortality.org)). Overall mortality (1–OS) was split into the probability of dying from HCT or relapse and the probability of dying from other causes.<sup>36,37</sup> Statistical analyses were performed with SPSS 27.0 (SPSS Inc.) and R 4.1.1 (R Development Core Team, URL: <https://www.R-project.org/>).

## RESULTS

A total of 29,327 acute leukemia patients underwent HCT between 2005 and 2012, 7229 with ALL and 22,098 with AML. Of these, 2701 ALL patients with a median age of 34 (range 18–73.5) years and 9027 AML patients with a median age of 48 (range 18–77.7) years met the study inclusion criteria (Data S1 and Figure S1). Most AML patients (85%) had de novo AML. The majority of patients (78.6% for ALL and 68.6% for AML) were in first complete remission (CR1) with undetectable MRD (68.3% for ALL and 78.9% for AML). There were similar numbers of MSD transplants (43.7% for ALL and 45.6% for AML) and unrelated donor (UD) transplants

(53.2% for ALL and 49.5% for AML). Most patients received peripheral blood (PB) grafts (75.7% for ALL and 85.2% for AML) without antithymocyte globulin (ATG) in about half of the cases (55.7% for ALL and 46.8% for AML). Conditioning regimens also varied, with MAC used extensively in most ALL patients (86.5%) but only in half of AML cases (57.5%). Characteristics of patients in these two groups are shown in Table 1.

The 10-year probabilities of OS and LFS were 81.3% and 78.2%, respectively, for ALL patients (Figure 1) and 76.2% and 72.3%, respectively, for AML patients (Figure 2). The cumulative RI and NRM at 10 years was 9.9% and 11.9%, respectively, for ALL patients (Figure 1) and 15.6% and 12.1%, respectively, for AML patients (Figure 2). The probability of cGRFS at 10 years was 73.3% for ALL patients and 68.1% for AML patients (Table 2).

Multivariate analysis of long-term HCT outcomes in ALL patients (Tables 3 and S2<sup>2</sup>) showed the following:

#### Patient- and disease-specific

- OS and LFS decreased with increasing recipient age (HR [per 10-year increment] 1.20, 95% CI: 1.08–1.33,  $p = 0.0005$ , and HR 1.19, 95% CI: 1.08–1.31,  $p = 0.0003$ , respectively and higher NRM [HR 1.36, 95% CI: 1.19–1.54,  $p < 0.0001$ ]).
- CR2/3 patients and those with advanced disease were associated with lower OS (HR: 1.78, 95% CI: 1.29–2.46,  $p = 0.0004$  and HR: 2.02, 95% CI: 1.35–3.05,  $p = 0.0007$ , respectively) and worse LFS (HR: 1.90, 95% CI: 1.42–2.54,  $p < 0.0001$  and HR: 2.06, 95% CI: 1.41–3.01,  $p = 0.0002$ , respectively) with higher rates of relapse (HR: 2.32, 95% CI: 1.54–3.47,  $p < 0.0001$  and HR: 2.53, 95% CI: 1.48–4.32,  $p = 0.0007$ , respectively) and higher NRM for CR2/3 (HR: 1.56, 95% CI: 1.02–2.39,  $p = 0.04$ ).

#### Transplant-specific

- Transplants from UD were associated with worse OS (HR: 1.34, 95% CI: 1–1.8,  $p = 0.047$ ) and higher NRM (HR: 1.67, 95% CI: 1.17–2.39,  $p = 0.005$ ) compared to transplants from MSD.
- There were significant differences in long-term outcomes based on graft source. PB grafts were associated with inferior OS (HR: 1.54, 95% CI: 1.11–2.14,  $p = 0.009$ ), LFS (HR: 1.57, 95% CI: 1.16–2.12,  $p = 0.003$ ), and cGVHD (HR: 1.99, 95% CI: 1.14–3.48,  $p = 0.015$ ), as well as higher NRM (HR: 1.71, 95% CI: 1.12–2.61,  $p = 0.012$ ) and cGRFS (HR: 1.64, 95% CI: 1.25–2.14,  $p = 0.0003$ ) compared to bone marrow (BM) grafts.
- ATG was associated with improved OS (HR: 0.62, 95% CI: 0.46–0.84,  $p = 0.002$ ) and LFS (HR: 0.70, 95% CI: 0.53–0.92,  $p = 0.009$ ) and lower NRM (HR: 0.48, 95% CI: 0.33–0.69,  $p < 0.0001$ ).
- Total body irradiation (TBI) was not significantly associated with differences in OS, LFS, or relapse.

In AML patients, multivariate analysis (Tables 4 and S2<sup>2</sup>) showed the following:

#### Patient- and disease-specific

- Increasing recipient age was associated with worse OS (HR [per 10-year increment]: 1.30, 95% CI: 1.23–1.37,  $p < 0.0001$ ) and LFS (HR: 1.24, 95% CI: 1.18–1.30,  $p < 0.0001$ ), as well as higher rates of both relapse (HR: 1.12, 95% CI: 1.06–1.19,  $p = 0.0002$ ) and NRM (HR: 1.43, 95% CI: 1.32–1.54,  $p < 0.0001$ ).
- Adverse cytogenetic profiles were associated with adverse OS (HR: 2.27, 95% CI: 1.67–3.09,  $p < 0.0001$ ) and LFS (HR: 2.06, 95% CI: 1.56–2.72,  $p < 0.0001$ ) outcomes.

#### Transplant-specific

- RIC versus MAC was associated with higher OS (HR: 1.21, 95% CI: 1.06–1.37,  $p = 0.004$ ), LFS (HR: 1.15, 95% CI: 1.02–1.29,  $p = 0.021$ ), and NRM (HR: 1.21, 95% CI: 1.01–1.44,  $p = 0.039$ ), but no significant differences in relapse, cGRFS, or cGVHD.

- PB grafts were associated with inferior OS (HR: 1.2, 95% CI: 1–1.43,  $p = 0.048$ ) and higher NRM (HR: 1.45, 95% CI: 1.11–1.89,  $p = 0.006$ ) compared to BM grafts.
- Female donor to male patient combination was associated with inferior OS (HR: 1.32, 95% CI: 1.15–1.51,  $p < 0.0001$ ) and LFS (HR: 1.22, 95% CI: 1.08–1.39,  $p = 0.002$ ) with a higher risk of NRM (HR: 1.72, 95% CI: 1.44–2.06,  $p < 0.0001$ ).
- ATG was associated with improved OS (HR: 0.67, 95% CI: 0.59–0.76,  $p < 0.0001$ ) and LFS (HR: 0.78, 95% CI: 0.69–0.88,  $p < 0.0001$ ) and lower risk of NRM (HR: 0.48, 95% CI: 0.40–0.57,  $p < 0.0001$ ) and cGVHD (HR: 0.60, 95% CI: 0.46–0.77,  $p < 0.0001$ ).
- TBI was associated with lower relapse rates (HR: 0.81, 95% CI: 0.69–0.95,  $p = 0.009$ ) but did not significantly affect NRM, LFS, or OS.

For patients transplanted in the 26 countries with available mortality tables (Data S2) (92% of ALL patients and 91% of AML patients in our cohort), the probabilities of death from other causes were minimal (1.5% and 3.7% for ALL and AML, respectively), whereas the probabilities of death from HCT were 16.8% and 20.4%, respectively, 10 years after HCT. Survival probability stratified by time since BMT ( $\geq 2$ ,  $\geq 4$ ,  $\geq 6$ , and  $\geq 8$ ) among BMT survivors showed survival probabilities of 81.3% and 78.2% for 2-year survivors, 89.3% and 85.6% for 4-year survivors, 93.6% and 91.0% for 6-year survivors, and 96.7% and 96.1% for 8-year survivors for ALL and AML, respectively (Figure 3). Relapse and cGVHD were the most common causes of late mortality, accounting for 31.9% and 27.3% of ALL deaths and 42.7% and 17.0% of AML deaths, respectively, followed by infection, and secondary malignancy (Table S3). No patients reported to have died from infection had cGVHD. Out of 72 deaths by infection in ALL, 14 (19%) occurred after a relapse. Out of 221 deaths by infection in AML, 61 (28%) occurred after a relapse.

## DISCUSSION

In the current landscape of advancing knowledge in acute leukemia, there is an urgent need for a better understanding of patient characteristics and hematologic conditions to sustain this positive trajectory. This is particularly important when considering candidate selection for allogeneic HCT, the only potentially curative strategy for high-risk acute leukemia, which represents a significant portion of the patient population. In this analysis of two left-truncated studies, we observed long-term survival outcomes in patients who underwent HCT for acute leukemia. It is important to note that we include both ALL and AML but report the results separately because they differ between AML and ALL, as they are not the same disease. In patients with ALL who remained alive and relapse-free at 2 years, the 10-year OS was a remarkable 81.3%, while AML patients showed an encouraging 76.2% OS at 10 years. However, it is important to recognize the limitations of this study, including its retrospective nature, and significant gaps in data completeness, particularly with regard to cytogenetics, MRD, and cause of death.

In AML patients, older age and unfavorable cytogenetics are associated with a worse prognosis. Advanced age is associated with poorer performance status, lower white blood cell counts and a lower percentage of blasts in the BM. Patients aged over 75 years also have higher rates of chemotherapy resistance and less favorable cytogenetics. The effects of age on the patient and the disease are reflected in a higher incidence of early death after induction therapy, lower CR rates, and a decreased likelihood of long-term survival as patients age.<sup>38–41</sup> In addition, NRM increased with age. A study conducted in Germany between 1998 and 2018<sup>42</sup> found similar results, with a higher NRM in patients over 70 years of age, a median relapse-free survival shorter by more than 1 year, and therefore a higher relapse-free

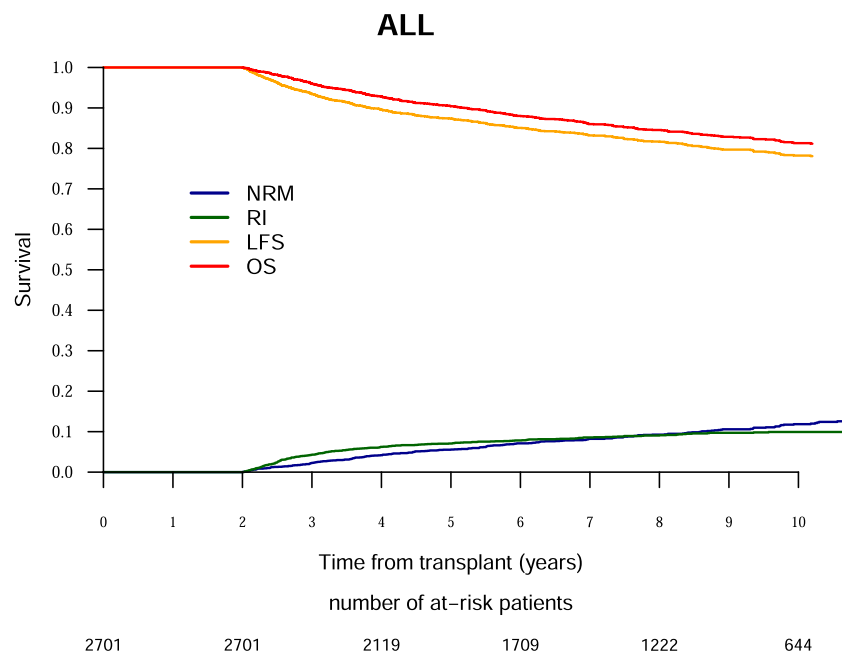
**TABLE 1** Population baseline characteristics of ALL and AML (continued on next page).

		ALL patients, n = 2701	AML patients, n = 9027	
Follow-up, months	Median [IQR]	99.46 [97.85–101.82]	98.18 [97.09–99.19]	
Female	n (%)	1087 (40.3%)	4373 (48.5%)	
Age at HCT, years	median (min-max) [IQR]	34 (18–73.5) [24.3–45.9]	48.5 (18–77.7) [37.2–57.6]	
KPS	≥90	1592 (77.5%)	5578 (78.9%)	
Diagnosis	Phineg B ALL	463 (17.1%)	AML de novo	7632 (84.5%)
	Phipos B ALL	635 (23.5%)	AML secondary	1395 (15.5%)
	T ALL	663 (24.5%)	Cytogenetics favorable	600 (6.6%)
	Missing	940 (34.8%)	Cytogenetics intermed	3091 (34.2%)
			Cytogenetics adverse	682 (7.6%)
			Cytogenetics missing	4654 (51.6%)
			FLT3 positive	592 (24.7%)
		NPM1 positive	476 (22.3%)	
Status at transplant	CR1	2124 (78.6%)	6193 (68.6%)	
	≥CR2	411 (15.2%)	1567 (17.4%)	
	Advanced	166 (6.1%)	1267 (14%)	
MRD pretransplant	Negative	840 (68.3%)	1726 (78.9%)	
	Positive	389 (31.7%)	461 (21.1%)	
	missing	1306	5573	
Type of donor	MSD	1180 (43.7%)	4120 (45.6%)	
	UD	1436 (53.2%)	4472 (49.5%)	
	Other relative	85 (3.1%)	435 (4.8%)	
Female to male	Yes	516 (19.3%)	1523 (17%)	
Cell source	BM	655 (24.3%)	1339 (14.8%)	
	PB	2046 (75.7%)	7688 (85.2%)	
Patient CMV	Positive	1409 (58.4%)	5346 (66.1%)	
Donor CMV	Positive	1167 (48.2%)	4241 (52.3%)	
ATG	Yes	1091 (44.3%)	4387 (53.2%)	
Conditioning	MAC	2320 (86.5%)	5151 (57.5%)	
	RIC	361 (13.5%)	3806 (42.5%)	
	CT	630 (23.5%)	6309 (70.1%)	
	BuCy ± Other		2013 (23.4%)	
	BuFlu ± Other		2171 (25.2%)	
	Other CT		1731 (20.1%)	
	TBI	2054 (76.5%)	2686 (29.9%)	
HCT-CI	0	538 (72.5%)	1558 (62%)	
	1 or 2	118 (15.9%)	537 (21.4%)	
	≥3	86 (11.6%)	416 (16.6%)	
Acute GVHD < 2 y	Yes	837 (32.3%)	2103 (24%)	
	Grade I	577	1930	
	Grade II	616	1598	
	Grade III	183	424	
	Grade IV	38	81	

**TABLE 1** (Continued)

		ALL patients, n = 2701	AML patients, n = 9027
No aGvHD present		1175	4727
missing		112	267
Chronic GVHD < 2 y	Yes	1335 (52.2%)	4531 (52.5%)
GVHD prevention	CSA	221 (9%)	1200 (14.6%)
	CSA + MTX	1665 (67.8%)	4015 (48.8%)
	CSA + MMF	288 (11.7%)	1911 (23.2%)
	Other	282 (11.7%)	1098 (13.4%)
PTCy			126 (1.5%)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; BM, bone marrow; BuCy, busulfan cyclophosphamide; BuFlu, busulfan fludarabine; CMV, Cytomegalovirus; CR, complete remission; CR1, 1st Complete Remission; CR2, 2nd Complete Remission; CR3, 3rd Complete Remission; CSA, cyclosporine A; CT, chemotherapy; Cytogenetics, Risk According to MRC Classification (Blood 2010;116:354–65); cGRFS, composite graft-versus-host disease-free, relapse-free survival; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HCT-CI, HCT-Specific Comorbidity Index; HR, hazard ratio; IQR, interquartile range; Intermed, intermediate; KPS, Karnofsky Performance Status; LFS, leukemia-free survival; MAC, myeloablative conditioning; min, minimum; max, maximum; MMF, mycophenolate mofetil; MSD, matched sibling donor; MTX, methotrexate; NA, not available; NRM, non-relapse mortality; OS, overall survival; Phineg, Philadelphia chromosome negative; Phipos, Philadelphia chromosome positive; Ref, reference; RI, relapse incidence; TBI, total body irradiation; TCD, T cell depletion; UD, unrelated donor, y, year.



**FIGURE 1** Ten-year outcomes analysis after allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia. The red line represents overall survival (OS), the orange line represents leukemia-free survival (LFS), the green line represents relapse incidence (RI), the blue line represents nonrelapse mortality (NRM).

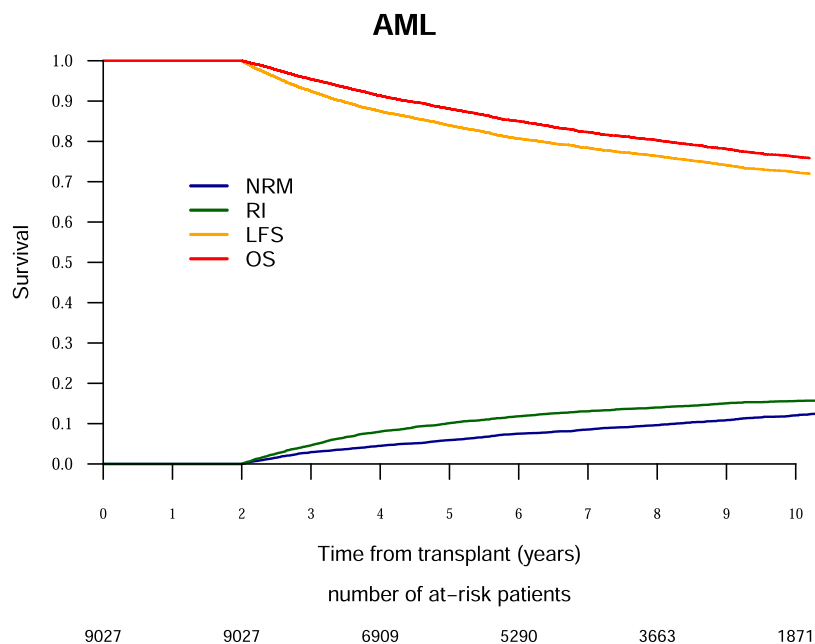
mortality. This underscores the fact that despite major therapeutic advances over the past 20 years, age remains a limiting factor in the management of leukemia patients due to disease severity and unrelated comorbidities. Furthermore, despite the problem of missing data, unfavorable cytogenetics has shown a consistent association with unfavorable OS and LFS, underscoring the impact of disease biology on long-term prognosis.<sup>38,41,43–47</sup>

As previously described, pre-transplant disease status is emerging as an important marker of long-term survival. Indeed, several studies have already shown that achieving MRD-negative status prior to allogeneic HCT improves relapse-free survival and OS. Despite intensive induction/consolidation chemotherapy with

complete hematologic remission rates of 80%–90%, approximately 30%–50% of adult patients with ALL develop MRD. However, many patients relapse while awaiting HCT, and detectable pre-transplant MRD is associated with a higher relapse rate after HCT.<sup>48–53</sup>

In ALL patients, the use of BM was associated with better outcomes. In an analysis spanning four decades, Bhatia et al. found a greater reduction in late mortality in people who received BM.<sup>2</sup>

In AML patients, furthermore, the influence of donor sex on HCT outcomes remains controversial.<sup>54–57</sup> In our study, donor-recipient sex mismatch had a notable impact, particularly the association of lower OS and LFS with being male and receiving a female donor graft.



**FIGURE 2** Ten-year outcomes analysis after Allogeneic hematopoietic cell transplantation for acute lymphoblastic leukemia. The red line represents overall survival (OS), the orange line represents leukemia-free survival (LFS), the green line represents relapse incidence (RI), the blue line represents nonrelapse mortality (NRM).

**TABLE 2** Main outcomes.

Outcomes post HCT % (95% CI)	ALL		AML	
	5 years	10 years	5 years	10 years
RI	7.1 (6.1–8.1)	9.9 (8.7–11.2)	10.1 (9.5–10.8)	15.6 (14.7–16.5)
NRM	5.6 (4.7–6.5)	11.9 (10.4–13.4)	5.9 (5.4–6.4)	12.1 (11.3–12.9)
OS	90.4 (89.2–91.5)	81.3 (79.4–83)	88.1 (87.4–88.8)	76.2 (75.1–77.3)
LFS	87.3 (86–88.6)	78.2 (76.3–80)	84 (83.1–84.7)	72.3 (71.2–73.4)
CGRFS	83.5 (81.9–84.9)	73.3 (71.2–75.2)	80.1 (79.2–81)	68.1 (66.9–69.2)
Chronic GVHD after 2 y	4.8 (4–5.7)	6.3 (5.3–7.4)	4.6 (4.2–5.1)	5.9 (5.4–6.5)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CGRFS, cGVHD-free, relapse-free survival; CI, confidence interval; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; LFS, leukemia-free survival; NRM, nonrelapse mortality; OS, overall survival; RI, relapse incidence.

Ali et al.<sup>27</sup> demonstrated that sex-mismatched grafts were associated with increased GVHD, resulting in a decreased risk of relapse and improved OS. However, this observation contrasts with the findings of Bortin et al.<sup>58</sup> and Ramsay et al.,<sup>59</sup> who did not consider gender mismatch as a significant parameter in the development of GVHD. Furthermore, RIC is associated with lower OS and LFS than MAC, fueling the ongoing debate about optimal conditioning intensity. The lower rates of GVHD observed with RIC contribute to the nuanced discussion regarding the trade-off between antileukemic efficacy and transplant-related morbidity. On the other hand, NRM seems to be higher with RIC than in MAC. Del Galy et al.<sup>60</sup> found a 10-year incidence rate of relapse and relapse-free mortality of 13.9% and 13.4%, respectively, after HCT with RIC. Late relapse was the most common cause of death, but a significant number of patients developed second malignancies, with a cumulative 10-year incidence of 12.9%, which was significantly higher than in the general population. In addition, high rates of cardiovascular complications and venous thromboembolic events were observed at 10 years (15.1% and 11.7%, respectively).

In both AML and ALL, the use of ATG has shown significant benefits, including reduced NRM, improved OS and LFS, and a trend toward reduced GVHD. Currently, the optimal amount of T cells to introduce into the graft remains difficult to determine and is likely to vary between different donor–recipient pairs.<sup>61–64</sup> Donor T cells play a pivotal role in shaping the posttransplant immune response and significantly influence the incidence of GVHD.<sup>65</sup> The incidence of GVHD is dependent on graft characteristics, with unmanipulated grafts associated with a higher likelihood of acute GVHD. In contrast, T cell-depleted grafts have demonstrated the ability to mitigate these risks and offer significant benefits in terms of patient quality of life.<sup>66,67</sup> Despite these advances, uncertainties remain regarding the optimal role of ATG in HCT. Critical issues such as the appropriate selection of eligible patients, optimal methods of marrow or stem cell purification, and the administration of adjunctive medications to manage the graft and prevent GVHD remain unresolved.<sup>61</sup> cGVHD is often a major factor in HCT-related mortality. Severe complications of GVHD can lead to organ failure and other serious medical problems, contributing to posttransplant deaths.<sup>65,68–73</sup> Treatments to

**TABLE 3** Multivariate analysis of long-term HCT outcomes for ALL.

	Relapse HR (95% CI)	p Value	NRM HR (95% CI)	p Value	LFS HR (95% CI)	p Value	OS HR (95% CI)	p Value	CGRFS HR (95% CI)	p Value	Chronic GVHD HR (95% CI)	p Value
Donor MSC (ref)	1		1		1		1		1		1	
UD	0.77 (0.51-1.15)	0.2	1.67 (1.17-2.39)	0.005	1.19 (0.91-1.55)	0.21	1.34 (1-1.8)	0.047	1.15 (0.9-1.46)	0.26	1.22 (0.75-1.97)	0.42
Other relative	0.89 (0.38-2.09)	0.79	0.68 (0.21-2.19)	0.52	0.85 (0.43-1.68)	0.64	0.84 (0.39-1.83)	0.66	0.91 (0.5-1.64)	0.75	0.93 (0.29-3.05)	0.91
CR2/3	2.32 (1.54-3.47)	<0.0001	1.56 (1.02-2.39)	0.04	1.9 (1.42-2.54)	<0.0001	1.78 (1.29-2.46)	0.0004	1.67 (1.29-2.18)	0.0001	1.26 (0.72-2.2)	0.41
Active disease	2.53 (1.48-4.32)	0.0007	1.68 (0.97-2.88)	6.20E-02	2.06 (1.41-3.01)	0.0002	2.02 (1.35-3.05)	0.0007	1.71 (1.2-2.43)	0.003	1.19 (0.54-2.59)	0.67
Age (per 10 y)	1.03 (0.9-1.19)	0.64	1.36 (1.19-1.54)	<0.0001	1.19 (1.08-1.31)	0.0003	1.2 (1.08-1.33)	0.0005	1.19 (1.09-1.29)	<0.0001	1.16 (0.98-1.37)	0.083
Year of HSCT	1 (0.92-1.09)	0.96	0.98 (0.91-1.06)	0.63	0.99 (0.93-1.05)	0.73	1.01 (0.94-1.07)	0.85	0.98 (0.94-1.04)	0.55	0.96 (0.87-1.06)	0.43
Diagnosis (Ref = Phineg B ALL) <sup>a</sup>	1		1		1		1		1		1	
Phipos B ALL	1.45 (0.9-2.33)	0.12	1.16 (0.73-1.84)	0.52	1.28 (0.92-1.77)	0.15	0.99 (0.69-1.42)	0.96	1.19 (0.89-1.59)	0.24	1.2 (0.66-2.19)	0.55
T ALL	0.72 (0.42-1.23)	0.23	0.82 (0.5-1.36)	0.44	0.77 (0.53-1.11)	0.16	0.73 (0.49-1.07)	0.11	0.74 (0.54-1.03)	0.07	0.67 (0.34-1.32)	0.24
Missing	0.76 (0.47-1.24)	0.27	1.13 (0.73-1.76)	0.59	0.94 (0.68-1.3)	0.7	0.89 (0.63-1.26)	0.52	0.96 (0.72-1.28)	0.78	1.19 (0.67-2.11)	0.56
RIC vs. MAC	1.05 (0.64-1.73)	0.84	0.97 (0.61-1.55)	0.91	1.04 (0.74-1.47)	0.81	1.06 (0.73-1.54)	0.77	0.96 (0.71-1.31)	0.8	0.65 (0.32-1.3)	0.22
TBI	0.77 (0.52-1.15)	0.2	1.04 (0.7-1.54)	0.84	0.91 (0.69-1.2)	0.49	0.94 (0.69-1.27)	0.68	0.91 (0.71-1.16)	0.44	0.98 (0.59-1.64)	0.95
PB vs. BM	1.42 (0.92-2.17)	0.11	1.71 (1.12-2.61)	0.012	1.57 (1.16-2.12)	0.003	1.54 (1.11-2.14)	0.009	1.64 (1.25-2.14)	0.0003	1.99 (1.14-3.48)	0.015
Female to male donor	0.85 (0.55-1.3)	0.45	1.63 (1.14-2.32)	0.007	1.21 (0.93-1.59)	0.16	1.23 (0.91-1.66)	0.18	1.21 (0.95-1.54)	0.12	1.43 (0.9-2.26)	0.13
KPS >= 90	1.15 (0.78-1.7)	0.48	0.81 (0.58-1.12)	0.21	0.94 (0.74-1.21)	0.65	0.83 (0.63-1.08)	0.16	0.99 (0.79-1.23)	0.9	1.11 (0.69-1.77)	0.66
In vivo TCD	1.12 (0.74-1.69)	0.59	0.48 (0.33-0.69)	<0.0001	0.7 (0.53-0.92)	9.00E-03	0.62 (0.46-0.84)	0.002	0.71 (0.56-0.9)	0.005	0.71 (0.44-1.15)	0.16

Abbreviations: ALL, acute lymphoblastic leukemia; BM, bone marrow; CGRFS, cGVHD-free, relapse-free survival; CI, confidence interval; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HR, hazard ratio; LFS, leukemia-free survival; MAC, myeloablative conditioning; NRM, nonrelapse mortality; OS, overall survival; PB, peripheral blood; RI, relapse incidence; RIC, reduced intensity conditioning; TCD, T cell depletion.  
<sup>a</sup>As a missing category was included in the model, HR is not reliable for a type of ALL.

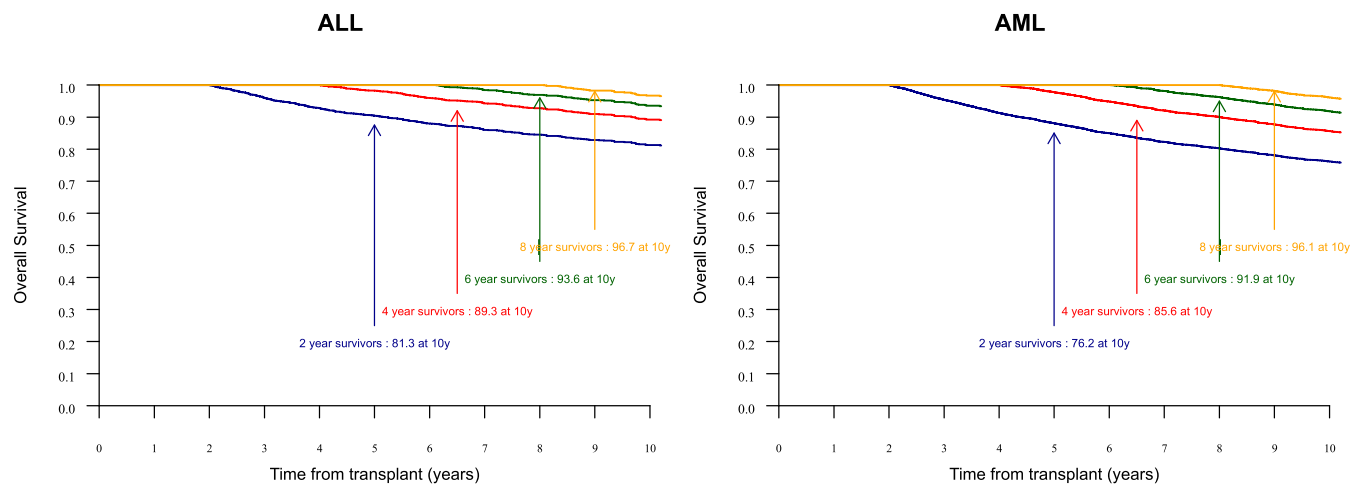
**TABLE 4** Multivariate analysis of long-term HCT outcomes for AML

	Relapse		NRM		LFS		OS		CGRFS		Chronic GVHD	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Donor MSC (ref)	1		1		1		1		1		1	
UD	0.84 (0.72–0.98)	0.026	1.28 (1.07–1.53)	0.008	1.01 (0.9–1.14)	0.88	1 (0.88–1.13)	0.97	1.06 (0.95–1.18)	0.31	1.13 (0.88–1.46)	0.33
Other relative	0.59 (0.37–0.95)	0.031	1.5 (0.99–2.26)	0.054	0.93 (0.68–1.26)	0.63	0.99 (0.71–1.38)	0.98	0.93 (0.7–1.23)	0.61	0.92 (0.48–1.76)	0.8
CR2/3	1.16 (0.97–1.4)	0.11	1.12 (0.91–1.38)	0.3	1.14 (0.99–1.31)	0.063	1.15 (0.98–1.34)	0.082	1.17 (1.03–1.33)	0.018	1.25 (0.94–1.66)	0.13
Active disease	1.7 (1.43–2.01)	<0.0001	1.48 (1.21–1.81)	<0.0001	1.59 (1.4–1.81)	<0.0001	1.65 (1.43–1.9)	<0.0001	1.49 (1.32–1.69)	<0.0001	1.25 (0.92–1.71)	0.15
Age (per 10 y)	1.12 (1.06–1.19)	0.0002	1.43 (1.32–1.54)	<0.0001	1.24 (1.18–1.3)	<0.0001	1.3 (1.23–1.37)	<0.0001	1.19 (1.14–1.25)	<0.0001	1.09 (0.99–1.19)	0.092
Year of HSCT	1.04 (1.01–1.08)	0.021	1 (0.96–1.04)	0.86	1.02 (1–1.05)	0.089	1.01 (0.98–1.04)	0.47	1.03 (1.01–1.06)	0.008	1.08 (1.01–1.14)	0.014
Cytogenetics (Ref = Favorable risk) <sup>a</sup>	1		1		1		1		1		1	
Intermediate	1.57 (1.11–2.22)	0.011	1.02 (0.72–1.45)	0.91	1.29 (1.01–1.66)	0.042	1.27 (0.96–1.68)	0.088	1.32 (1.06–1.66)	0.015	1.42 (0.86–2.36)	0.18
Adverse	3 (2.06–4.36)	<0.0001	1.16 (0.76–1.79)	0.49	2.06 (1.56–2.72)	<0.0001	2.27 (1.67–3.09)	<0.0001	2.09 (1.62–2.69)	<0.0001	1.96 (1.1–3.5)	0.022
Missing	1.55 (1.1–2.18)	0.011	1.05 (0.75–1.48)	0.78	1.3 (1.02–1.66)	0.031	1.32 (1.01–1.74)	0.043	1.34 (1.07–1.67)	0.009	1.42 (0.87–2.32)	0.16
RIC vs. MAC	1.08 (0.92–1.25)	0.35	1.21 (1.01–1.44)	0.039	1.15 (1.02–1.29)	0.021	1.21 (1.06–1.37)	0.004	1.07 (0.97–1.2)	0.19	0.75 (0.58–0.97)	0.028
TBI	0.81 (0.69–0.95)	0.009	0.99 (0.83–1.17)	0.87	0.89 (0.79–1)	0.054	0.91 (0.8–1.03)	0.14	0.93 (0.84–1.04)	0.22	1.12 (0.89–1.42)	0.33
PB vs. BM	0.99 (0.81–1.21)	0.93	1.45 (1.11–1.89)	0.006	1.16 (0.99–1.37)	0.065	1.2 (1–1.43)	0.048	1.13 (0.98–1.31)	0.095	1.15 (0.84–1.57)	0.39
Female to male donor	0.91 (0.76–1.1)	0.33	1.72 (1.44–2.06)	<0.0001	1.22 (1.08–1.39)	0.002	1.32 (1.15–1.51)	<0.0001	1.16 (1.03–1.3)	0.018	0.87 (0.64–1.17)	0.35
KPS > = 90	0.96 (0.82–1.12)	0.58	0.87 (0.73–1.03)	0.11	0.92 (0.82–1.03)	0.16	0.9 (0.79–1.02)	0.097	0.95 (0.85–1.05)	0.32	1.11 (0.84–1.46)	0.46
in vivo TCD	1.14 (0.97–1.34)	0.11	0.48 (0.4–0.57)	<0.0001	0.78 (0.69–0.88)	<0.0001	0.67 (0.59–0.76)	<0.0001	0.74 (0.66–0.82)	<0.0001	0.6 (0.46–0.77)	<0.0001

Abbreviations: ALL, acute lymphoblastic leukemia; BM, bone marrow; CGRFS, cGVHD-free, relapse-free survival; CI, confidence interval; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HR, hazard ratio; LFS, leukemia-free survival; MAC, myeloablative conditioning; NRM, nonrelapse mortality; OS, overall survival; PB, peripheral blood; RI, relapse incidence; RIC, reduced intensity conditioning; TCD, T cell depletion.

<sup>a</sup>As a missing category was included in the model, HR are not reliable for cytogenetics.





**FIGURE 3** Ten-year survival probability stratified by time survived since blood marrow transplantation (BMT) ( $\geq 2$ ,  $\geq 4$ ,  $\geq 6$ , and  $\geq 8$ ) among BMT survivors. Arrows indicate survival rates at specific time points: 2-year survivors (blue), 4-year survivors (red), 6-year survivors (green), and 8-year survivors (orange). BMT, blood marrow transplantation.

control GVHD, such as immunosuppression may also have adverse effects, including an increased risk of infection and other complications associated with a weakened immune system.<sup>74–77</sup>

The 10-year OS reported in this study, which includes patients transplanted between 2005 and 2012, shows some improvement but is not significantly better than previous studies by the CIBMTR<sup>24</sup> and the EBMT,<sup>25</sup> which included patients transplanted before 2004 and 2005, respectively. However, the most recent EBMT analysis highlights a significant improvement in survival for patients who underwent allogeneic HCT. This improvement is primarily attributed to a reduction in NRM. Several factors have likely contributed to this positive trend, including advances in supportive care, better management of GVHD, and improved infection control.<sup>70,73,77,78</sup> The introduction of novel immunosuppressive agents and improved GVHD prophylaxis protocols have significantly reduced the incidence and severity of acute and cGVHD, which were major contributors to NRM in earlier cohorts.<sup>16,59,72,75,79</sup> However, the current study did not provide detailed data on the severity of cGVHD or the need for systemic treatment. In addition, there were no reported deaths from infections in patients with cGVHD, which may indicate a gap in data collection and reporting. Improved infection control practices and the use of newer antiviral and antifungal agents have led to a significant reduction in infection-related mortality.<sup>80,81</sup> These developments have led to a reduction in the complications that have historically contributed to NRM. Despite these advances, survival rates in the current cohort still reflect significant challenges.

A study conducted between 1974 and 2014<sup>2</sup> found that late mortality in allogeneic HCT has decreased over the past 40 years. The leading causes of all-cause mortality included infections, subsequent malignancies, cardiovascular disease, and pulmonary disease. Relative mortality compared to the general population remained high even 30 years after transplantation, with a 20.8% reduction in life expectancy. Survival analyses show that each 2-year relapse-free period after transplantation significantly improves long-term survival, with a particularly notable benefit at 6 years. This underscores the importance of rigorous, ongoing follow-up, as each relapse-free year significantly improves long-term survival.<sup>2</sup> Similarly, another study of 4485 patients who underwent HCT for hematologic malignancies between 1976 and 2014<sup>82</sup> found that half of all deaths in the entire cohort were due to the primary disease, but this proportion was only 10% among survivors

at 15 years. The main causes of late NRM were subsequent malignancies (26.1%) and cardiopulmonary disease (20.2%). In our study, one can speculate that the likelihood of death from other causes 10 years after HCT was minimal. Cardiac toxicity was not predominant, but there were 7.6% secondary cancers in ALL and 11.3% in AML. Therefore, it seems essential to develop new strategies to predict, monitor and treat these long-term complications.

In conclusion, the landscape of HCT for acute leukemia has evolved significantly over the past two decades. For both leukemia types, the impact of donor type, graft source, and the use of ATG on transplant outcomes was evident. While ATG showed benefits in reducing NRM and cGVHD, differences in outcomes based on donor–recipient sex mismatch and graft source (PB vs. BM) require careful consideration in clinical decision-making. Furthermore, late mortality was predominantly due to relapse and cGVHD, highlighting the critical need for targeted interventions and surveillance strategies in long-term survivorship care. Importantly, infections emerged as a significant cause of mortality, particularly in the context of relapsed disease, highlighting gaps in infection prophylaxis and management strategies. Our study highlights the need to refine and optimize pretransplant strategies and integrate comprehensive survivorship programs to improve long-term outcomes in acute leukemia patients undergoing HCT. Continued research efforts are essential to address remaining challenges and improve overall patient care in this evolving field.

#### AUTHOR CONTRIBUTIONS

Mohamad Mohty and Myriam Labopin conceived and designed the study; all authors collected the data. Mohamad Mohty, Marion Larue and Myriam Labopin analyzed the data. Mohamad Mohty, Marion Larue, and Myriam Labopin wrote the manuscript. All authors critically revised and approved the final manuscript. Mohamad Mohty is the guarantor of the study, has full access to all the data, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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data. Following EBMT publication rules, co-authorship was offered to centers contributing the highest number of patients.

### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

### DATA AVAILABILITY STATEMENT

Data sharing is available through the ALWP office ([myriam.labopin@upmc.fr](mailto:myriam.labopin@upmc.fr)).

### FUNDING

None to declare.

### ETHICS STATEMENT

The ALWP of the EBMT approved the study according to the tenets of the Declaration of Helsinki. Data were provided by the EBMT registry after informed consent of the patients and according to local regulations in place at the time of transplantation.

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### SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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