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Ordinary Paper

Residual disease is a strong prognostic marker in patients with acute lymphoblastic leukaemia with chemotherapy refractory or relapsed disease prior to allogeneic stem cell transplantation.

Running short title: Prognostic factors in allo-HSCT for non-CR ALL

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Patient consent statement: Written informed consent was obtained individually at each institution.

Abstract

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is one of the curative treatment options for acute lymphoblastic leukemia (ALL). However, the outcomes in patients transplanted without complete remission (non-CR) have not yet been fully reported, and detailed analyses are required to identify subgroups in which optimal prognosis is expected and to optimize pre-transplant therapeutic strategies. Hence, we performed a multi-centered retrospective cohort study including a total of 663 adult ALL patients transplanted at non-CR status; the median bone marrow (BM) blast counts at HSCT was 13.2%, and 203 patients (30.6%) were treated at primary induction failure status. The overall survival (OS) was 31.1% at 2 years, and the multivariate analyses identified five prognostic risk factors, including older age (≥50 years), increased BM blasts (≥10%), poor performance status, high HCT-CI, and relapsed disease status, among which BM blast was the most significantly related. The predictive scoring system composed of these risk factors clearly stratified OS (15.6%–59.5% at 2 year). In conclusion, this is the first large-scale study to analyze the correlation of patient characteristics with post-transplant prognosis in ALL transplanted at non-CR status. The importance of blast control before HSCT should be focused on for better patient prognosis.

Introduction

Patients with acute lymphoblastic leukemia (ALL), characterized by the monoclonal proliferation of immature cells in the lymphoid lineage(NCCN 2020), often respond to the induction chemotherapies; >80% of adult ALL patients can achieve complete hematological response (CR)(Kantarjian, *et al* 2004). However, the relapse rate ranges from 44% to 50% after the initial remission status(Fielding, *et al* 2007, Ganzel, *et al* 2020, Oriol, *et al* 2010), and this is related to non-optimal overall survival (OS)(Pulte, *et al* 2009, Pulte, *et al* 2014, Sive, *et al* 2012).

One of the treatment options for such chemotherapy-refractory or relapsed (r/r) ALL is allogeneic hematopoietic stem cell transplantation (allo-HSCT)(NCCN 2020). Because of the low expectancy to retrieve remission with chemotherapies after relapse(Camera, *et al* 2004, Tavernier, *et al* 2007), allo-HSCT for r/r ALL is often performed at non-CR status. A previous research has shown that allo-HSCT in patients with non-CR status is associated with inferior OS (20% at 3 years after HSCT) than in those with CR status (OS 38%–56%)(Gokbuget, *et al* 2012); however, few studies have studied the prognostic risk factors exclusively in r/r ALL patients without CR. A study from Japan(Tachibana, *et al* 2020) proposed the prognostic scoring system, but their model is not completely robust due to the smaller number of patients (N = 104). Therefore, prognostic stratification should be performed to identify subgroups where the optimal prognosis is expected after allo-HSCT.

Hence, we analyzed the outcomes in adult r/r ALL patients who underwent their first allo-HSCT in Japan at non-CR status. The analyses were then applied to establish a predictive risk stratification system for survival, with a particular focus on the residual disease loads before HSCT. Our study will help to determine the indication for allo-HSCT in patients who have not achieved CR, and to make a treatment decision regarding the most appropriate bridging therapies before HSCT to improve the overall prognosis in this cohort.

Patients and Methods

Inclusion and exclusion criteria

We enrolled adult patients (age ≥ 16 years) with ALL who underwent allo-HSCT in Japan for the first time from January 1, 2008, to December 31, 2018. Patients missing either of the following data were excluded; BM blast counts before HSCT, or date of the last follow-up. Our protocol complied with the Declaration of Helsinki and was approved by the Adult ALL Working Group of the Japanese Society for Hematopoietic Cell Transplantation (JSHCT) and the institutional review board of the Kyoto University Hospital. Written informed consent was obtained individually at each institution.

Data collection and definition of each covariate

The dataset was obtained from the Japanese Transplant Registry Unified Management Program sponsored by the JSHCT and Japanese Data Center for Hematopoietic Cell Transplantation(Atsuta 2016). We extracted data on basic pre-transplant characteristics and post-transplant clinical courses. CR was determined at the hematological level. According to the response criteria by CIBMTR (Center for international blood and marrow transplant research), CR meets BM blasts < 5%, normal maturation of all cellular components in the BM, no extramedullary disease, absolute neutrophil count ≥ 1,000/μL, platelets ≥ 100,000/μL, and transfusion independent. The patients were categorized into two groups as per performance status (PS; 0–1 *vs*. 2–4) and HCT comorbidity index (HCT-CI; 0–2 *vs*. ≥3). In addition, the patients were divided into three age groups almost equally in the patient number. The patients were also divided into three groups according to BM blasts (<10% *vs.* 10-49% and 50% or more) referring to the previous reports(Haferlach*, et al* 2004, Matsuo*, et al* 2003). As for the conditioning regimens, myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) were defined based on the previously published consensus criteria(Giralt*, et al* 2009). HLA disparity in HLA-A, B, and DR antigens was determined at serology level for related bone marrow transplantation (BMT), related PBSCT, and CBT; a 6/6 match was categorized into an HLA-matched group, and the others were

categorized into the HLA-mismatched group. For unrelated BMT and PBSCT, the HLA disparity was identified at the DNA-allelic level; an 8/8 match (HLA-A, -B, -C, and -DR) was categorized in an HLA-matched group and the others in HLA-mismatched groups.

Statistical analyses

Overall survival (OS) and event-free survival (EFS) were calculated using the Kaplan–Meier method and compared with log-rank tests for each covariant related to pre-transplant patient characteristics. The relapse rate and non-relapse mortality (NRM) were calculated using Gray's method(Gooley*, et al* 1999), considering NRM and relapse events as competing risks, respectively. Cox proportional hazards regression models were used to evaluate the influence of each variable on OS. P values were calculated per categories as well as per variables (using Wald test). Two-sided p values of <0.05 were considered to indicate statistical significance, and factors appearing as significant in the univariate analysis were subjected to the multivariate analyses. Differences in patient characteristics between non-CR and CR ALL patients were examined using Fisher's exact test for categorical variables.

The prognostic model was established using significant variables in the multivariate analysis, and each variable was weighted using regression coefficients determined using Cox proportional hazards regression model (log(hazard ratio)) after excluding patients with missing data. To build the categorical risk scoring system concisely, the numbers provided for the risk scoring values were rounded off(Greenberg*, et al* 1997). All the statistical analyses were performed using R (The R Foundation for Statistical Computing, version 3.6.0, Vienna, Austria).

Results

Patient characteristics

Total 663 r/r ALL patients who underwent allogeneic HSCT for the first time at non-CR status were enrolled (Table 1). The median patient age at the time of HSCT was 38 y (range: 16–74 y). BM blast counts at the initiation of conditioning regimens ranged from 0% to 100% (median, 13.2%); 255 patients (39.9%) had low blast count (<10%), while 195 (30.5%) had high blast count (≥50%). Disease status was primary induction failure (PIF) in 203 patients (30.6%) and "relapse" (after preceding remission status) in 460 patients (69.4%). Conditioning regimens were composed of MAC in 470 (70.9%) and RIC in 193 (29.1%) patients. Bone marrow was most commonly used as the stem cell source (262 patients; 39.5%), followed by a single umbilical cord blood unit (211; 31.8%) and peripheral blood stem cells (190; 28.7%). The average follow-up duration for survivors was 31.2 months (range, 1.47–133.7 months). Other variables are presented in Table 1.

Overall outcomes after allo-HSCT in the whole population of non-CR patients

The overall outcomes of the whole cohort are shown in Figure 1. Figures 1A and B show the OS and EFS curves, indicating that the 2 y OS and EFS are 31.1% (95% CI, 27.6%–35.0%) and 22.3% (95% CI, 19.1%–25.7%), respectively. Total 496 (74.8%) patients had achieved CR after HSCT, and the cumulative incidence of hematological relapse (including the 113 patients who were refractory to HSCT) was 55.9% (95% CI, 51.9%–59.7%) at 2 y (Figure 1C). On the other hand, the NRM at 2 y was 21.8% (95% CI, 18.7%–25.1%) (Figure 1D).

Pre-HSCT variables statistically associated with the outcomes

To identify the pre-transplant variables statistically related to the post-HSCT outcome, we first performed univariate analyses using patient-related variables, information regarding the underlying disease, or transplantation factors (Table 2). Older age (≥50 y), poorer PS, higher HCT-CI, larger BM

blast counts (≥10%), disease status (relapsed disease), conditioning without myeloablative dose TBI, cord blood graft, and HLA-mismatched donors were significant risk factors for lower OS (Table 2).

Multivariate analysis based on these univariate analyses showed that older patient age, poorer PS, higher HCT-CI, higher BM blast count at HSCT, and disease status with relapse were significantly associated with a shorter OS duration. Furthermore, BM blasts showed the most significant correlation (10%–49%; HR, 1.72, 95% CI, 1.36–2.16, $p < 0.01$, and ≥50%; HR, 1.96, 95%CI, 1.58–2.43, $p < 0.01$ compared with those with BM blast counts of <10%) (Table 2).

OS was also graphically compared as per these significant covariates (Figure 2), and independently stratified OS curves for age (Figure 2A), PS (Figure 2B), HCT-CI (Figure 2C), BM blast counts (Figure 2D), and disease status (Figure 2E) supported the statistically significant HRs calculated in the multivariate analyses shown in Table 2.

Subgroup analyses focusing on BM blast counts

Hence, the BM blast count was the most significant risk factor for OS in the whole cohort analyses of non-CR ALL patients (Table 2, Figure 2). We then performed subgroup analyses focusing on the blast counts in each patient subgroup regarding pre-HSCT variables, such as age, PS, HCT-CI, disease status (Figure 3), sex, WBC count at first diagnosis, immunophenotype, Ph status, prior history of extramedullary disease, conditioning, TBI, graft type, GVHD prophylaxis, and donor-recipient HLA disparity (Supplemental Figure 1). Compared with medium BM blast count (10%–49%) and higher BM blast count (≥50%), lower BM blast count (<10%) was associated with significantly superior OS in nearly all the subgroups. These analyses can support the robustness of the multivariate analyses indicating that a lower BM blast count is a predicting factor for superior OS (Table 2) and can be used as a universal indicator for better patient prognosis.

Subgroup analyses focusing on disease status

Disease status at transplantation (PIF *vs.* relapse) was first reported in this study as a significant factor influencing the outcomes (Table 2). Thus, we performed more detailed subgroup analyses. With respect to OS, the 2 y OS was 25.2% (95% CI, 21.3%–29.8%) in the relapse group, whereas it was 44.3% (95% CI, 37.7%–52.1%) in the PIF group ($p < 0.001$) (Supplemental Figure 2A). The 2 y cumulative incidence of hematological relapse was 59.0% (95% CI, 54.2%–63.5%) in the relapse group and 48.9% in the PIF group (95% CI, 41.7%–55.7%) ($p < 0.001$) (Supplemental Figure 2B). NRM at 2 y was 23.6% (95% CI, 19.7%–27.6%) in the relapse group compared to 17.8% (95% CI, 12.7%–23.6%) in the PIF group ($p = 0.040$) (Supplemental Figure 2C). These data indicate that the superior OS in the PIF group was derived from both suppressed relapse and NRM. Time from diagnosis to transplantation was longer in the relapse group (median; 11.2 months) than in the PIF group (median; 5.7 months) ($p < 0.001$).

Prognostic scoring system

To categorize each patient for the expected prognosis using the above-mentioned five risk factors identified on multivariate analyses (*i.e.*, age ≥ 50 y, BM blast counts ≥ 10%, PS ≥ 2, HCT-CI ≥ 3, and relapsed disease status), a prognostic scoring system was established. The scores for each covariate were calculated as per the values of the HRs for OS in the multivariate analyses, and Table 3 presents the designated points. The total score in our patient population ranged from 0 to 11 (median score 4). Patients with the worst score category (≥5, $N = 316$) showed the worst prognosis (OS at 2 y, 15.6%), whereas those with the best score category (0–2, $N = 139$) demonstrated significantly superior outcomes (OS at 2 y; 59.5%) (Figure 4A). EFS, relapse, and NRM were clearly stratified with the risk score (Figure 4B-D and Supplemental Figure 3).

Although they underwent transplantation at non-CR status, the prognosis in patients within the best score category was inferior but closest to that in those who underwent HSCT after achieving CR (OS at 2 y, 71.6%) (Supplemental Figure 4). These data indicate that properly controlled (*i.e.*, BM

blast counts < 10%) non-CR ALL patients, if transplanted, can achieve the benefit of HSCT and expect longer OS. However, we must acknowledge that there can be several confounding factors in the comparison of patients who achieved CR and those who did not achieve CR because pre-HSCT factors, such as patient age, PS, HCT-CI, disease subtypes, and donor sources, were significantly skewed between the two groups (Supplemental Table 1).

Discussion

This retrospective multi-centered cohort study on post-HSCT prognosis in non-CR r/r ALL adult patients had three major findings, as follows, based on the real-world database: (1) total OS was suboptimal (31.1% at 2 y) mainly because of the higher incidence of post-HSCT relapse, (2) five prognostic risk factors, namely, older age, increased BM blast count, poor PS, high HCT-CI, and relapsed disease status, were identified, and among them, BM blast count showed the most significant association with patient prognosis, and (3) the predictive scoring system was established based on a combination of these risk factors. To our knowledge, this is the first large-scale study to examine the correlation of detailed patient characteristics with prognosis exclusively in adult ALL patients who underwent transplantation without achieving CR. Of notes, all of these risk factors are measured or determined routinely in the clinical setting.

First, our results on the prognosis of the total cohort were compatible with previous reports in that non-CR ALL patients had poor prognosis even if they underwent allo-HSCT(Duval, *et al* 2010, Fielding, *et al* 2007, Gokbuget, *et al* 2012). The detailed analysis on our dataset indicated that the poor OS was mainly attributed to the high relapse rate (55.9% at 2 y), whereas NRM was fairly controlled at 21.8%, the same level of HSCT for ALL in general(Atsuta, *et al* 2009). Post-transplant relapse of ALL is mainly attributable to leukemia cells that are the same as the ancestor clone carried over after the conditioning regimen(Mullighan, *et al* 2008). In fact, 80.5% of our cohort possessed the detectable ALL blasts in BM (≥1%) before the conditioning regimens, and it is expected that these residual leukemia cells could have originated during post-transplant relapse. OS and relapse incidence were not related to the concurrent of acute or chronic GVHD (not shown), indicating that the graft-versus-leukemia effect is limited in situations where hematological relapse was observed after HSCT because of excessive tumor load(Bradfield, *et al* 2004, Yeshurun, *et al* 2019). The clinical effects of post-transplant donor lymphocyte infusion (DLI) are also limited in this situation(Choi, *et al* 2005).

Now that we confirmed suboptimal prognosis in ALL patients transplanted at non-CR who underwent transplantation when they had not achieved CR, the following clinical question includes whether there exists a subgroup in which allo-HSCT is significantly effective. To answer this question, the risk factor analyses, and the prognostic scoring system establishment were performed.

Among the five risk factors related to inferior OS (*i.e.*, older age, increased BM blast count, poor PS, high HCT-CI, and relapsed disease status), increased BM blast count (≥10% compared with <10%) was the most significant and relevant risk factor. The superior OS in the patients with lower BM blast count (<10%) was statistically confirmed both in the whole cohort and in all the subgroups, with respect to various patient background characteristics, such as age, sex, PS, HCT-CI, immunophenotype, Ph status, donor sources, HLA disparity, and conditioning regimens.

The association with fewer BM blasts and better outcomes has been demonstrated in several previous studied(Duval*, et al* 2010, Oyekunle*, et al* 2006, Sierra*, et al* 1997); however, these studies failed to evaluate the relative impacts of the residual BM blast count. Our study indicated that this variable is the strongest indicator for post-transplant outcomes. These results suggest that a treatment strategy to reduce tumor burden before HSCT should be established as the first priority to improve the outcomes in r/r ALL patients.

In the risk factor analyses, our novel finding is that patients who underwent HSCT at PIF had a better prognosis than those transplanted at relapse. Previous reports also suggest superior outcomes in PIF patients(Duval*, et al* 2010, Greinix*, et al* 1998, Tachibana*, et al* 2020); however, these studies are insufficient because of the relatively smaller number of included patients or the heterogeneous study population that includes adults as well as children. Superiority in PIF patients can partially be explained by the lower NRM (23.6% in the relapsed group *vs.* 17.8% in the PIF group at 2 y) probably because of the heavier and more toxic chemotherapeutic regimens in the relapse group; the shorter time from diagnosis to HSCT (median; 11.2 months in the relapsed group *vs.* 5.7 months in PIF group)

may support this hypothesis that the therapeutic intensity was relatively low in the PIF group. These results raised a new clinical question as to what is the best timing for HSCT in r/r ALL patients; this issue should be analyzed in future studies.

By combining all five risk factors with respect to the higher risk in non-CR ALL patients, we established a predictive scoring system to find that the best prognosis group (risk score ≤ 2) had a remarkably good prognosis (2 y OS; 59.5%) with a lower incidence of relapse (40.6% at 2 y) and NRM (13.4% at 2 y). These predictive analyses indicate that the patients in this subgroup can overcome the disease even if they undergo transplantation without achieving CR. A similar prognostic scoring system has been developed, with a focus on relapsed or PIF patients (Duval*, et al* 2010), where four risk factors, such as first refractory relapse and second and additional relapse, ≥25% BM blasts, CMV-positive donor, and age > 10 y, were included. However, these analyses were non-specific and cannot be generalized because both children and adults were included, and patients with RIC regimen, poor PS, and higher HCT-CI were excluded. By contrast, our scoring system is more robust with respect to the inclusion of adult ALL patients at non-CR status because of more uniformed patient backgrounds. This system can be applied in the clinical field not only to accurately predict post-transplant prognosis for HSCT candidates but also to decide the treatment strategy before HSCT (*i.e.*, the reduction of BM blast counts to <10% or the improvement in PS and HCT-CI).

This study stratified the post-transplant prognosis in r/r ALL patients who had not achieved CR. However, there are certain limitations in this study. For example, this was a retrospective database study, and detailed information about pre-transplant chemotherapies and genomic information was not included. The judgment of hematological CR is confirmed at each institute without central review systems. The duration in remission before HSCT was also unknown; the longer duration in remission was reported to be related to superior OS in relapsed adult ALL patients (Fielding*, et al* 2007, Gokbuget*,*

et al 2012). The issue regarding the lack of external validation for the established prognostic scoring system should be overcome in future studies.

In conclusion, this study identified five risk factors in HSCT for non-CR ALL, and among them, the importance of blast control before HSCT was focused for improved prognosis. All of these risk factors are measuredly routinely in the actual clinical procedures. As per these analyses, novel molecular targeting drugs, such as blinatumomab, inotuzumab ozogamicin, or CD19-targeting chimeric antigen receptor (CAR) T cells (Kantarjian*, et al* 2017, Kantarjian*, et al* 2016, Maude*, et al* 2018) can be potential candidates for lowering the residual BM blast counts before HSCT and improve the prognosis after HSCT in r/r ALL patients.

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Authorship contributions

M.N., Y.Arai, and S.K. designed the study, reviewed, and analyzed data. S.H. and T.K. interpreted data and revised the manuscript; N.D., N.U., T.F., Y.O., M.T., M.S., Y.Katayama, Y.Kanda, S.S., H.N., S.Y., O.M., T.I., and Y.Atsuta contributed the data collection and provided critiques on the manuscript.

Competing Interests Statement

H.N. received Honoraria from Astellas Pharma Inc., Takeda Pharmaceutical Company Ltd., Chugai Pharmaceutical Co., Ltd., and Pfizer Japan Inc., and Research funding from Astellas Pharma Inc. T.I. received research funding from Abbie Inc., Chugai Pharmaceutical Co., CSL Behring, Eisai Co., Kyowa Kirin Co., Ono Pharmaceutical Co., Nippon Shinyaku Co., Repertoire Genesis Inc., Sumitomo Dainippon Pharma Co., Takeda Pharmaceutical Co., Zenyaku Kogyo Co., outside of this work. The other authors declare no competing financial interests.

References

Atsuta, Y. (2016) Introduction of Transplant Registry Unified Management Program 2 (TRUMP2): scripts for TRUMP data analyses, part I (variables other than HLA-related data). *Int J Hematol,* **103,** 3-10.

Atsuta, Y., Suzuki, R., Nagamura-Inoue, T., Taniguchi, S., Takahashi, S., Kai, S., Sakamaki, H., Kouzai, Y., Kasai, M., Fukuda, T., Azuma, H., Takanashi, M., Okamoto, S., Tsuchida, M., Kawa, K., Morishima, Y., Kodera, Y., Kato, S. & Japan Cord Blood Bank, N. (2009) Disease-specific analyses of unrelated cord blood transplantation compared with unrelated bone marrow transplantation in adult patients with acute leukemia. *Blood,* **113,** 1631-1638.

Bradfield, S.M., Radich, J.P. & Loken, M.R. (2004) Graft-versus-leukemia effect in acute lymphoblastic leukemia: the importance of tumor burden and early detection. *Leukemia,* **18,** 1156-1158.

Camera, A., Annino, L., Chiurazzi, F., Fazi, P., Cascavilla, N., Fabbiano, F., Marmont, F., Di Raimondo, F., Recchia, A., Vignetti, M., Rotoli, B. & Mandelli, F. (2004) GIMEMA ALL - Rescue 97: a salvage strategy for primary refractory or relapsed adult acute lymphoblastic leukemia. *Haematologica,* **89,** 145-153.

Choi, S.J., Lee, J.H., Lee, J.H., Kim, S., Lee, Y.S., Seol, M., Ryu, S.G., Lee, J.S., Kim, W.K., Jang, S., Park, C.J., Chi, H.S. & Lee, K.H. (2005) Treatment of relapsed acute lymphoblastic leukemia after allogeneic bone marrow transplantation with chemotherapy followed by G-CSF-primed donor leukocyte infusion: a prospective study. *Bone Marrow Transplant,* **36,** 163-169.

Duval, M., Klein, J.P., He, W., Cahn, J.Y., Cairo, M., Camitta, B.M., Kamble, R., Copelan, E., de Lima, M., Gupta, V., Keating, A., Lazarus, H.M., Litzow, M.R., Marks, D.I., Maziarz, R.T., Rizzieri, D.A., Schiller, G., Schultz, K.R., Tallman, M.S. & Weisdorf, D. (2010) Hematopoietic stem-cell transplantation for acute leukemia in relapse or primary induction failure. *J Clin Oncol,* **28,** 3730-3738.

Fielding, A.K., Richards, S.M., Chopra, R., Lazarus, H.M., Litzow, M.R., Buck, G., Durrant, I.J., Luger, S.M., Marks, D.I., Franklin, I.M., McMillan, A.K., Tallman, M.S., Rowe, J.M., Goldstone, A.H., Medical Research Council of the United Kingdom Adult, A.L.L.W.P. & Eastern Cooperative Oncology, G. (2007) Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood,* **109,** 944-950.

Ganzel, C., Wang, X.V., Rowe, J.M., Richards, S.M., Buck, G., Marks, D.I., Litzow, M.R., Paietta, E.M., Foroni, L., Luger, S.M., Willman, C.L., Mullighan, C.G., Roberts, K.G., Wiernik, P.H.,

Douer, D., Lazarus, H.M., Tallman, M.S. & Goldstone, A.H. (2020) At three years, patients with acute lymphoblastic leukaemia are still at risk for relapse. Results of the international MRC UKALLXII/ECOG E2993 trial. *Br J Haematol,* **191,** 37-43.

Giralt, S., Ballen, K., Rizzo, D., Bacigalupo, A., Horowitz, M., Pasquini, M. & Sandmaier, B. (2009) Reduced-intensity conditioning regimen workshop: defining the dose spectrum. Report of a workshop convened by the center for international blood and marrow transplant research. *Biol Blood Marrow Transplant,* **15,** 367-369.

Gokbuget, N., Stanze, D., Beck, J., Diedrich, H., Horst, H.A., Huttmann, A., Kobbe, G., Kreuzer, K.A., Leimer, L., Reichle, A., Schaich, M., Schwartz, S., Serve, H., Starck, M., Stelljes, M., Stuhlmann, R., Viardot, A., Wendelin, K., Freund, M., Hoelzer, D. & German Multicenter Study Group for Adult Acute Lymphoblastic, L. (2012) Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. *Blood,* **120,** 2032-2041.

Gooley, T.A., Leisenring, W., Crowley, J. & Storer, B.E. (1999) Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med,* **18,** 695-706.

Greenberg, P., Cox, C., LeBeau, M.M., Fenaux, P., Morel, P., Sanz, G., Sanz, M., Vallespi, T., Hamblin, T., Oscier, D., Ohyashiki, K., Toyama, K., Aul, C., Mufti, G. & Bennett, J. (1997) International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood,* **89,** 2079-2088.

Greinix, H.T., Reiter, E., Keil, F., Fischer, G., Lechner, K., Dieckmann, K., Leitner, G., Schulenburg, A., Hoecker, P., Haas, O.A., Knoebl, P., Mannhalter, C., Fonatsch, C., Hinterberger, W. & Kalhs, P. (1998) Leukemia-free survival and mortality in patients with refractory or relapsed acute leukemia given marrow transplants from sibling and unrelated donors. *Bone Marrow Transplant,* **21,** 673-678.

Haferlach, T., Kern, W., Schoch, C., Schnittger, S., Sauerland, M.C., Heinecke, A., Buchner, T., Hiddemann, W. & German, A.M.L.C.G. (2004) A new prognostic score for patients with acute myeloid leukemia based on cytogenetics and early blast clearance in trials of the German AML Cooperative Group. *Haematologica,* **89,** 408-418.

Kantarjian, H., Stein, A., Gokbuget, N., Fielding, A.K., Schuh, A.C., Ribera, J.M., Wei, A., Dombret, H., Foa, R., Bassan, R., Arslan, O., Sanz, M.A., Bergeron, J., Demirkan, F., Lech-Maranda, E., Rambaldi, A., Thomas, X., Horst, H.A., Bruggemann, M., Klapper, W., Wood, B.L., Fleishman, A., Nagorsen, D., Holland, C., Zimmerman, Z. & Topp, M.S. (2017) Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. *N Engl J Med,* **376,** 836-847.

Kantarjian, H., Thomas, D., O'Brien, S., Cortes, J., Giles, F., Jeha, S., Bueso-Ramos, C.E., Pierce, S.,

Shan, J., Koller, C., Beran, M., Keating, M. & Freireich, E.J. (2004) Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer,* **101,** 2788-2801.

Kantarjian, H.M., DeAngelo, D.J., Stelljes, M., Martinelli, G., Liedtke, M., Stock, W., Gokbuget, N., O'Brien, S., Wang, K., Wang, T., Paccagnella, M.L., Sleight, B., Vandendries, E. & Advani, A.S. (2016) Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N Engl J Med,* **375,** 740-753.

Matsuo, T., Kuriyama, K., Miyazaki, Y., Yoshida, S., Tomonaga, M., Emi, N., Kobayashi, T., Miyawaki, S., Matsushima, T., Shinagawa, K., Honda, S., Ohno, R. & Japan Adult Leukemia Study, G. (2003) The percentage of myeloperoxidase-positive blast cells is a strong independent prognostic factor in acute myeloid leukemia, even in the patients with normal karyotype. *Leukemia,* **17,** 1538-1543.

Maude, S.L., Laetsch, T.W., Buechner, J., Rives, S., Boyer, M., Bittencourt, H., Bader, P., Verneris, M.R., Stefanski, H.E., Myers, G.D., Qayed, M., De Moerloose, B., Hiramatsu, H., Schlis, K., Davis, K.L., Martin, P.L., Nemecek, E.R., Yanik, G.A., Peters, C., Baruchel, A., Boissel, N., Mechinaud, F., Balduzzi, A., Krueger, J., June, C.H., Levine, B.L., Wood, P., Taran, T., Leung, M., Mueller, K.T., Zhang, Y., Sen, K., Lebwohl, D., Pulsipher, M.A. & Grupp, S.A. (2018) Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med,* **378,** 439-448.

Mullighan, C.G., Phillips, L.A., Su, X., Ma, J., Miller, C.B., Shurtleff, S.A. & Downing, J.R. (2008) Genomic analysis of the clonal origins of relapsed acute lymphoblastic leukemia. *Science,* **322,** 1377-1380.

NCCN (2020) Acute Lymphoblastic Leukemia (Version 2.2020).

Oriol, A., Vives, S., Hernandez-Rivas, J.M., Tormo, M., Heras, I., Rivas, C., Bethencourt, C., Moscardo, F., Bueno, J., Grande, C., del Potro, E., Guardia, R., Brunet, S., Bergua, J., Bernal, T., Moreno, M.J., Calvo, C., Bastida, P., Feliu, E., Ribera, J.M. & Programa Espanol de Tratamiento en Hematologia, G. (2010) Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group. *Haematologica,* **95,** 589-596.

Oyekunle, A.A., Kroger, N., Zabelina, T., Ayuk, F., Schieder, H., Renges, H., Fehse, N., Waschke, O., Fehse, B., Kabisch, H. & Zander, A.R. (2006) Allogeneic stem-cell transplantation in patients with refractory acute leukemia: a long-term follow-up. *Bone Marrow Transplant,* **37,** 45-50.

Pulte, D., Gondos, A. & Brenner, H. (2009) Improvement in survival in younger patients with acute

lymphoblastic leukemia from the 1980s to the early 21st century. *Blood,* **113,** 1408-1411.

Pulte, D., Jansen, L., Gondos, A., Katalinic, A., Barnes, B., Ressing, M., Holleczek, B., Eberle, A., Brenner, H. & Group, G.C.S.W. (2014) Survival of adults with acute lymphoblastic leukemia in Germany and the United States. *PLoS One,* **9,** e85554.

Sierra, J., Storer, B., Hansen, J.A., Bjerke, J.W., Martin, P.J., Petersdorf, E.W., Appelbaum, F.R., Bryant, E., Chauncey, T.R., Sale, G., Sanders, J.E., Storb, R., Sullivan, K.M. & Anasetti, C. (1997) Transplantation of marrow cells from unrelated donors for treatment of high-risk acute leukemia: the effect of leukemic burden, donor HLA-matching, and marrow cell dose. *Blood,* **89,** 4226-4235.

Sive, J.I., Buck, G., Fielding, A., Lazarus, H.M., Litzow, M.R., Luger, S., Marks, D.I., McMillan, A., Moorman, A.V., Richards, S.M., Rowe, J.M., Tallman, M.S. & Goldstone, A.H. (2012) Outcomes in older adults with acute lymphoblastic leukaemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial. *Br J Haematol,* **157,** 463-471.

Tachibana, T., Kanda, J., Ishizaki, T., Najima, Y., Tanaka, M., Doki, N., Fujiwara, S.I., Kimura, S.I., Onizuka, M., Takahashi, S., Saito, T., Mori, T., Fujisawa, S., Sakaida, E., Matsumoto, K., Aotsuka, N., Gotoh, M., Watanabe, R., Shono, K., Usuki, K., Tsukada, N., Kanamori, H., Kanda, Y., Okamoto, S. & Kanto Study Group for Cell, T. (2020) Outcomes and Prognostic Factors for Patients with Relapsed or Refractory Acute Lymphoblastic Leukemia Who Underwent Allogeneic Hematopoietic Cell Transplantation: A KSGCT Multicenter Analysis. *Biol Blood Marrow Transplant,* **26,** 998-1004.

Tavernier, E., Boiron, J.M., Huguet, F., Bradstock, K., Vey, N., Kovacsovics, T., Delannoy, A., Fegueux, N., Fenaux, P., Stamatoullas, A., Tournilhac, O., Buzyn, A., Reman, O., Charrin, C., Boucheix, C., Gabert, J., Lheritier, V., Vernant, J.P., Dombret, H., Thomas, X., Group, G.-L., Swiss Group for Clinical Cancer Research, S., Australasian, L. & Lymphoma, G. (2007) Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. *Leukemia,* **21,** 1907-1914.

Yeshurun, M., Weisdorf, D., Rowe, J.M., Tallman, M.S., Zhang, M.J., Wang, H.L., Saber, W., de Lima, M., Sandmaier, B.M., Uy, G., Kamble, R.T., Cairo, M.S., Cooper, B.W., Cahn, J.Y., Ganguly, S., Camitta, B., Verdonck, L.F., Dandoy, C., Diaz, M.A., Savani, B.N., George, B., Liesveld, J., McGuirk, J., Byrne, M., Grunwald, M.R., Drobyski, W.R., Pulsipher, M.A., Abdel-Azim, H., Prestidge, T., Wieduwilt, M.J., Martino, R., Norkin, M., Beitinjaneh, A., Seo, S., Nishihori, T., Wirk, B., Frangoul, H., Bashey, A., Mori, S., Marks, D.I. & Bachanova, V. (2019) The impact of the graft-versus-leukemia effect on survival in acute lymphoblastic leukemia. *Blood Adv,* **3,** 670-680.

Figure Legends

Figure 1. Outcomes after allo-HSCT in the entire study population of non-CR adult ALL patients

(**A**) Overall survival, (**B**) event-free survival, and cumulative incidence of (**C**) relapse and (**D**) non-relapse mortality are shown in the whole cohort of non-CR adult ALL patients.

Figure 2. Comparisons of overall survival in terms of various pre-HSCT variables

Overall survival was compared with respect to various pre-HSCT variables, including (**A**) age, (**B**) PS, (**C**) HCT-CI, (**D**) BM blast counts, and (**E**) disease status. HRs and p values adjusted by multivariate analyses are displayed compared to the comparators described in thick lines.

Figure 3. Subgroup analyses for overall survival focusing on the stratified BM blast counts

Superior prognosis in low BM blast counts (<10%) at the time of HSCT was confirmed in subgroup analyses regarding various pre-HSCT characteristics, including (**A**) age, (**B**) PS, (**C**) HCT-CI, and (**D**) disease status. HRs are displayed compared to the comparators described in thick lines. P values are calculated with Wald test. Other characteristics are presented in Supplemental Figure 1.

Figure 4. Probability of overall survival after transplantation as per the risk score categories

Probability of (**A**) overall survival and (**B**) event-free survival and cumulative incidence of (**C**) relapse and (**D**) non-relapse mortality are displayed as per the newly developed risk score. The score was categorized into three groups, as best (score 0–2), intermediate (score 3–4), and worst (score ≥ 5).

Table 1 Patient Characteristics

Variables		non-CR ALL	
		No. (N = 663)	%
Patient-related factors			
Age at HSCT	median (range)	38 (16-74)	
	16-29 y	227	34.2
	30-49 y	235	35.4
	50 y or older	201	30.3
Sex	Male	382	57.6
	Female	281	42.4
PS	0 or 1	545	82.2
	2 or more	118	17.8
HCT-CI score	0-2	564	85.1
	3 or more	99	14.9
Leukemia-related factors			
WBC count at first diagnosis	Median (range)	17.1 (0-1157) $\times 10^9$/L	
	Less than 10 $\times$ 10^9/L	255	39.9
	10-49 $\times$ 10^9/L	189	29.6
	50 $\times$ 10^9/L or more	195	30.5
Immunophenotype	B-lineage	504	76.0
	T-lineage	135	20.4
	others	24	3.6
Ph status	Positive	139	21.0
Extramedullary disease	Positive	151	22.8
BM blast counts at HSCT	median (range)	13.2 (0-100)	
	Less than 10%	290	43.7
	10-49%	173	26.1
	50% or more	200	30.2
Disease status at HSCT	PIF	203	30.6
	Relapse	460	69.4
HSCT-related factors			
Conditioning	MAC	470	70.9
	RIC	193	29.1
Full TBI	Yes	420	63.3
	No	243	36.7
Graft type	Bone marrow	262	39.5
	Peripheral blood	190	28.7
	Cord blood	211	31.8
GVHD prophylaxis	TAC+MTX	291	44.0
	CsA+MTX	163	24.6
	TAC+MMF	79	11.9
	Others	129	19.5
Donor-recipient HLA disparity	HLA-matched	257	39.2
	HLA-mismatched	398	60.8

Abbreviations: CR, complete remission; ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplantation; PS, performance status; HCT-CI, Hematopoietic cell transplantation - specific comorbidity index; WBC, white blood cell; Ph, Philadelphia chromosome; PIF, primary induction failure; MAC, myeloablative

conditioning; RIC, reduced-intensity conditioning; TBI, total body irradiation; TAC, tacrolimus; MTX, methotrexate; CsA, cyclosporine; MMF, mycophenolate mofetil; and HLA, human leukocyte antigen.

Table 2 Univariate and multivariate analysis for OS with non-CR ALL

Variables		Univariate analysis			Multivariate analysis		
		HR	95%CI	p	HR	95%CI	p
Patient-related factors							
Age at HSCT	(per 5 y)	1.07	1.04-1.10	<0.001*			
	16-29 y	1.00		(<.001)	1.00		
	30-49 y	1.21	0.97-1.51	0.089	1.24	0.99-1.55	0.056
	50 y or older	1.64	1.31-2.05	<0.001*	1.48	1.18-1.86	<0.001*
Sex	Male	1.00					
	Female	0.87	0.72-1.04	0.125			
PS	0 or 1	1.00			1.00		
	2 or more	2.08	1.67-2.58	<0.001*	1.86	1.49-2.33	<0.001*
HCT-CI score	0-2	1.00			1.00		
	3 or more	1.70	1.34-2.15	<0.001*	1.38	1.07-1.76	<0.001*
Leukemia-related factors							
WBC count	(per 1×10^9/L)	1.00	1.00-1.00	0.977			
at first diagnosis	Less than 10×10^9/L	1.00		(0.600)			
	10-49 $\times 10^9$/L	1.11	0.89-1.39	0.336			
	50×10^9/L or more	1.05	0.84-1.31	0.672			
Immunophenotype	B-lineage	1.00		(0.300)			
	T-lineage	0.95	0.76-1.19	0.642			
	others	1.35	0.87-2.10	0.184			
Ph status	Positive	0.99	0.79-1.24	0.958			
Extramedullary disease	Positive	0.99	0.80-1.23	0.938			
BM blast counts	(per 5 %)	1.04	1.03-1.06	<0.001*			
at HSCT	Less than 10%	1.00		(<.001)	1.00		
	10-49%	1.85	1.48-2.33	<0.001*	1.72	1.36-2.16	<0.001*
	50% or more	2.08	1.68-2.58	<0.001*	1.96	1.58-2.44	<0.001*
Disease status at HSCT	PIF	1.00			1.00		
	Relapse	1.52	1.24-1.86	<0.001*	1.50	1.21-1.84	<0.001*
HSCT-related factors							
Conditioning	MAC	1.00					
	RIC	1.21	0.99-1.47	0.059			
Full TBI	Yes	0.76	0.63-0.92	0.003*			
	No	1.00					
Graft type	Bone marrow	1.00		(0.090)			
	Peripheral blood	1.12	0.90-1.40	0.305			
	Cord blood	1.27	1.02-1.58	0.029*			
GVHD prophylaxis	TAC+MTX	1.00		(0.400)			
	CsA+MTX	1.04	0.83-1.30	0.750			
	TAC+MMF	0.94	0.69-1.28	0.698			
	Others	1.20	0.95-1.53	0.132			
Donor-recipient HLA	HLA-matched	1.00					
disparity	HLA-mismatched	1.28	1.06-1.54	0.010*			

Abbreviations: CR, complete remission; ALL, acute lymphoblastic leukemia; PS, performance status; HCT-CI, Hematopoietic cell transplantation - comorbidity index; WBC, white blood cell; Ph, Philadelphia chromosome; HSCT; hematopoietic stem cell transplantation, PIF, primary induction failure; MAC, myeloablative conditioning;

RIC, reduced-intensity conditioning; TBI, total body irradiation; TAC, tacrolimus; MTX, methotrexate; CsA, cyclosporine; MMF, mycophenolate mofetil; and HLA, human leukocyte antigen. * indicates statistically significant. P values in () indicate the results from Wald test (per variable).

Table 3 Predictive scoring system for prognosis risk in non-CR ALL

Variables		Point
Age		
	30-49 y	1
	50 y or older	2
PS		
	2 or more	3
HCT-CI		
	3 or more	1
BM blast counts at HSCT		
	10-49%	2
	50% or more	3
Disease status		
	Relapse	2

Abbreviations: CR, complete remission; ALL, acute lymphoblastic leukemia; PS, performance status; HCT-CI, Hematopoietic cell transplantation - specific comorbidity index, BM; bone marrow, and HSCT; hematopoietic stem cell transplantation.

Figure 1

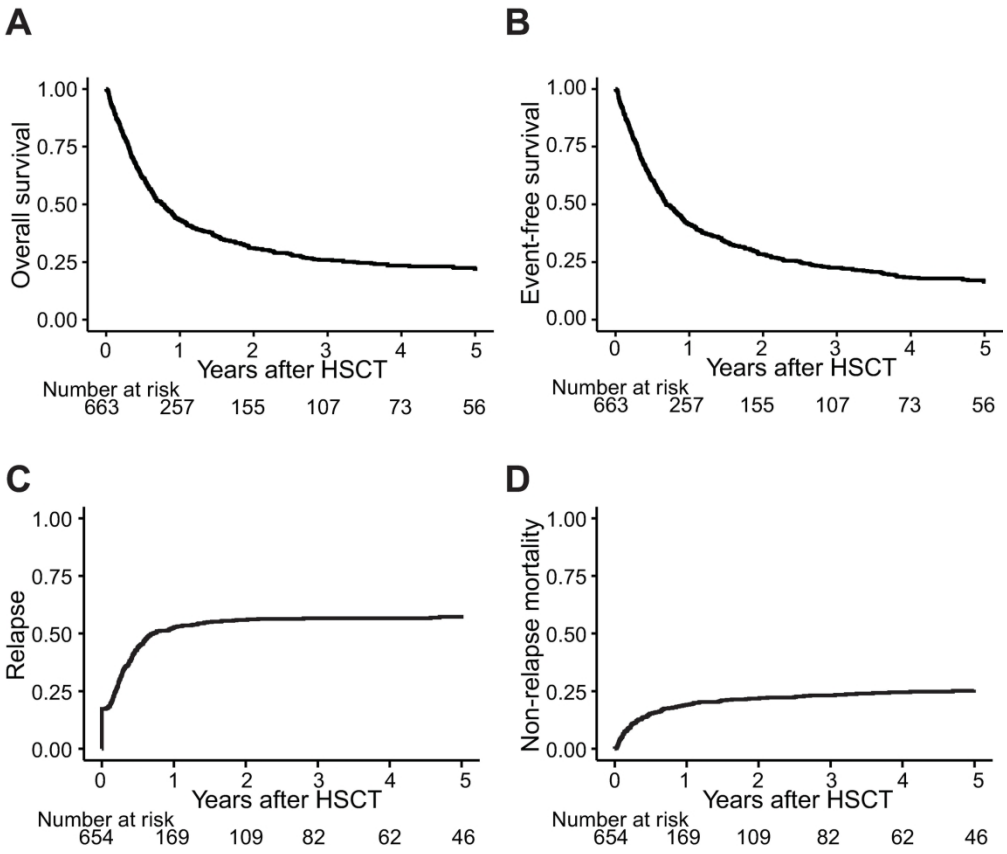

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Figure 2

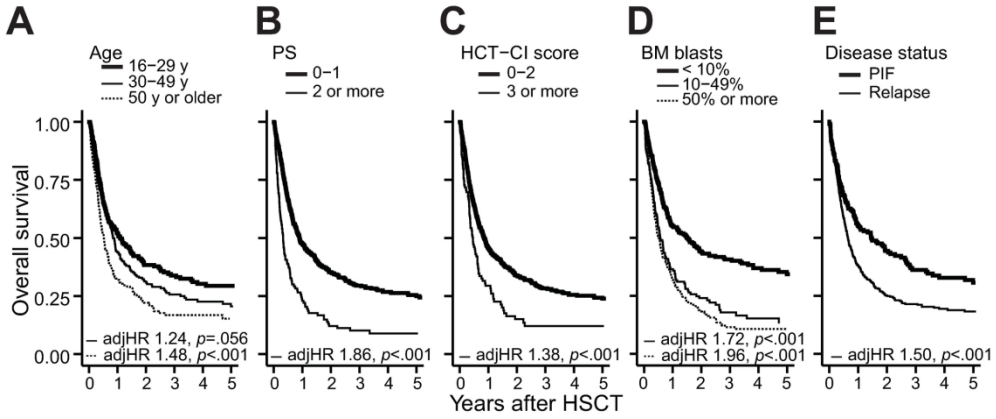

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Figure 3

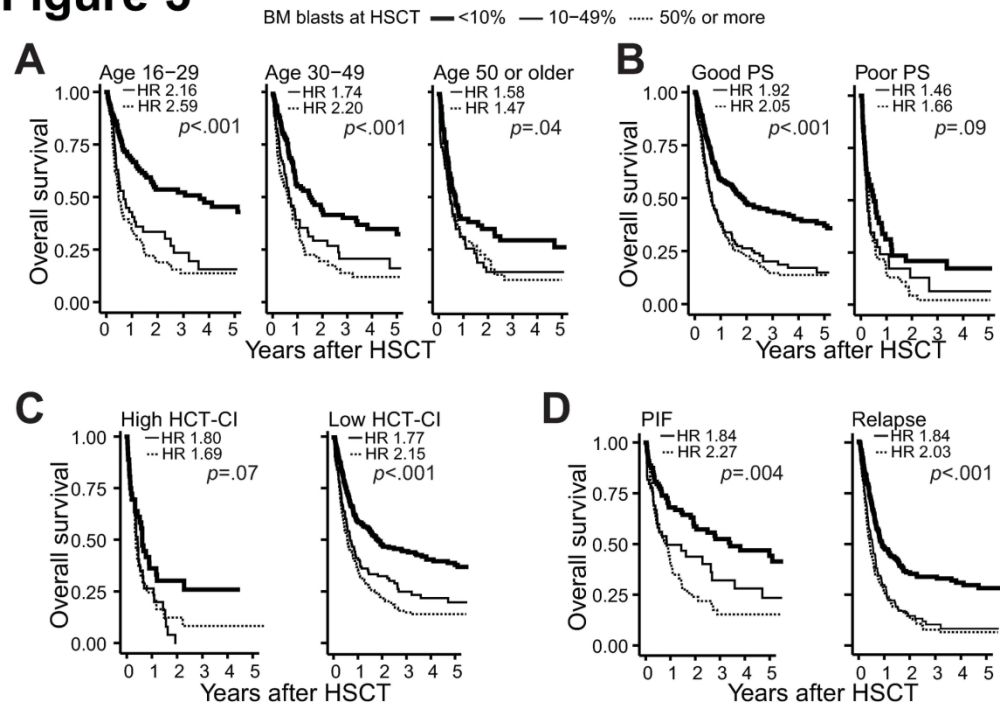

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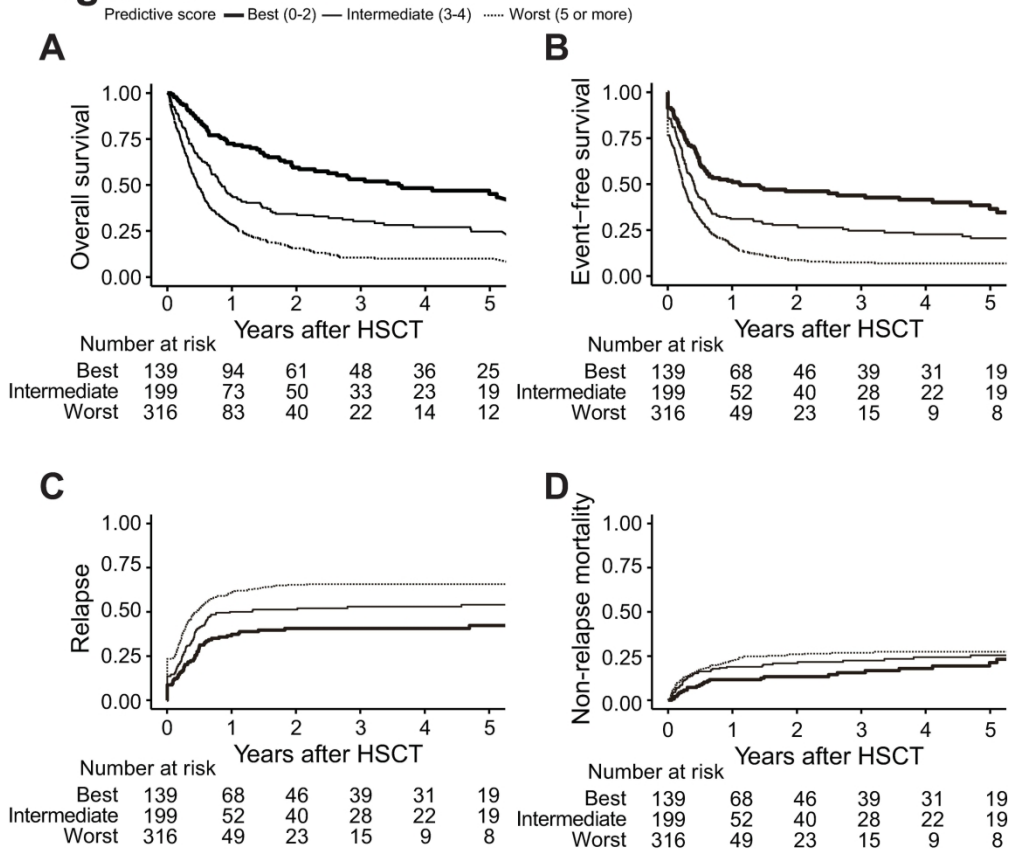
Figure 4



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Supplemental Figure Legends

Supplemental Figure 1. Subgroup analyses for overall survival focusing on the stratified BM blast counts

Overall survival was compared with respect to various pre-HSCT variables, including (**A**) sex, (**B**) initial WBC, (**C**) immunophenotype, (**D**) Ph status, (**E**) extramedullary disease, (**F**) conditioning, (**G**) full TBI, (**H**) graft type, (**I**) GVHD prophylaxis, and (**J**) HLA disparity. HRs are calculated in each blast counts compared to the comparators described in thick lines, and p values are displayed after Wald test.

Supplemental Figure 2. Differences in the outcomes as per the disease status

(**A**) Overall survival and cumulative incidence of (**B**) relapse and (**C**) non-relapse mortality are shown separately as per the disease status of PIF *vs.* relapse.

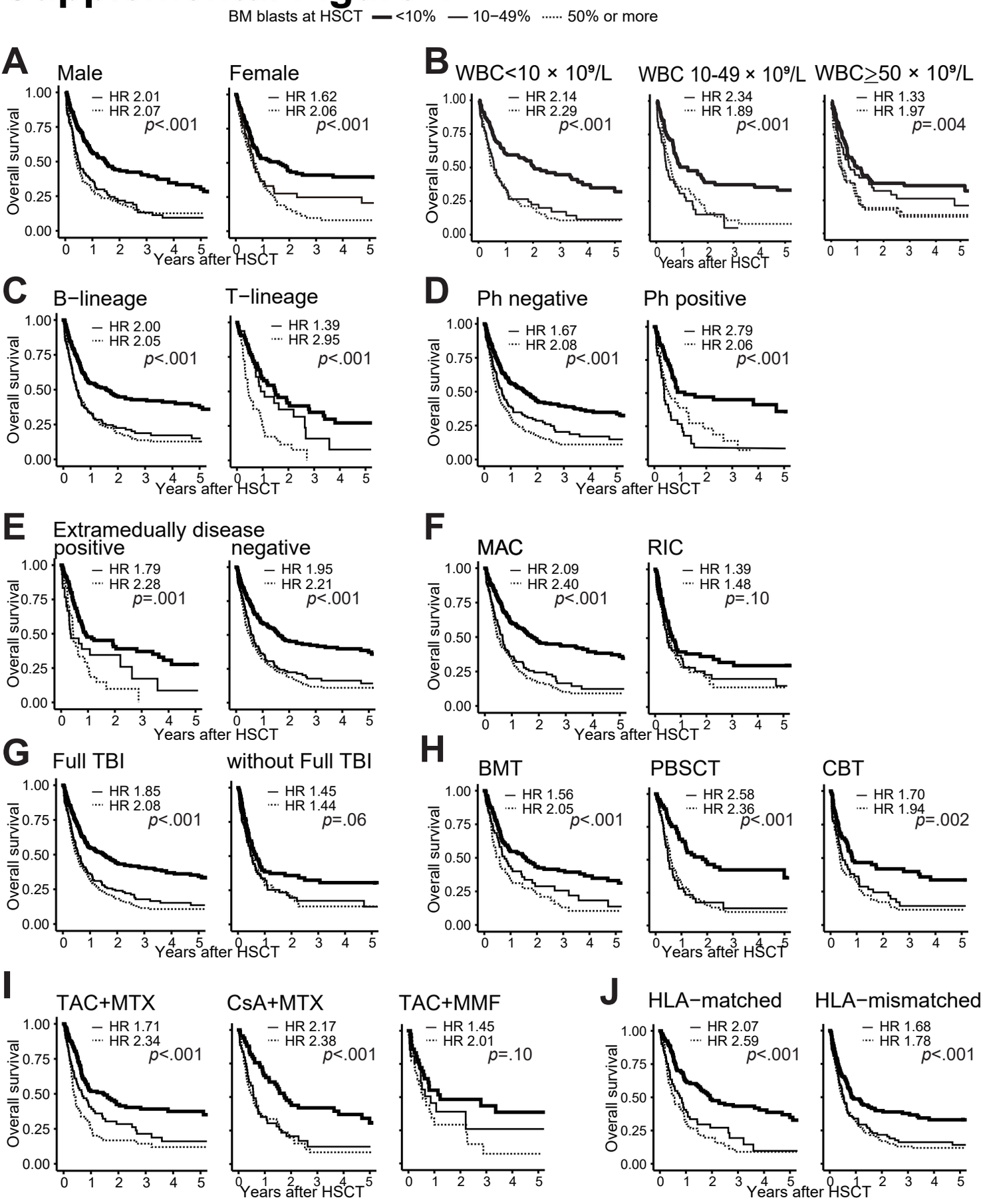
Supplemental Figure 3. Outcomes following allo-HSCT in adult ALL patients according to the prognostic scoring

Overall survival curves are shown per prognostic categories with each score.

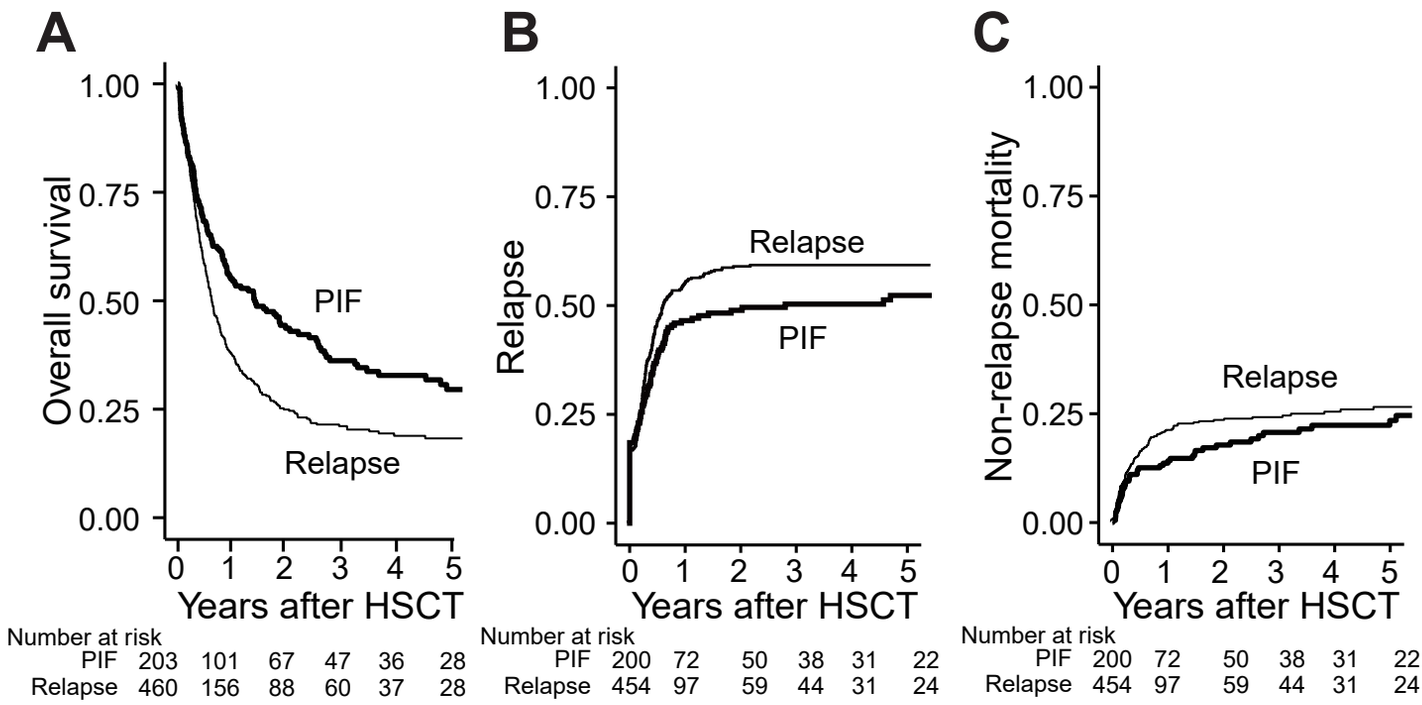
Supplemental Figure 4. Outcomes following allo-HSCT in adult ALL patients who had achieved CR

(**A**) Overall survival, (**B**) event-free survival, and cumulative incidence of (**C**) relapse and (**D**) non-relapse mortality are shown in the adult ALL patients who had achieved CR.

Supplemental Figure 1



Supplemental Figure 2



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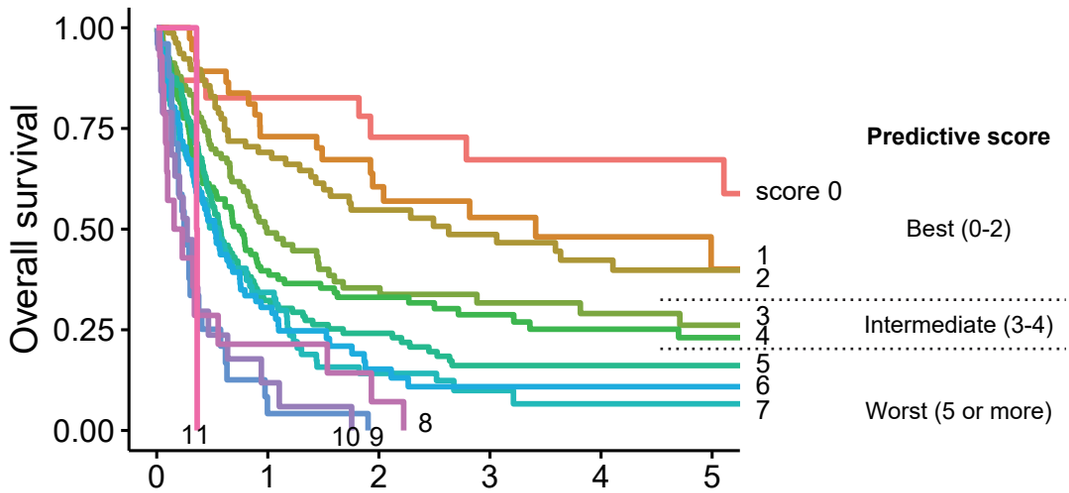

Supplemental Figure 4