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Version: Accepted Version

Article:
Montoro, J., Ferhat, A.-T., Dhedin, N. et al. (2025) Impact of pre-transplant induction cycles on post-transplant outcomes in patients with ALL: a study from the ALWP EBMT. Bone Marrow Transplantation, 60 (10). pp. 1309-1315. ISSN: 0268-3369

https://doi.org/10.1038/s41409-025-02669-0

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Impact of pre-transplant induction cycles on post-transplant outcomes in patients with ALL: a study from the ALWP EBMT

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Word counts: abstract (188), main text (2611)
Figures: 4
Tables: 3
Reference count: 11

ABSTRACT

The impact of the number of induction cycles required to achieve first complete remission (CR1) on transplant outcomes in adult acute lymphoblastic leukemia (ALL) patients remains unknown. We conducted a retrospective EBMT registry analysis (2000–2022) of ALL patients who underwent transplantation in CR1 after one (n=2038), two (n=296), or three or more (n=110) induction cycles. Median age was 40 years (range 18–73); 79% had B-ALL. At 2 years, relapse incidence was 23%, 31%, and 32%, while non-relapse mortality was 17%, 18%, and 16%, for those achieving CR1 after one, two, and ≥ 3 cycles, respectively. Multivariable analysis showed that requiring ≥ 2 cycles was associated with increased relapse risk. Leukemia-free survival (LFS) at 2 years was 60%, 51%, and 52%, and overall survival (OS) was 68%, 61%, and 60%, for patients needing one, two, and ≥3 cycles, respectively. Multivariable analysis confirmed significantly worse LFS and OS in patients requiring multiple cycles versus one. These findings suggest that the number of induction cycles to achieve CR1 is a key prognostic factor for post-transplant outcomes in adult ALL and support the development of risk-adapted strategies in this setting.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the preferred post-remission therapy for adult patients with acute lymphoblastic leukemia (ALL) in first complete remission (CR1) who have a reduced likelihood of long-term survival using conventional chemotherapy alone[1,2]. Transplant outcomes in these patients are

influenced by various pre-transplant factors, including patient and disease characteristics, as well as the effects of prior treatments on transplant-related mortality and relapse rates[3,4]. These factors are crucial for optimizing transplant strategies. However, the impact of the number of induction cycles required to achieve CR on transplant outcomes in ALL remains unclear.

This study aimed to evaluate how the number of induction cycles to obtain CR1 influences outcomes in adult ALL patients undergoing allogeneic HCT. Using data from the European Society for Blood and Marrow Transplantation (EBMT) registry, we analyzed patients with ALL in CR1 who received HCT, focusing on the relationship between induction cycle count on post-transplant outcomes.

PATIENTS AND METHODS

Study Design and Data Source

This is a retrospective, registry-based analysis conducted on behalf of the Acute Leukemia Working Party (ALWP) of the EBMT. The EBMT is a voluntary working group of more than 650 transplantation centers, all of which are required to report all consecutive stem cell transplantations and follow-up data annually. The EBMT registry maintains an internal quality control program to ensure data accuracy and consistency, with regular audits performed to address missing or incorrect data and to prompt follow-up. All transplantation centers are required to obtain written informed consent before data submission to the EBMT, in accordance with the 1975 Declaration of Helsinki. The ALWP of the EBMT approved this study.

Inclusion Criteria

The study included all adult patients (aged ≥18 years) with a diagnosis of ALL who underwent their first allogeneic HCT from any donor between January 2000 and December 2022, as reported to the EBMT registry. For this analysis, we focused on transplants performed in CR1 after one, two, and three or more induction therapies. To maintain a more homogeneous study population undergoing standard allogeneic HCT, we excluded patients who had received cord blood transplantation or ex vivo T-cell-depleted grafts.

Endpoints and definitions

The primary endpoint was leukemia-free survival (LFS) after one, two, and three or more induction therapies. Secondary endpoints were acute GVHD (aGVHD) and chronic GVHD (cGVHD), relapse incidence, non-relapse mortality (NRM), GVHD-free, relapse-free survival (GRFS), and overall survival (OS) within the same subgroups and the analysis of risk factors for each outcome.

Neutrophil recovery was defined as the first day of an absolute neutrophil count of 0.5 $x10^9$/L lasting for ≥3 consecutive days. aGVHD and cGVHD were defined and graded according to standard criteria[5,6]. Relapse was defined as disease recurrence and appearance of blasts in the peripheral blood or bone marrow (> 5%), or by clinical and/or radiologic confirmation of leukemic involvement at extramedullary sites after achieving CR. LFS was calculated until the date of first relapse, death from any cause, or the last follow-up. NRM was defined as death from any cause other than relapse. The composite endpoint GRFS was defined as survival without the following events: stage III–IV aGVHD, severe cGVHD, disease

relapse, or death from any cause after HCT[7]. Myeloablative conditioning (MAC) was defined as a regimen containing either total body irradiation (TBI) with a dose > 6 Gy, a total dose of oral busulfan > 8 mg/kg, or a total dose of intravenous busulfan > 6.4 mg/kg[8]. All other regimen intensities were defined as reported by the centers.

Statistical Analysis

For univariable survival analysis, the Kaplan-Meier method were used to calculate OS, LFS, and GRFS. Cumulative incidence functions were used to estimate relapse incidence, NRM, aGVHD and cGvHD. Competing risks were death for relapse incidence and relapse for NRM, and relapse or death for aGvHD and cGvHD. Survival probabilities are given at 2 years as percentages and 95% confidence intervals (CIs).

For multivariable analysis, a Cox proportional hazards model was performed including the following variables for adjustment: number of induction cycles to CR1, Karnofsky performance status score, age of the patient at transplant (per 10 years), year of transplantation (per 5 years), reduced intensity conditioning (RIC) or MAC regimen, female donor to male patient combinations, cell source (bone marrow or peripheral blood) and type of ALL. To take into account the heterogeneity in the effect of a characteristic or a treatment across centers, we introduced a random effect into the Cox multivariate models. Hazard ratios (HR) were calculated together with corresponding 95% confidence intervals (95% CI).

The significance level was fixed at 0.05, and P-values were two-sided. P-values for secondary endpoints should be cautiously interpreted due to multiple comparisons. Statistical analyses and adjusted survival curves were performed

using the R statistical software version 4.2.3 (R Foundation for Statistical Computing, Austria, Vienna; available online at http://www.R-project.org).

RESULTS

Patient and Transplant Characteristics

Patient, disease, and transplant characteristics for the overall study population, as well as according to the number of induction cycles, are summarized in Table 1. A total of 2444 patients were included in the study, with 2038 transplanted after one induction cycle, 296 after two cycles, and 110 after three or more cycles. Among the latter group, 15 patients received four induction cycles and 12 patients received five. The median patient age was 40 years (range 18-73), and 58% were male. ALL was of B-cell origin in 1931 (79%) patients and 948 (39%) were Philadelphia chromosome (Ph) positive, 672 (27%) Ph negative and the Ph data were missing for 311 patients. Matched sibling donors were the most common donor type (n=1035, 47%), followed by matched unrelated donors (n=730, 33%) and haploidentical donors (n=172, 8%). Peripheral blood was the stem cell source in 1734 (71%) patients. Regarding conditioning regimens, this was TBI-based in 1806 (74%) and 2007 (82%) received MAC. Anti-thymocyte globulin serotherapy for in vivo T-cell depletion was administered to 1089 (45%) patients. Most patients (n=1460, 60%) received GVHD prophylaxis with a calcineurin inhibitor plus methotrexate.

Patients who achieved CR1 after one induction cycle had a higher proportion of Ph positive B-ALL ($p<0.001$), while those requiring three or more cycles were more

often transplanted in recent years (p<0.001) and more frequently received peripheral blood grafts (p=0.032). No significant differences were observed in patient characteristics, donor type, conditioning regimen, or GHVD prophylaxis between the three cohorts.

Engraftment

The cumulative incidence of neutrophil recovery at 30 days was 96% (95% CI 95–96) for the single-induction cohort, 95% (95% CI 92-97) for the two-induction cohort, and 95% (95% CI 88-97) for the cohort receiving three or more cycles (Table 2). The 60-day cumulative incidence of platelet recovery in similar order was 94% (95% CI, 93-95), 93% (89-95), and 93% (95% CI, 86-97) (Table 2).

GVHD

The cumulative incidence of aGVHD grades II–IV and III-IV at 180 days was 36% (95% CI; 34-39) and 13% (95% CI; 11-14) for the single-induction cohort, 31% (95% CI; 26-36) and 10% (95% CI; 7-14) for the two-induction cohort, and 36% (95% CI; 27-45) and 12% (95% CI; 6-19) for the cohort receiving three or more cycles (Table 2). In the multivariable analysis (Table 3), more recent transplants were associated with a reduced risk of aGVHD grades II–IV (HR 0.9; 95% CI, 0.83-0.97; p=0.008) and grades III-IV (HR 0.87; 95% CI, 0.76-0.99; p=0.04). The use of MAC-TBI was associated with an increased risk of aGVHD grades II–IV (HR 1.53; 95% CI, 1.18-1.99; p=0.001) compared to RIC.

The 2-year cumulative incidence of cGVHD was 41% (95% CI; 38-43) for the single-induction cohort, 40% (95% CI; 34-46) for the two-induction cohort, and 42% (95% CI; 31-52) for the cohort receiving three or more cycles (Table 2). The cumulative incidence of extensive cGVHD was 19% (95% CI; 17-21) for the single-induction cohort, 17% (95% CI; 12-22) for the two-induction cohort, and 20% (95% CI; 12-29) for the three or more cycles cohort (Table 2). In the multivariable analysis (Table 3), factors associated with a higher risk of cGVHD included female donor to male recipient transplants (HR 1.35; 95% CI, 1.12–1.63; p=0.001), increasing patient age per decade (HR 1.11; 95% CI, 1.04-1.19; p=0.002), and the use of MAC-TBI (HR 1.31; 95% CI, 1.03-1.67; p=0.026). The use of peripheral blood as the graft source was associated with an increased risk of both cGVHD (HR 1.36; 95% CI, 1.11-1.66; p=0.003) and extensive cGVHD (HR 1.65; 95% CI, 1.21-2.25; p=0.002). Conversely, earlier year of transplantation (per 5-year period) was associated with a lower risk of cGVHD (HR 0.78; 95% CI, 0.72–0.85; p<0.001) and extensive cGVHD (HR 0.87; 95% CI, 0.78-0.98; p=0.02).

Relapse

The median time to relapse was 7.1 months (interquartile range [IQR] 3.8-13). The cumulative incidence of relapse at 2 years was 23% (95% CI; 21-25) for patients who achieved CR1 after one induction cycle, 31% (95% CI; 26-37) for those after two cycles, and 32% (95% CI; 23-42) for those after three or more cycles (Table 2) (Figure 1). In multivariable analysis (Table 3), compared to achieving CR1 after one induction cycle, both two cycles (HR 1.45, 95% CI, 1.11-1.91; p=0.007) and

three or more cycles (HR 1.64, 95% CI, 1.06-2.52; p=0.025) were associated with a higher risk of relapse. Other factors associated with a higher risk of relapse included earlier year of transplantation per 5 years (HR 0.84, 95% CI, 0.76-0.92; p<0.001) and use of RIC rather than MAC-TBI (HR 0.48, 95% CI, 0.37-0.63; p<0.001).

NRM and causes of death

The 2-year cumulative incidence of NRM was 17% (95% CI; 15-19) in the single-induction cohort, 18% (95% CI; 14-23) in the two-induction cohort, and 16% (95% CI; 9-24) in the cohort receiving three or more cycles (Table 2) (Figure 2). In multivariable analysis (Table 3), factors associated with increased NRM included older patient age (per 10-year increase, HR 1.31; 95% CI 1.18-1.46; p<0.001), earlier year of transplantation (per 5-year period, HR 0.69, 95% CI, 0.61-0.78; p<0.001), use of MAC-TBI (HR 1.62, 95% CI, 1.13-2.34; p=0.009), and use of MAC-chemotherapy (HR 1.73, 95% CI, 1.11-2.69; p=0.015).

At the last follow-up, 965 (39.5%) patients had died, of whom 502 (52%) were due to a variety of non-relapse causes, distributed as follows: 415 (53%) in the single-induction cohort, 68 (47%) in the two-induction cohort, and 19 (43%) in the cohort receiving three or more cycles. The main causes of transplant-related deaths were infections and GVHD, accounting for 290 (70%) in the single-induction cohort, 46 (68%) in the two-induction cohort, and 15 (79%) in the cohort receiving three or more cycles, results not shown.

Survival

For the entire cohort, the 2-year LFS, OS, and GRFS were 58% (95% CI 56–60), 67% (95% CI 65–69), and 40% (95% CI 39–43), respectively.

In the single-induction cohort, the 2-year LFS was 60% (95% CI; 57-62), compared to 51% (95% CI; 45-57) in the two-induction cohort and 52% (95% CI; 41-62) in patients receiving three or more cycles (Table 2) (Figure 3). Multivariate analysis (Table 3) identified that patients undergoing two cycles (HR 1.35, 95% CI,1.09-1.68, p= 0.007) or three or more cycles (HR 1.67, 95% CI,1.18-2.35, p=0.004) had a higher risk of worse LFS compared to those receiving a single cycle. Additional risk factors associated with a lower LFS included increasing patient age per decade (HR, 1.16; 95% CI, 1.09-1.24; p<0.001), earlier year of transplantation (per 5-year period, HR 0.77, 95% CI, 0.72-0.84; p<0.001), and the use of RIC rather than MAC-TBI (HR 0.77, 95% CI, 0.62-0.95; p=0.015). When comparing patients receiving two cycles versus three or more cycles, earlier year of transplantation (per 5-year period HR 0.81, 95% CI, 0.69-0.95; p=0.011) and the use of RIC instead of MAC-TBI (HR 0.52, 95% CI, 0.27-0.1; p=0.05) were also associated with reduced LFS.

For OS, the 2-year rate was 68% (95% CI; 66-70) in the single-induction cohort, 61% (95% CI; 54-66) in the two-induction cohort, and 60% (95% CI; 49-70) for patients receiving three or more cycles (Table 2) (Figure 4). In the multivariate analysis (Table 3), receiving two cycles (HR 1.34, 95% CI,1.06-1.7, p=0.016) or three or more cycles (HR 1.86, 95% CI,1.28-2.68, p=0.001) was associated with lower OS compared to those who received one cycle. Other factors associated with a worse

OS were increasing patient age per decade (HR, 1.24; 95% CI, 1.15-1.33; p<0.001), earlier year of transplantation (per 5-year period HR 0.72, 95% CI, 0.66-0.79; p<0.001), and T-cell lineage ALL compared to Ph positive B-ALL (HR 0.76, 95% CI, 0.6-0.96; p=0.019).

Regarding GRFS, the 2-year rates were 41% (95% CI; 39-44) for the single-induction cohort, 36% (95% CI; 30-42) for the two-induction cohort, and 36% (95% CI; 26-46) in patients who received three or more cycles (Table 2). In the multivariable analysis (Table 3), increasing patient age per decade (HR 1.08; 95% CI, 1.02-1.14; p=0.008), and earlier year of transplantation (per 5-year period, HR 0.87; 95% CI, 0.82–0.93; p<0.001) were associated with a lower GRFS.

DISCUSSION

This study reveals that adult ALL patients undergoing allogeneic HCT in CR1 after a single induction cycle experience significantly lower relapse rates and improved LFS and OS compared to those requiring two or more cycles. Notably, NRM remained consistent across groups, and outcomes did not differ meaningfully between patients needing two versus three or more cycles to achieve CR1. These findings underscore the number of induction cycles as a key prognostic factor for HCT outcomes. Clinically, this insight could refine risk stratification, enhance transplant candidate selection, and guide tailored post-transplant management strategies for ALL patients.

As a retrospective, registry-based study, some potential biases cannot be ruled out. To reduce one major source of bias, we restricted the cohort to patients in

CR1. However, patients who required more induction cycles inherently had to survive long enough to reach CR1 and proceed to transplant, introducing the risk of immortal time bias. This may lead to an overestimation of benefit in early responders or an underestimation of risk in late responders. Furthermore, differences in conditioning regimens, ALL subtypes, and graft sources—such as a higher frequency of peripheral blood stem cell use in patients receiving three or more induction cycles—as well as the use of anti-thymocyte globulin and variations in GVHD prophylaxis, were not fully balanced between cohorts. These factors introduce heterogeneity that may affect outcomes independently of induction response. Although the multivariable analysis adjusted for several key covariates, important data such as extended genetic profiles, detailed pretransplant treatment history, minimal residual disease status at transplant, use of tyrosine kinase inhibitors in Ph-positive ALL, and donor lymphocyte infusion were not available in the registry. Despite these limitations, the study's design and large sample size allowed for a robust assessment of the association between the number of induction cycles and post-transplant outcomes in adult with ALL.

Research on the impact of induction cycle number on HCT outcomes has primarily focused on acute myeloid leukemia (AML)[9,10] , with limited data specific to ALL. Our observation of higher relapse rate driving reduced survival in patients requiring two or more cycles aligns with AML studies[9,10] and likely reflects underlying disease resistance. Patients needing multiple induction cycles to reach CR may harbor leukemias with high-risk genetic features or aggressive biology that increase chemotherapy resistance. Notably, relapse risk did not increase progressively

beyond two cycles, as outcomes were comparable between the two-cycle and three or more-cycle groups. This plateau effect deserves further ALL-specific investigation to clarify its implications and guide treatment strategies.

Beyond the influence of induction cycle number, our study also confirmed a marked improvement in nearly all outcomes over time, consistent with prior EBMT findings in this setting[11]. This trend likely reflects advances in transplant practices and supportive care. We also confirmed established prognostic factors, including recipient age, conditioning intensity, and ALL subtype, with T-cell ALL showing poorer OS than Ph+ B-ALL. Together, these observations position induction cycle number as a valuable predictor within a broader landscape of evolving HCT outcomes.

In conclusion, this study highlights the number of induction cycles required to achieve CR1 as a significant determinant of HCT outcomes in adult ALL patients, with a single cycle linked to reduced relapse and improved survival. While these findings offer a practical tool for risk stratification and clinical decision-making, the retrospective design and unmeasured variables, such as MRD, underscore the need for cautious interpretation. Consistent with prior EBMT observations, our results affirm the evolving success of allogeneic HCT and position induction cycle number as an accessible marker within this landscape. Prospective studies integrating genetic and residual disease data are essential to validate these insights and optimize treatment strategies for ALL patients undergoing transplantation.

ACKOWLEDGEMENTS

The authors are particularly thankful to all centers from the Acute Leukemia Working Party of the EBMT, who kindly agreed to participate in this study

AUTHORSHIP CONTRIBUTION

Conception and design: JM and JS

Data analysis and interpretation: JM, ATF, and JS

Manuscript writing: JM

Final approval of manuscript: JM, ATF, ND, IYA, JV, DB, MB, EF, CCL, PC, MR, JS, LM, US, GE, JAS, JP, DW, JM, AH, SG, ZP, MM, FC.

CONFLICT OF INTEREST DISCLOSURES

The authors declare no conflict of interest related to this manuscript.

DATA AVAILABILITY

All data can be obtained from corresponding author for appropriated reasons.

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TABLE LEGENDS

Table 1 Patient and transplant characteristics in the whole cohort and stratified by induction cycles.

Table 2 Univariable analysis of transplant outcomes according to number of induction cycles.

Table 3 Multivariate analysis of transplant outcomes.

FIGURE LEGENDS

Figure 1 Cumulative incidence of relapse by number of induction cycles

Figure 2 Cumulative incidence of non-relapse mortality by number of induction cycles

Figure 3 Probability of leukemia-free survival by number of induction cycles

Figure 4 Probability of overall survival by number of induction cycles

		NUMBER OF INDUCTION CYCLES			p-value
CHARACTERISTIC	**TOTAL N = 2444**	**1 N = 2038**	**2 N = 296**	**≥ 3 N = 110**	
Median age at transplant, years (IQR)	40 (18-73)	41 (18-73)	38 (18-73)	36 (18-70)	0.067
Gender, n (%)					0.15
Female	1015 (42)	862 (42)	107 (36)	46 (42)	
Male	1428 (58)	1176 (58)	188 (64)	64 (58)	
Missing	1	0	1	0	
Karnofsky performance status, n (%)					0.14
≥ 90	1346 (70)	1134 (71)	146 (64)	66 (72)	
< 90	577 (30)	470 (29)	81 (36)	26 (28)	
Missing	521	434	69	18	
Type of ALL, n (%)					<0.001
T-cell	513 (21)	392 (19)	82 (28)	39 (36)	
B-cell Ph positive	948 (39)	845 (41)	82 (28)	21 (19)	
B-cell Ph negative	672 (27)	544 (27)	88 (29)	40 (36)	
B-cell Ph unknown	311 (13)	257 (13)	44 (15)	10 (9)	
Year of transplant, median (IQR)	2013 (2007-2018)	2013 (2008- 2018)	2011 (2006- 2017)	2017 (2009- 2019)	<0.001
Conditioning intensity, n (%)					0.9
MAC	2007 (82)	1670 (82)	245 (83)	92 (84)	
RIC	434 (18)	366 (18)	50 (17)	18 (16)	
Missing	3	2	1	0	
Type of conditioning, n (%)					0.72
Chemotherapy-based	635 (26)	528 (26)	81 (27)	26 (24)	
TBI-based	1806 (74)	1508 (74)	214 (73)	84 (76)	
Missing	3	2	1	0	
Donor-recipient CMV serostatus, n (%)					0.47
Positive/Positive	812 (34)	674 (34)	109 (38)	29 (27)	
Positive/Negative	285 (12)	237 (12)	31 (11)	17 (16)	

Negative/Positive	490 (20)	406 (20)	58 (20)	26 (24)	
Negative/Negative	812 (34)	683 (34)	92 (32)	37 (34)	
Missing	45	38	6	1	
Female donor to male recipient, n (%)	446 (18)	369 (18)	64 (22)	13 (12)	0.059
Stem cell source, n (%)					0.032
Bone marrow	710 (29)	610 (30)	79 (27)	21 (19)	
Peripheral blood	1734 (71)	1428 (70)	217 (73)	89 (81)	
Type of donor, n (%)					0.47
Matched sibling	1035 (47)	883 (48)	115 (46)	37 (38)	
Matched unrelated	730 (33)	604 (33)	84 (34)	42 (43)	
Haploidentical	172 (8)	141 (8)	23 (9)	8 (8)	
Mismatched unrelated	244 (11)	205 (11)	28 (11)	11 (11)	
Missing	263	204	45	11	
In vivo T-cell depletion, n (%)	1089 (45)	896 (44)	138 (48)	55 (50)	0.27
GVHD prophylaxis, n (%)					0.45
CNI + MTX	1460 (60)	1231 (60)	163 (55)	66 (60)	
PT-Cy based	204 (8)	172 (8)	21 (7)	11 (10)	
Other	780 (32)	635 (32)	112 (38)	33 (30)	

Abbreviations: ALL acute lymphoblastic leukemia, Ph Philadelphia chromosome, MAC myeloablative conditioning, RIC reduced intensity conditioning, TBI total body irradiation, CMV cytomegalovirus, GVHD graft-versus-host-disease, CNI calcineurin inhibitor, MTX methotrexate, PT-Cy posttransplant cyclophosphamide

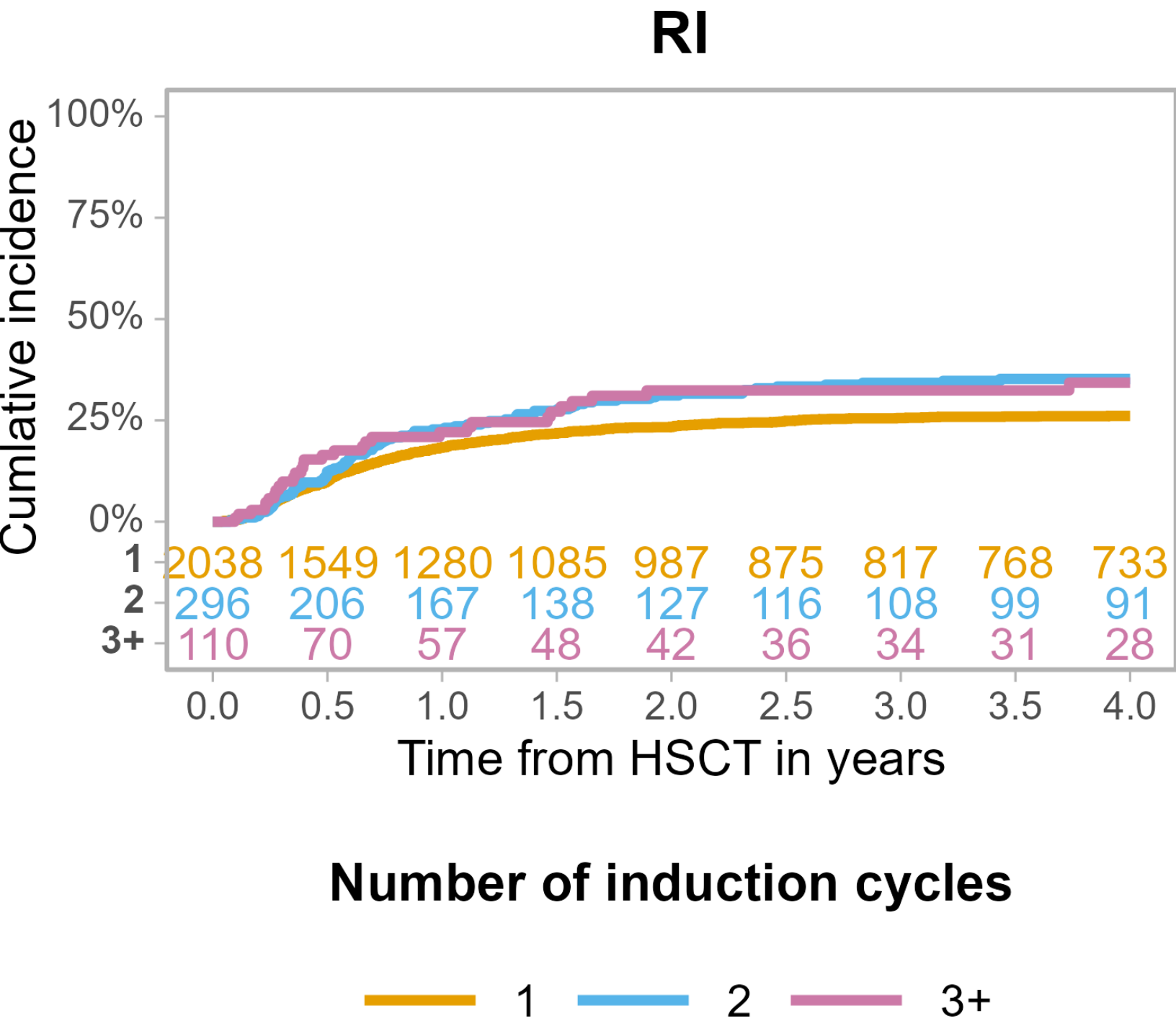
OUTCOME	1	2	≥ 3
Myeloid engraftment, CI at 30 days (%)	96 (95-96)	95 (92-97)	95 (88-97)
Platelet engraftment, CI at 60 days (%)	94 (93-95)	93 (89-95)	93 (86-97)
aGVHD grades II-IV, CI at 180 days (%)	36 (34-39)	31 (26-36)	36 (27-45)
aGVHD grades III-IV, CI at 180 days (%)	13 (11-14)	10 (7-14)	12 (6-19)
Overall cGVHD, 2-year CI (%)	41 (38-43)	40 (34-46)	42 (31-52)
Extensive cGVHD, 2-year CI (%)	19 (17-21)	17 (12-22)	20 (12-29)
NRM, 2-year CI (%)	17 (15-19)	18 (14-23)	16 (9-24)
RI, 2-year CI (%)	23 (21-25)	31 (26-37)	32 (23-42)
LFS, 2-year CI (%)	60 (57-62)	51 (45-57)	52 (41-62)
OS, 2-year CI (%)	68 (66-70)	61 (54-66)	60 (49-70)
GRFS, 2-year CI (%)	41 (39-44)	36 (30-42)	36 (26-46)

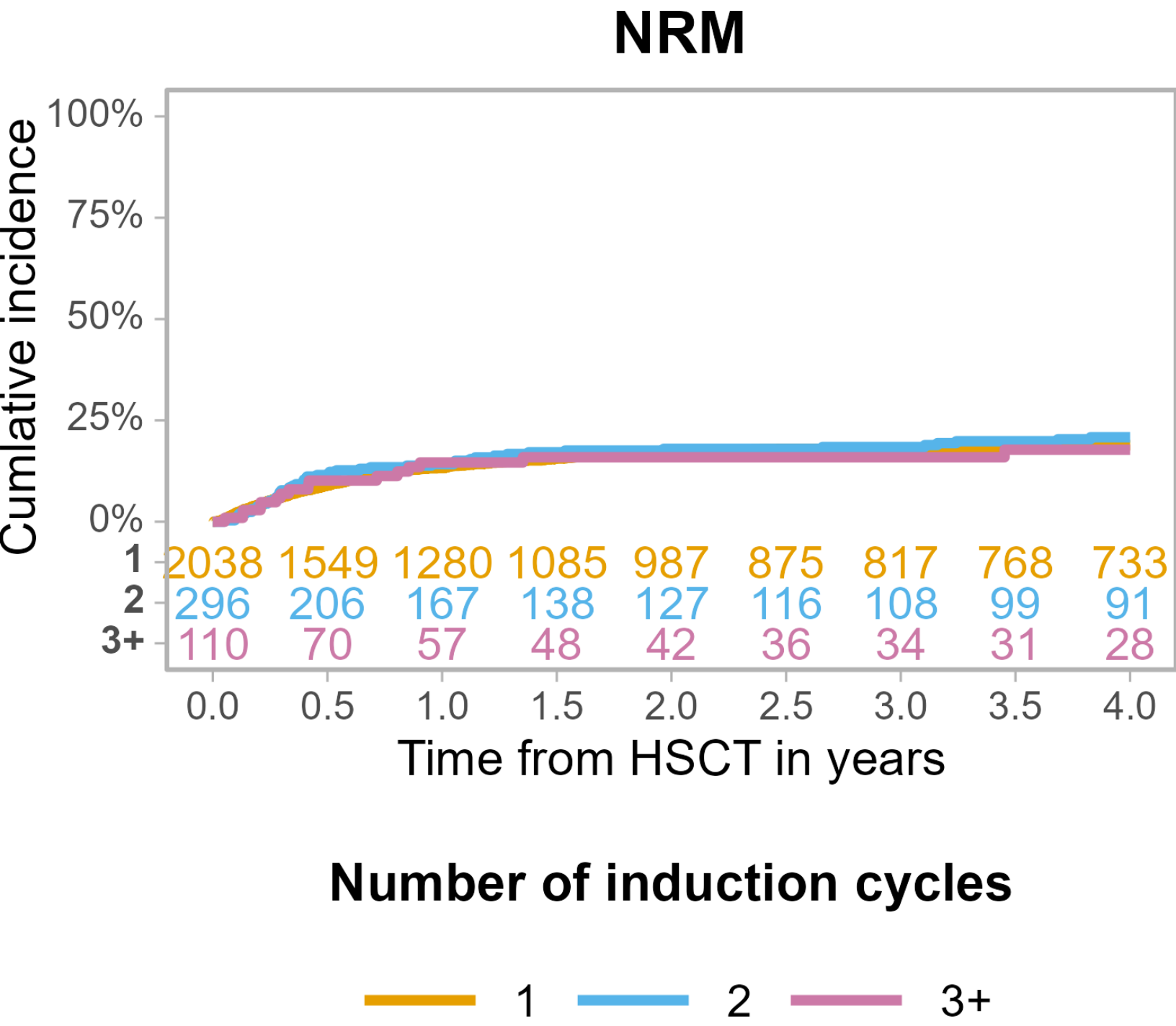
Abbreviations: aGVHD acute graft-versus-host-disease, cGVHD chronic graft-versus-host-disease, NRM non-relapse mortality, RI relapse incidence, LFS leukemia-free survival, OS overall survival, GRFS GVHD-free, relapse-free survival

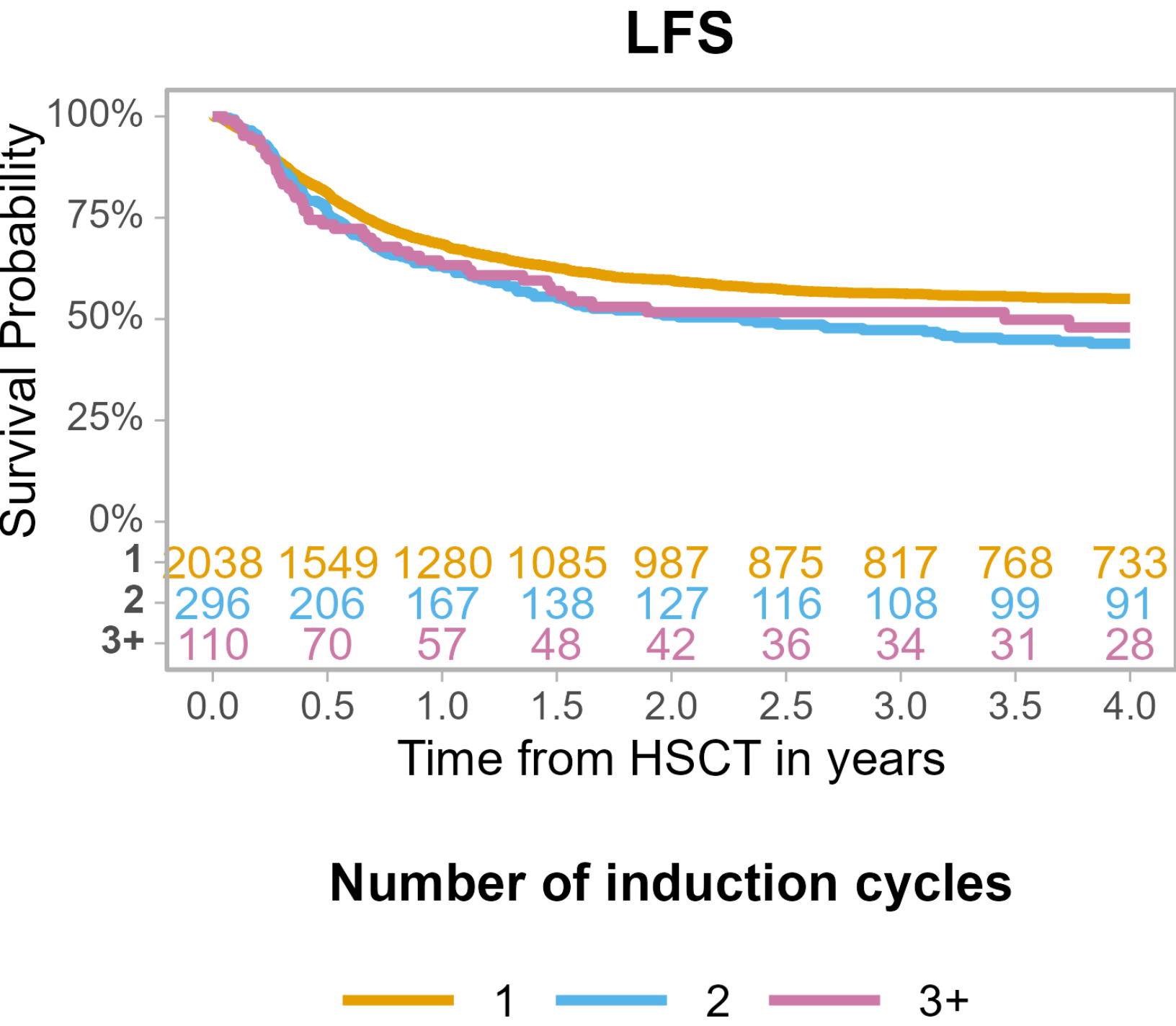
		aGvHD II-IV		aGvHD III-IV		cGvHD		Extensive cGvHD		RI		NRM	
Covariate	**Group**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**HR (95% CI)**	**p**	**OR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Number of induction cycles	1												
	2	0.87 (0.66-1.15)	0.33	0.82 (0.51-1.32)	0.41	1.01 (0.78-1.3)	0.93	1.15 (0.79-1.65)	0.46	1.45 (1.11-1.91)	**0.007**	1.22 (0.86-1.73)	0.27
	≥ 3	1.27 (0.87-1.86)	0.22	1.05 (0.54-2.03)	0.88	1.23 (0.83-1.84)	0.29	1.27 (0.73-2.21)	0.39	1.64 (1.06-2.52)	**0.025**	1.72 (0.97-3.02)	0.06
Patient age (per 10 years)		1.03 (0.96-1.11)	0.36	0.94 (0.84-1.07)	0.35	1.11 (1.04-1.19)	**0.002**	1.09 (0.99-1.2)	0.07	1.07 (0.98-1.16)	0.12	1.31 (1.18-1.46)	**<0.001**
Karnofsky performance status score	≥ 90												
	<90	0.87 (0.73-1.05)	0.15	0.99 (0.73-1.34)	0.93	1.11 (0.94-1.32)	0.21	1.12 (0.87-1.42)	0.38	1.03 (0.84-1.27)	0.75	1.17 (0.91-1.52)	0.21
Female donor to male recipient	Yes	1.02 (0.83-1.24)	0.88	1.17 (0.83-1.64)	0.37	1.35 (1.12-1.63)	**0.001**	1.29 (0.99-1.7)	0.06	0.98 (0.77-1.25)	0.88	0.88 (0.64-1.21)	0.43
Type of ALL	T												
	Ph+	0.97 (0.78-1.21)	0.77	0.96 (0.67-1.38)	0.83	1.06 (0.86-1.32)	0.57	1.08 (0.79-1.47)	0.63	0.96 (0.73-1.26)	0.78	1.05 (0.76-1.47)	0.76
	Ph -	0.99 (0.78-1.24)	0.9	0.73 (0.49-1.09)	0.12	0.98 (0.78-1.23)	0.83	1.03 (0.75-1.43)	0.85	1.04 (0.78-1.37)	0.8	0.97 (0.68-1.39)	0.88
	Ph NA	0.8 (0.58-1.09)	0.16	0.66 (0.38-1-15)	0.14	0.97 (0.72-1.3)	0.83	0.86 (0.55-1.36)	0.52	0.94 (0.65-1.37)	0.74	1.11 (0.71-1.72)	0.65
Type of conditioning	RIC												
	MAC-TBI	1.53 (1.18-1.99)	**0.001**	1.2 (0.77-1.86)	0.41	1.31 (1.03-1.67)	**0.026**	1.17 (0.83-1.65)	0.36	0.48 (0.37-0.63)	**<0.001**	1.62 (1.13-2.34)	**0.009**
	MAC-chemo	1.08 (0.77-1.5)	0.67	0.89 (0.51-1.54)	0.66	1.27 (0.94-1.72)	0.12	1.14 (0.74-1.76)	0.55	0.75 (0.54-1.04)	0.08	1.73 (1.11-2.69)	**0.015**
Stem cell source	Bone marrow												
	Peripheral blood	1.01 (0.82-1.24)	0.95	1.01 (0.72-1.42)	0.95	1.36 (1.11-1.66)	**0.003**	1.65 (1.21-2.25)	**0.002**	0.86 (0.68-1.09)	0.21	1.23 (0.91-1.67)	0.17
Year of transplant (per 5 years)		0.9 (0.83-0.97)	**0.008**	0.87 (0.76-0.99)	**0.04**	0.78 (0.72-0.85)	**<0.001**	0.87 (0.78-0.98)	**0.02**	0.84 (0.76-0.92)	**<0.001**	0.69 (0.61-0.78)	**<0.001**

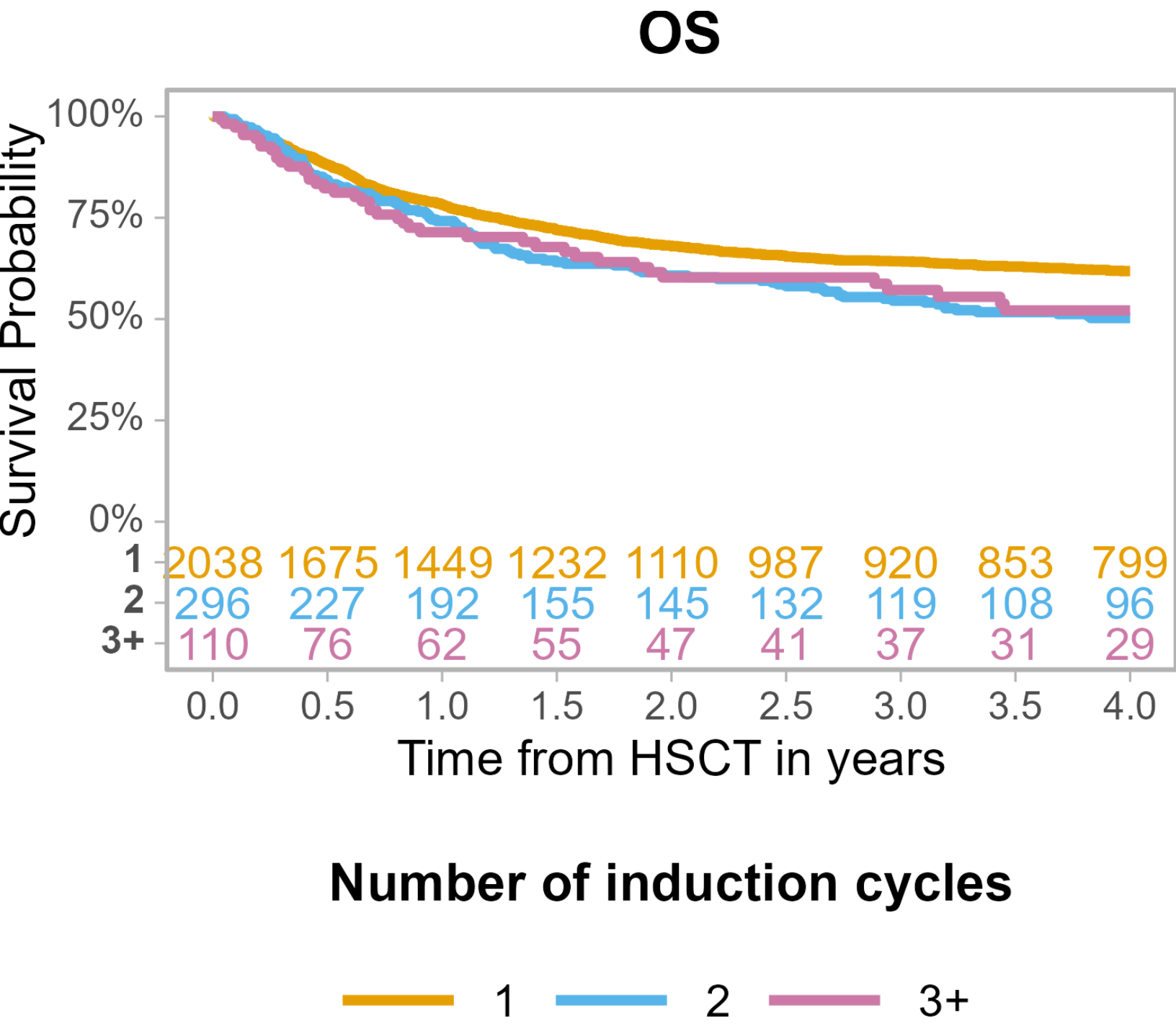
		LFS		OS		GRFS	
Covariate	**Group**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Number of induction cycles	1						
	2	1.35 (1.09-1.68)	**0.007**	1.34 (1.06-1.7)	**0.016**	1.18 (0.98-1.43)	0.07
	≥ 3	1.67 (1.18-2.35)	**0.004**	1.86 (1.28-2.68)	**0.001**	1.31 (0.98-1.76)	0.06
Patient age (per 10 years)		1.16 (1.08-1.24)	**<0.001**	1.24 (1.15-1.33)	**<0.001**	1.08 (1.02-1.14)	**0.008**
Karnofsky performance status score	≥ 90						
	<90	1.1 (0.93-1.29)	0.27	1.18 (0.98-1.41)	0.07	1.09 (0.96-1.25)	0.19
Female donor to male recipient	Yes	0.94 (0.77-1.14)	0.53	0.92 (0.74-1.15)	0.47	1.07 (0.92-1.26)	0.37
Type of ALL	T						
	Ph+	0.99 (0.8-1.22)	0.93	0.76 (0.6-0.96)	**0.019**	0.96 (0.8-1.14)	0.6
	Ph -	1.01 (0.81-1.26)	0.91	0.95 (0.75-1.21)	0.69	0.93 (0.78-1.12)	0.44
	Ph NA	1.01 (0.76-1.35)	0.93	1.06 (0.78-1.44)	0.7	0.87 (0.68-1.11)	0.25
Type of conditioning	RIC						
	MAC-TBI	0.77 (0.62-0.95)	**0.015**	0.91 (0.72-1.16)	0.4	0.87 (0.72-1.04)	0.12
	MAC-chemo	1.02 (0.79-1.33)	0.88	1.25 (0.93-1.68)	0.13	0.95 (0.76-1.19)	0.65
Stem cell source	Bone marrow						
	Peripheral blood	0.99 (0.82-1.2)	0.93	1.07 (0.86-1.32)	0.56	1.12 (0.96-1.32)	0.154
Year of transplant (per 5 years)		0.77 (0.72-0.84)	**<0.001**	0.72 (0.66-0.79)	**<0.001**	0.87 (0.82-0.93)	**<0.001**

Abbreviations: ALL acute lymphoblastic leukemia, Ph Philadelphia chromosome, MAC myeloablative conditioning, RIC reduced intensity conditioning, TBI total body irradiation, aGVHD acute graft-versus-host-disease, cGVHD chronic graft-versus-host-disease, NRM non-relapse mortality, RI relapse incidence, LFS leukemia-free survival, OS overall survival, GRFS GVHD-free, relapse-free survival.


RI
Cumlative incidence
100%
75%
50%
25%
0%
1 2038 1549 1280 1085 987 875 817 768 733
2 296 206 167 138 127 116 108 99 91
3+ 110 70 57 48 42 36 34 31 28
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Time from HSCT in years
Number of induction cycles
1
2
3+


NRM
Cumlative incidence
100%
75%
50%
25%
0%
1 2038 1549 1280 1085 987 875 817 768 733
2 296 206 167 138 127 116 108 99 91
3+ 110 70 57 48 42 36 34 31 28
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Time from HSCT in years
Number of induction cycles
1
2
3+


LFS
Survival Probability
100%
75%
50%
25%
0%
1 2038 1549 1280 1085 987 875 817 768 733
2 296 206 167 138 127 116 108 99 91
3+ 110 70 57 48 42 36 34 31 28
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Time from HSCT in years
Number of induction cycles
1
2
3+


OS
Survival Probability
100%
75%
50%
25%
0%
1 2038 1675 1449 1232 1110 987 920 853 799
2 296 227 192 155 145 132 119 108 96
3+ 110 76 62 55 47 41 37 31 29
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Time from HSCT in years
Number of induction cycles
1
2
3+