Haploidentical donor hematopoietic cell transplantation for myelodysplastic/myeloproliferative overlap neoplasms: results from a North American collaboration

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Abstract

Haploidentical donors offer a potentially readily available donor, especially for non-White patients, for hematopoietic cell transplantation (HCT). In this North American collaboration, we retrospectively analyzed outcomes of first HCT using haploidentical donor and post-transplantation cyclophosphamide (PTCy) in myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) overlap neoplasms (MDS/MPN). We included 120 consecutive patients who underwent HCT using a haploidentical donor for MDS/MPN across 15 centers. Median age was 62.5 years and 38% were of non-White/Caucasian ethnicity. The median follow-up was 2.4 years. Graft failure was reported in seven of 120 (6%) patients. At 3 years, non-relapse mortality (NRM) was 25% (95% confidence interval [CI]: 17-34), relapse 27% (95% CI: 18-36), grade 3-4 acute graft-*versus*-host disease 12% (95% CI: 6-18), chronic graft-*versus*-host disease requiring systemic immunosuppression 14% (95% CI: 7-20), progression-free survival (PFS) 48% (95% CI: 39-59), and overall survival (OS) 56% (95% CI: 47-67). On multivariable analysis, NRM was statistically significantly associated with advancing age at HCT (per decade increment, subdistribution hazard ratio [sdHR] =3.28; 95% CI: 1.30-8.25); relapse with the presence of mutation in *EZH2/RUNX1/SETBP1* (sdHR=2.61; 95% CI: 1.06-6.44); PFS with advancing age at HCT (per decade increment, HR=1.98, 95% CI: 1.13-3.45); and OS with advancing age at HCT (per decade increment, HR=2.01; 95% CI: 1.11-3.63) and splenomegaly at HCT/prior splenectomy (HR=2.20; 95% CI: 1.04-4.65). Haploidentical donors are a viable option for HCT in MDS/MPN, especially for those disproportionately represented in the unrelated donor registry. Hence, donor mismatch should not preclude HCT for patients with MDS/MPN, an otherwise incurable malignancy. In addition to patient age, disease-related factors including splenomegaly and high-risk mutations dominate outcomes following HCT.

Introduction

Myelodysplastic/myeloproliferative overlap neoplasms (MDS/MPN) are a group of clonal myeloid neoplasms and per the 2022 World Health Organization (WHO) classification include the diagnoses of chronic myelomonocytic leukemia (CMML), MDS/MPN with neutrophilia (or atypical chronic myeloid leukemia or aCML per 2016 WHO classification), MDS/MPN with *SF3B1* mutation and thrombocytosis, MDS/MPN not otherwise specified (MDS/MPN-NOS).[1-3] Over the years, several mostly small retrospective studies have established the curative potential of allogeneic hematopoietic cell transplantation (HCT) in MDS/MPN,[4-7] but none of these incorporated related HLA-haploidentical donors in a meaningful way. In the current era, the use of haploidentical donors in the broad scope of HCT has evolved significantly since the advent of post-transplantation cyclophosphamide (PTCy).[8-11] The role of haploidentical donors in MDS/MPN offers the potential advantage of available donors in a timely manner for an otherwise incurable malignancy. Additionally, finding a fully matched donor in the donor registry can be challenging for non-White patients due to the lower diversity of donors from these populations. Therefore, haploidentical donors can often be suitable donor options for patients who may be ethnically underrepresented in the donor registry. On the other hand, theoretical concerns of delayed engraftment or graft failure have been raised with haploidentical donor HCT owing to disease-related marrow fibrosis and splenomegaly. Hence, we conducted this study via our North American collaboration to systematically evaluate the clinical outcomes in MDS/MPN after haploidentical donor-PTCy HCT.

Genomic landscape plays a notable role in the prognostication of all MDS/MPN entities with worse prognoses attributed to higher number of mutations and specific high-risk mutations.[12-15] Prior work has demonstrated that mutation(s) in *EZH2, RUNX1*, or *SETBP1 (E/R/S)* is associated with a lower likelihood of response to hypomethylating agents, a commonly used non-transplantation therapeutic approach in MDS/MPN.[12] Therefore, in this study, we sought to explore the role of genomic landscape, including a specific evaluation of *E/R/S* mutations, in determining outcomes of haploidentical donor HCT.

Since the prevalence of these diseases is low and morphological distinction for these individual entities is often obscure, we grouped the various MDS/MPN entities in this study. At the same time, features of dysplasia, as well as proliferation, remain a unifying feature of MDS/MPN entities. Furthermore, the prognosis of these individual entities especially with advanced or high-risk disease is poor, unless remission is achieved followed by consolidation with HCT.[12]

Methods

Patient selection and multi-institutional collaboration

This study leverages an ongoing multi-institutional collaboration of HCT centers across the USA and Canada to evaluate the role of HCT in rare myeloid malignancies. Fifteen institutions participated in this retrospective study, with Johns Hopkins University, (Baltimore, MD, USA) as the coordinating site (IRB00292283, approved on September 19, 2021). Each participating institution obtained approval from its respective Institutional Review Board and data was transferred to Johns Hopkins University upon completion of data-sharing agreements with each participating site. The study was designed in keeping with the tenets of the Declaration of Helsinki. This study was designed prior to the publication of the 2022 update of World Health Organization (WHO) and International Consensus Classification definitions.[1,2] Hence, the diagnosis of CMML, MDS/MPN with neutrophilia, MDS/MPN with *SF3B1* mutation and thrombocytosis, and MDS/MPN-NOS was in accordance with the 2016 WHO classification for MDS/MPN.[3] Bone marrow biopsy reports of all included patients were reviewed by the participating site investigator as well as the coordinating site investigator (TJ) for adjudication of MDS/MPN diagnosis. Additional inclusion criteria for all centers were: (i) adult (age ≥18 years) patients who underwent a first HCT, (ii) HCT using haploidentical donor defined as family donor mismatched for haplotype, and PTCy-based graft-*versus*-host disease (GvHD) platform, and (iii) HCT timeline between January 2011 and December 2021. Patients who had a transformation to blast phase (>20% blasts in blood or marrow) at any point in the disease course and those who underwent haploidentical donor cord blood HCT were excluded. All patients at all the collaborating institutions who met these criteria were included in the analysis.

Definitions

Revised International Prognostic Scoring System (R-IPSS), clinical/molecular CMML-specific prognostic scoring system (CPSS-mol), and MDS/MPN responses to therapy were assessed as previously published.[16-18] Spleen size was measured by imaging or physical exam. Given the variability of this measurement, we labeled spleen size of <12 cm on imaging or non-palpable on physical exam as normal, and ≥12 cm on imaging or palpable below costal margin on physical exam was considered enlarged. Time to neutrophil engraftment was defined as days from the day of HCT to the first of the 3 consecutive days when the absolute neutrophil count was ≥500/μL, while time to platelet engraftment was defined as days from the day of HCT to the first of the 3 consecutive data of platelets >20,000/μL in the absence of platelet transfusions for 7

consecutive days.[19] Graft failure was defined as a lack of donor hematopoietic cell engraftment following HCT (<5% donor chimerism) at any time following HCT, without evidence of disease relapse.[20] Non-relapse mortality (NRM) was death from any cause in the absence of disease relapse. Acute and chronic GvHD were graded per standard criteria.[21,22] Day 0 of HCT was used as the reference day for time-to-event outcomes. Overall survival (OS) was defined from the date of HCT (day 0) to the date of death from any cause or censored at the last follow-up date for alive patients. The events of progression-free survival (PFS) included relapse or death, whichever occurred first.

Cytogenetic and somatic mutation data

Cytogenetic results were deemed "high-risk" per those included in intermediate, high, and very high-risk categories of R-IPSS.[17] Next-generation sequencing (NGS) was used to obtain somatic mutation data at individual participating institutions and results from these respective tests were used for analysis. NGS was obtained prior to HCT in all patients on whom the data is available, either at diagnosis or with the pre-HCT evaluations. High-risk mutations on NGS included mutations in *NRAS, SETBP1, RUNX1, EZH2, TP53, ASXL1*, and *STAG2* as previously described.[14,15,23-25] NGS was done at individual participating institutions and included commonly reported mutations in myeloid malignancies.

Statistical analysis

For outcomes subject to competing events, cumulative incidences were reported and the distribution differences between groups were compared via Gray's K-sample tests.[26] When estimating the cumulative incidence function of relapse, NRM was the competing event and *vice versa*. When estimating the cumulative incidence of GvHD, the competing events included graft failure and death without graft failure and without the corresponding GvHD event. OS and PFS were estimated via Kaplan-Meier method, and the distribution differences between groups were compared via log-rank test. Patients who did not relapse or die were censored on the date of last follow-up.

Cox proportional hazards model was applied in univariate and multivariable analyses to estimate the hazard ratio of OS and PFS.[27] Fine-Gray subdistribution hazards model was used univariate and multivariable analyses of relapse, NRM, or GvHD outcomes.[28] Covariates in multivariable analyses were selected based on clinical relevance and statistical significance noted on univariate analysis. All hypothesis testing was two-sided based on a significance level of 0.05 without considering multiplicity. Analyses were conducted in R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Baseline patient, disease, and hematopoietic cell transplantation details (N=120).

Characteristic	N=120
Patient details	
Median age at HCT in years (range)	62.5 (18-75)
Median months from diagnosis to HCT (range)	10.35 (1.1-399.2)
Male sex, N (%)	77 (64.2)
Race/ethnicity, N (%)	
Caucasian	74 (61.7)
African American	21 (17.5)
Hispanic	13 (10.8)
Asian	11 (9.2)
Alaskan Native	1 (0.8)
Diagnosis, N (%)	
CMML	61 (50.8)
MDS/MPN-NOS	48 (40.0)
MDS/MPN with neutrophilia	5 (4.2)
MDS/MPN with *SF3B1* and thrombocytosis	6 (5.0)
HCT-CI, N (%)	
0-1	65 (54.2)
≥2	55 (45.8)
Disease-related details	
High-risk cytogenetics, N (%)*	25 (20.8)
Number of high-risk mutations on NGS (total N=90), N (%)	
0	32 (35.6)
1	26 (28.9)
≥2	32 (35.6)
Mutations in *E/R/S* present, total N=90, N (%)	28 (31.1)
R-IPSS risk category, N (%)	
Very low/ low	48 (40)
Intermediate/ high/ very high	72 (60)
Spleen size at HCT, N (%)	
Normal	67 (55.8)
Enlarged	50 (41.7)
Splenectomy	3 (2.5)
Marrow blasts at HCT, N (%)	
<10%	113 (94.2)
≥10%	7 (5.8)
HCT-related details	
HCT year, N (%)	
2011-2018	63 (52.5)
2019-2021	57 (47.5)
Recipient CMV seropostive, N (%)	80 (66.7)
Donor age at HCT in years	
<30	33 (27.5)
30-45	62 (51.7)
>45	25 (20.8)
Conditioning regimen intensity, N (%)	
Myeloablative	22 (18.3)
Reduced-intensity	44 (36.7)
Non-myeloablative	54 (45.0)
GvHD prophylaxis (with PTCy), N (%)	
Tacrolimus MMF	97 (80.8)
Sirolimus MMF	19 (15.8)
ATG-cyclosporin	4 (3.3)
Graft source, N(%)	
Bone marrow	25 (20.8
Peripheral blood	95 (79.2)
Median $CD34^+$ cell dose $x10^6$/kg (range)	5 (0.86-23.8)

*Per R-IPSS, del(7q), +8, +19, i(17q), -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 or more abnormalities. CMV: cytomegalovirus; *E/R/S*: *EZH2/RUNX1/SRSF2*; HCT: hematopoietic cell transplant; HCT-CI: HCT comorbidity index; PTCy: post-transplantation cyclophosphamide; R-IPSS: Revised-International Prognostic Scoring System; GvHD: graft-*versus*-host disease; MDS/MPN: myelodysplastic/myeloproliferative overlap neoplasm; NGS: next-generation sequencing; MDS/MPN-NOS: MDS/MPN not otherwise specified; MMF: mycophenolate mofetil, CMML: chronic myelomonocytic leukemia.

Results

Baseline patient and hematopoietic cell transplantation details

We identified 120 patients across the 15 participating institutions who underwent a first haplo-HCT for MDS/MPN using PTCy-based GvHD prophylaxis. A descriptive summary of these patients is shown in Table 1. Patients were more commonly of male sex (64%) and over one third (37%) were ≥65 years of age, in keeping with the male predominance and older median age of diagnosis of MDS/MPN.[15,29] Forty-six (38%) patients were of non-White/Caucasian race/ethnic background, who are disproportionately represented on the donor registry. Karnofsky performance score was <90 in 46 (39%) patients at the time of HCT. R-IPSS was low or very low in 40% of patients who underwent HCT, most commonly due to the presence of high-risk somatic mutations and/or younger age. Cytogenetic analysis revealed normal karyotype in 75 (63%) patients, as is often the case in MDS/MPN. NGS data was available in 90 patients and 87 had at least one detectable mutation on the NGS panel with 45 (50%) harboring >3 mutations, while 58 (64%) had one or more high-risk somatic mutations (Figure 1). Consistent with prior reports, men had a higher median number of mutations than women (4 *vs*. 3; *P*=0.015), but the proportion of men with high-risk somatic mutations or those with *E/R/S* mutations, while higher, was not statistically significantly different than women (70% *vs*. 56%; *P*=0.19; 32% *vs*. 29%, *P*=0.79; *Online Supplementary Table S1*).[15] As anticipated, bridging treatment prior to HCT varied significantly across all patients and hypomethylating agents were the most common agent for bridging used in 88 (73%) patients, hydroxyurea only in five (4%), and induction chemotherapy (including venetoclax-based regimens) in 19 (16%) patients. Of the 106 patients who underwent bridging therapy, 40 (38%) achieved a complete response/partial response (CR/PR) per international consortium criteria prior to HCT.[18] Seven (6%) patients had 10% or more blasts in the bone marrow at the time of HCT. Three patients had undergone splenectomy prior to HCT, two due to MDS/MPN, and one for a different malignancy. Consistent with established institutional protocols, a diverse range of specific conditioning regimens were used as detailed in *Online Supplementary Table S2*.

Clinical outcomes

The median follow-up on this study is 2.4 years after HCT, based on the reverse Kaplan-Meier method. *Online Sup-*

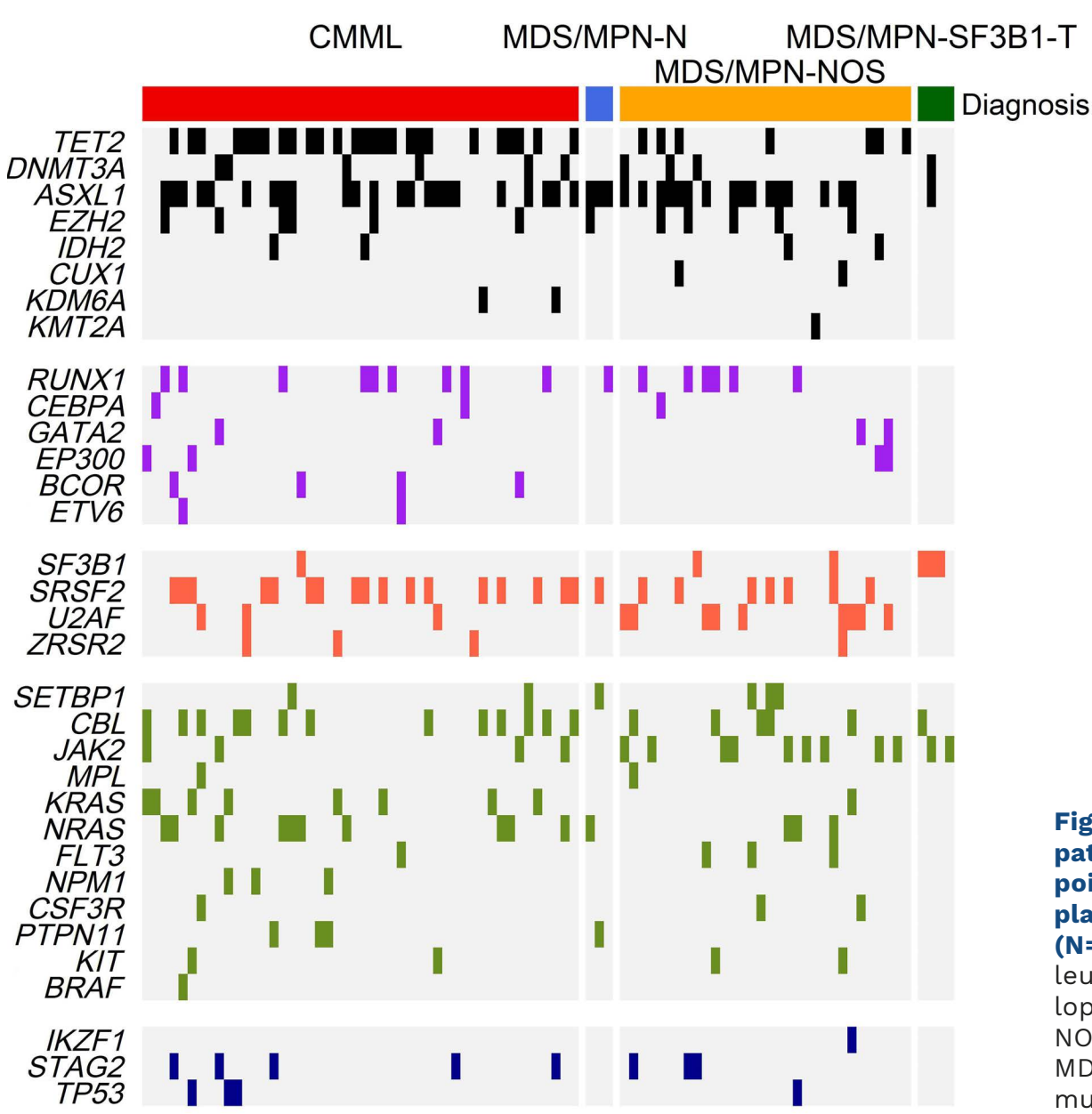

Figure 1. Mutational landscape of subset of patients undergoing haploidentical hematopoietic cell transplantation for myelodysplastic/myeloproliferative overlap neoplasm (N=90). CMML: chronic myelomonocytic leukemia; MDS/MPN: myelodysplastic/myeloproliferative overlap neoplasm; MDS/MPN-NOS: MDS/MPN-not otherwise specified; MDS/MPN-SF3B1-T: MDS/MPN with *SF3B1* mutation and thrombocytosis.

plementary Table S3 summarizes engraftment, NRM, relapse, acute and chronic GvHD, PFS and OS. Figure 2 provides Kaplan-Meier analysis of all clinical outcomes. The OS and PFS for CMML (n=61/120, 51%) and MDS/MPN-NOS (n=48, 40%), which comprised over 90% of patients, were not statistically different (hazard ratio [HR] =0.94; 95% CI: 0.54-1.66; *P*=0.84 for OS; and HR=1.06; 95% CI: 0.62-1.81; *P*=0.82 for PFS). These HR are suggestive of very similar outcomes. Next, a comparison of CMML, MDS/MPN-NOS, MDS/MPN with neutrophilia, and MDS/MPN with *SF3B1* mutations and thrombocytosis as separate entities also found no statistically significant difference (Figure 3A). Given this finding in addition to the known low prevalence of these diagnoses and overall clinicopathological overlap, we combined the four entities for subsequent analyses.

Engraftment and outcomes after graft failure

Median time to neutrophil engraftment was 18 (interquartile range [IQR] =16-22) days and platelet engraftment was 31 (IQR=22.5-41) days (*Online Supplementary Table S3*). Seven (6%) patients had graft failure, all of whom had received reduced intensity conditioning (RIC)/non-myeloablative conditioning (NMAC), six had used a peripheral blood graft, and two received anti-thymocyte globulin and PTCy for GvHD prophylaxis. Three of these seven patients (43%) died before day +100 due to infections. The remaining four underwent a second HCT, and two of those are alive at the last follow-up at day +481 and day +2,337, respectively. One of the second HCT was done using the same donor (peripheral blood graft instead of marrow graft) and the remaining three were done using a different donor. Of note, there were a total four patients who received anti-thymocyte globulin and PTCy which accounts for a notable 50% graft failure with this regimen, while acknowledging the small size of this subset.

Non-relapse mortality and relapse

The cumulative incidence of NRM was 20% (95% CI: 13-28) at 1-year and 25% (95% CI: 17-34) at 3 years (Figure

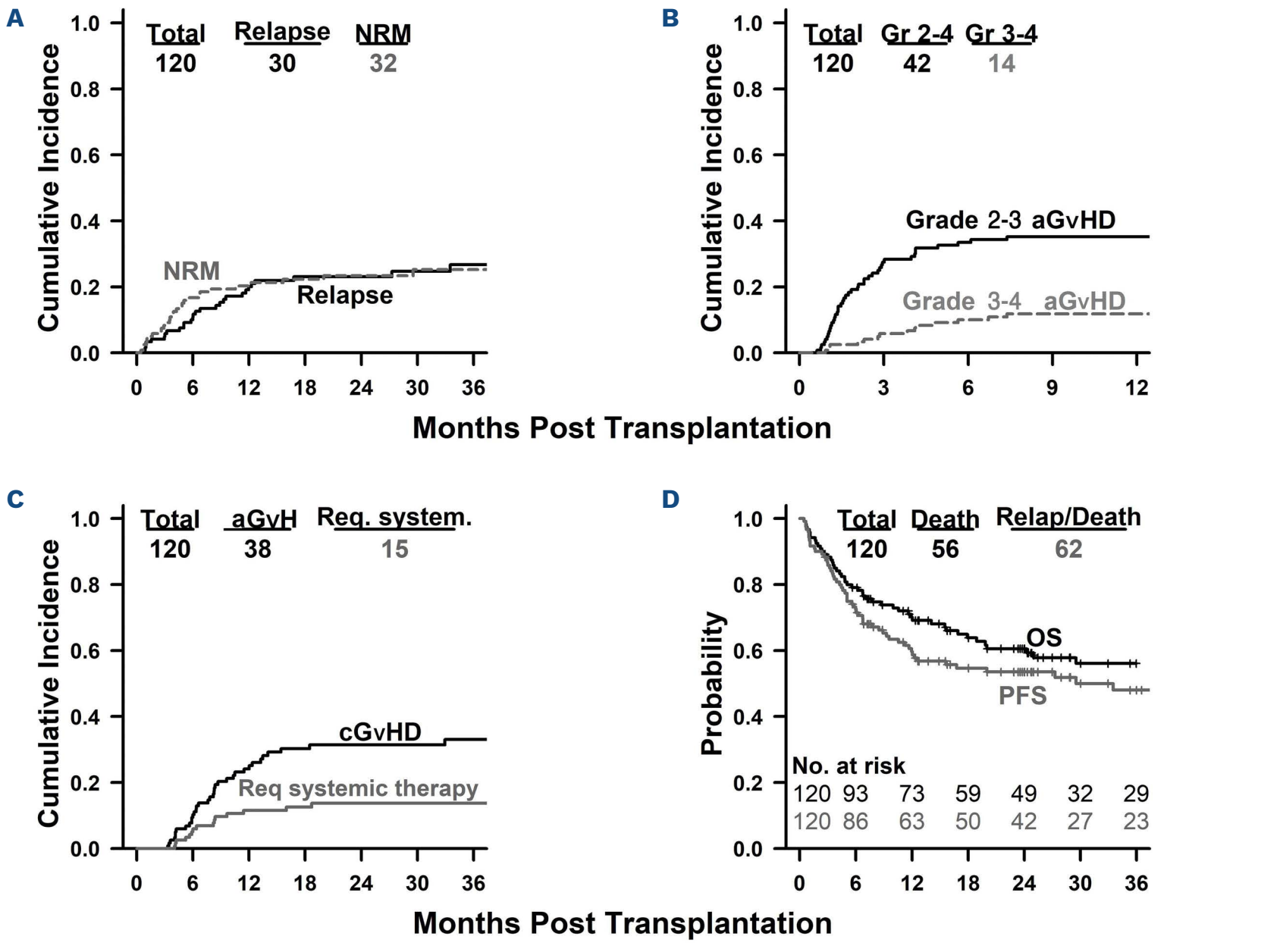

Figure 2. Clinical outcomes for entire cohort (N=120). (A) Cumulative incidence of non-relapse mortality (NRM) and relapse; (B) acute graft-*versus*-host disease (aGvHD) grades 2-4 and grades 3-4; (C) chronic GvHD (cGVHD) all grade and cGvHD requiring systemic immunosuppression; and (D) Kaplan Meier estimates of overall survival (OS) and progression-free survival (PFS). Gr: grade; Req. system: requiring systemic immunosuppression; Relap: relapse.

2A; *Online Supplementary Table S3*). The cause of death among these patients were infection in 17 (14%), GvHD in five (4%), organ toxicity in six (5%), another malignancy in two (2%), and unknown in three patients (3%). The cumulative incidence of relapse was 20% (95% CI: 13-27) at 1 year and 27% (95% CI: 18-36) at 3 years. In total, 30 (25%) patients had relapsed of whom 24 (20%) had died as a result of relapsed disease, by the last follow-up. Seven patients underwent donor lymphocyte infusion (DLI), most commonly for molecular relapse, of whom two restored full donor chimerism while one had only a transient improvement in chimerism. Four patients underwent a second HCT after relapse, two of whom had received a prior DLI also. All four of these patients are deceased at the last follow-up from persistent disease.

Acute and chronic graft-*versus*-host disease

Most patients who experienced acute GvHD had highest grade of grade 2. At 1 year, the cumulative incidence of acute GvHD grade 2-4 was 35% (95% CI: 27-44) and grade 3-4 acute GvHD was 12% (95% CI: 6-18) (Figure 2B; *Online Supplementary Table S3*). The skin and gut were the most commonly involved organs in 27 of 42 (64%) patients. The cumulative incidence of chronic GvHD at 3 years was 33% (95% CI: 24-42) and chronic GvHD requiring systemic therapy was 14% (95% CI: 7-20) (Figure 2C; *Online Supplementary Table S3*).

Progression-free survival and overall survival

At 1 year and 3 years, the probability of PFS was 60% (95% CI: 51-69) and 48% (95% CI: 39-59) and the probability of OS was 70% (95% CI: 62-79) and 56% (95% CI: 47-67), re-

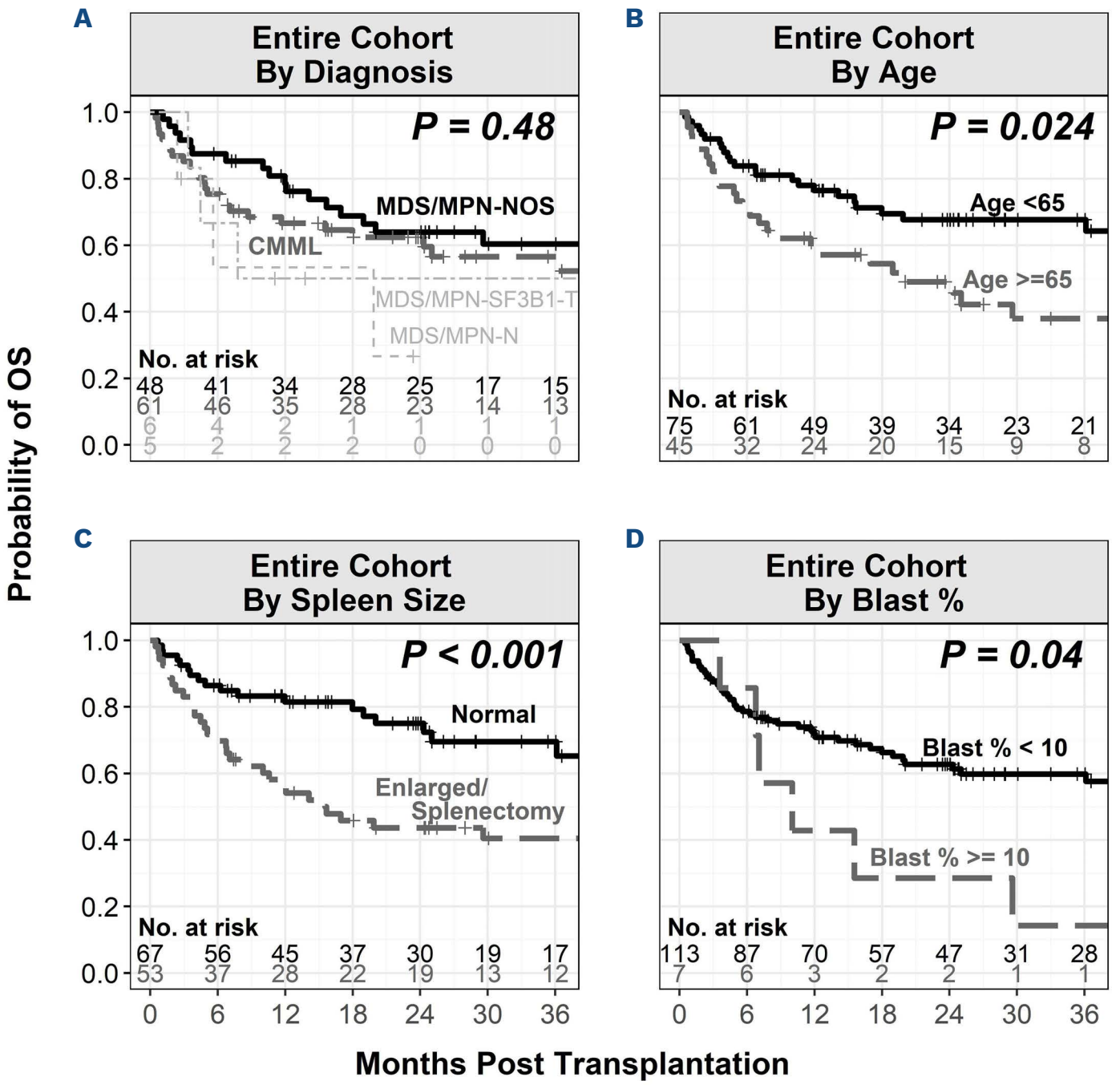

Figure 3. Difference in overall survival by diagnosis, age, spleen size and marrow blasts in the total cohort of 120 patients. (A) Overall survival (OS) by diagnosis entities of chronic myelomonocytic leukemia (CMML), myelodysplastic/myeloproliferative overlap neoplasm (MDS/MPN) with neutrophilia (MDS/MPN-N), MDS/MPN not otherwise specified (MDS/MPN-NOS), and MDS/MPN with *SF3B1* mutation and thrombocytosis (MDS/MPN-SF3B1-T). (B) OS by patient age at hematopoietic cell transplantation (HCT). (C) OS by spleen size at HCT. (D) OS by bone marrow blast percentage.

Table 2. Univariate analysis for non-relapse mortality, relapse, progression-free survival and overall survival (N=120).

	NRM		Relapse		PFS		OS	
	sdHR (95% CI)	*P*	sdHR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at HCT (10-year increment)	1.40 (0.88-2.23)	0.15	1.51 (1.00-2.28)	0.05	1.63 (1.15-2.02)	0.006	1.53 (1.07-2.18)	0.02
Sex (female *vs.* male)	0.80 (0.38-1.67)	0.55	0.72 (0.34-1.55)	0.40	0.70 (0.41-1.19)	0.19	0.72 (0.41-1.27)	0.25
Race/ethnicity								
Caucasian	Ref		Ref		Ref		Ref	
African American	0.75 (0.26-2.16)	0.59	1.30 (0.52-3.24)	0.57	1.04 (0.51-2.11)	0.91	0.96 (0.44-2.09)	0.92
Hispanic/Asian/Alaskan Native American	1.58 (0.73-3.42)	0.24	1.20 (0.51-2.80)	0.68	1.53 (0.84-2.79)	0.16	1.70 (0.92-3.11)	0.09
Years from diagnosis to HCT	1.08 (1.02-1.14)	0.01	0.86 (0.70-1.05)	0.15	1.03 (0.96-1.11)	0.39	1.05 (0.97-1.13)	0.21
HCT year (2019-2021 *vs.* 2011-2018)	0.41 (0.18-0.92)	0.04	0.64 (0.30-1.38)	0.26	0.47 (0.27-0.82)	0.008	0.44 (0.23-0.82)	0.01
Diagnosis								
CMML	Ref		Ref		Ref		Ref	
MDS/MPN-NOS	1.30 (0.62-2.71)	0.48	0.93 (0.46-1.90)	0.85	1.06 (0.62-1.81)	0.82	0.94 (0.54-1.66)	0.84
MDS/MPN-N or MDS/MPN-SF3B1-T	2.98 (1.07-8.34)	0.04	0.33 (0.05-2.27)	0.26	1.48 (0.61-3.59)	0.39	1.84 (0.75-4.51)	0.18
KPS (≥90 *vs.* <90)	0.96 (0.48-1.93)	0.91	0.50 (0.25-1.02)		0.65 (0.39-1.07)	0.09	0.83 (0.48-1.41)	0.48
HCT-CI (≥2 *vs.* 0-1)	1.32 (0.67-2.62)	0.42	0.88 (0.43-1.78)		1.07 (0.65-1.76)	0.79	1.16 (0.69-1.96)	0.58
R-IPSS (intermediate/high/very high *vs.* very low/low)	1.84 (0.85-3.98)	0.12	0.94 (0.46-1.95)		1.42 (0.82-2.43)	0.21	1.40 (0.79-2.46)	0.25
Bridging therapy								
None	Ref		Ref		Ref		Ref	
Hydrea only	2.14 (0.32-14.16)	0.43	No relapse		0.93 (0.19-4.63)	0.93	1.15 (0.22-5.99)	0.86
HMA/ JAK inhibitor/IMiD	1.16 (0.36-3.73)	0.80	1.35 (0.42-4.33)	0.61	1.33 (0.56-3.14)	0.51	1.38 (0.54-3.53)	0.50
Induction	1.58 (0.46-5.40)	0.46	1.32(0.32-5.42)	0.70	1.51 (0.57-4.05)	0.41	1.55 (0.54-4.49)	0.42
CR/PR prior to HCT	0.79 (0.38-1.63)	0.52	1.88 (0.81-4.34)	0.14	1.20 (0.69-2.09)	0.52	2.38 (1.01-5.59)	0.047
Spleen size at HCT (enlarged/splenectomy *vs.* normal)	2.10 (1.04-4.25)	0.04	1.68 (0.82-3.45)	0.15	2.17 (1.31-3.61)	<0.005	0.90 (0.47-1.75)	0.76
Marrow blasts at HCT (≥10% *vs.* >10%)	1.60 (0.55-4.70)	0.39	1.86 (0.58-5.95)	0.29	1.97 (0.84-4.60)	0.12	0.99 (0.49-1.98)	0.98
High-risk cytogenetics (presence *vs.* absence)	1.06 (0.47-2.41)	0.88	0.68 (0.27-1.73)	0.42	0.83 (0.44-1.56)	0.57	1.23 (0.63-2.41)	0.54
High-risk NGS (presence *vs.* absence)	0.70 (0.29-1.72)	0.44	2.65 (0.87-8.12)	0.09	1.34 (0.69-2.63)	0.39	1.18 (0.59-2.34)	0.64
Number of high-risk mutations (≥2 *vs.* 0-1)	0.61 (0.23-1.60)	0.32	2.70 (1.20-6.05)	0.02	1.51 (0.81-2.83)	0.19	1.21 (0.97-1.51)	0.09
E/R/S mutation (presence *vs.* absence)	0.56 (0.19-1.60)	0.28	3.33 (1.47-7.52)	<0.005	1.72 (0.92-3.23)	0.09	0.87 (0.46-1.65)	0.68
Donor age (10-year increment)	1.20 (0.88-1.63)	0.25	1.12 (0.84-1.50)	0.45	1.21 (0.98-1.49)	0.07	1.21 (0.97-1.51)	0.09
Graft source (blood *vs.* marrow)	0.85 (0.37-1.95)	0.70	0.91 (0.38-2.14)	0.82	0.85 (0.47-1.55)	0.60	0.87 (0.46-1.65)	0.68
GvHD prophylaxis								
Tacrolimus	Ref		Ref		Ref		Ref	
Sirolimus	0.36 (0.08-1.62)	0.18	2.02(0.95-4.33)	0.07	1.07 (0.54-2.11)	0.85	0.87 (0.41-1.85)	0.71
ATG cyclosporine	4.16 (1.29-13.48)	0.02	No relapse	-	2.07 (0.64-6.68)	0.22	2.26 (0.70-7.33)	0.17
Conditioning intensity								
MAC	Ref		Ref		Ref		Ref	
RIC/NMAC	1.77 (0.70-4.49)	0.23	3.42 (0.81-14.39)	0.09	2.90 (1.35-6.76)		2.44 (1.04-5.71)	0.04
CMV reactivation requiring intervention	1.37 (0.69-2.68)	0.37	0.43 (0.16-1.15)	0.09	0.76 (0.43-1.33)	0.33	0.87(0.49-1.54)	0.63

NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; sdHR: subdistribution hazard ratio; CI: confidence interval; ATG: anti-thymocyte globulin; CMV: cytomegalovirus; *E/R/S*: *EZH2/RUNX1/SRSF2*; GvHD: graft-*versus*-host disease; HCT: hematopoietic cell transplant; HCT-CI: HCT comorbidity index; HMA: hypomethylating agent; ImiD: immunomodulatory drugs; JAK: Janus kinase; KPS: Karnofsky performance score; R-IPSS: Revised-International Prognostic Scoring System; MAC: myeloablative conditioning; MDS/MPN: myelodysplastic/myeloproliferative overlap neoplasm; MDS/MPN-NOS: MDS/MPN not otherwise specified; MDS/MPN-N: MDS/MPN with neutrophilia; MDS/MPN-SF3B1-T: MDS/MPN with *SF3B1* mutation and thrombocytosis; NGS: next-generation sequencing; NMAC: non-myeloablative conditioning; RIC: reduced-intensity conditioning; Ref: reference.

spectively, as tabulated in the *Online Supplementary Table S3*. The respective Kaplan-Meier curves for PFS and OS are shown in Figure 2D.

Univariate analysis

The univariate analysis including patient, disease, and HCT variables for NRM, relapse, PFS, and OS is detailed in Table 2. In the univariate analysis for OS, advanced patient age at HCT (HR=1.53 per decade increase in age, 95% CI: 1.07-2.18; *P*=0.02; Figure 3B), year of HCT prior to 2019 (HR=0.44; 95% CI: 0.23-0.82; *P*=0.01), splenomegaly at HCT /prior splenectomy (HR=2.57; 95% CI: 1.48-4.44; *P*<0.005; Figure 3C), ≥10% blasts in marrow at HCT (HR=2.38; 95% CI: 1.01-5.59; *P*=0.046; Figure 3D), and RIC/NMAC (HR=2.44; 95% CI: 1.04-5.71; *P*=0.04) were associated with inferior OS. The presence of ≥2 high-risk mutations (subdistribution HR [sdHR] =2.70; 95% CI: 1.20-6.05; *P*=0.02; Figure 4A), and *E/R/S* mutations (sdHR=3.33; 95% CI: 1.47-7.51; *P*<0.005; Figure 4B), were associated with a significantly higher risk of relapse following HCT.

Multivariable analysis

Patient age at HCT, year of HCT, RIPSS, presence of *E/R/S* mutation, splenomegaly at HCT, donor age, and intensity of conditioning regimen were included in the multivariable analysis. Blast percentage was not included in the multivariable analysis because only seven patients had blasts over 10%. A complete multivariable analysis is shown in Table 3. Advanced age at HCT (sdHR=3.28 for every 10 years increment in age; 95% CI: 1.30-8.25; *P*=0.01) was as-

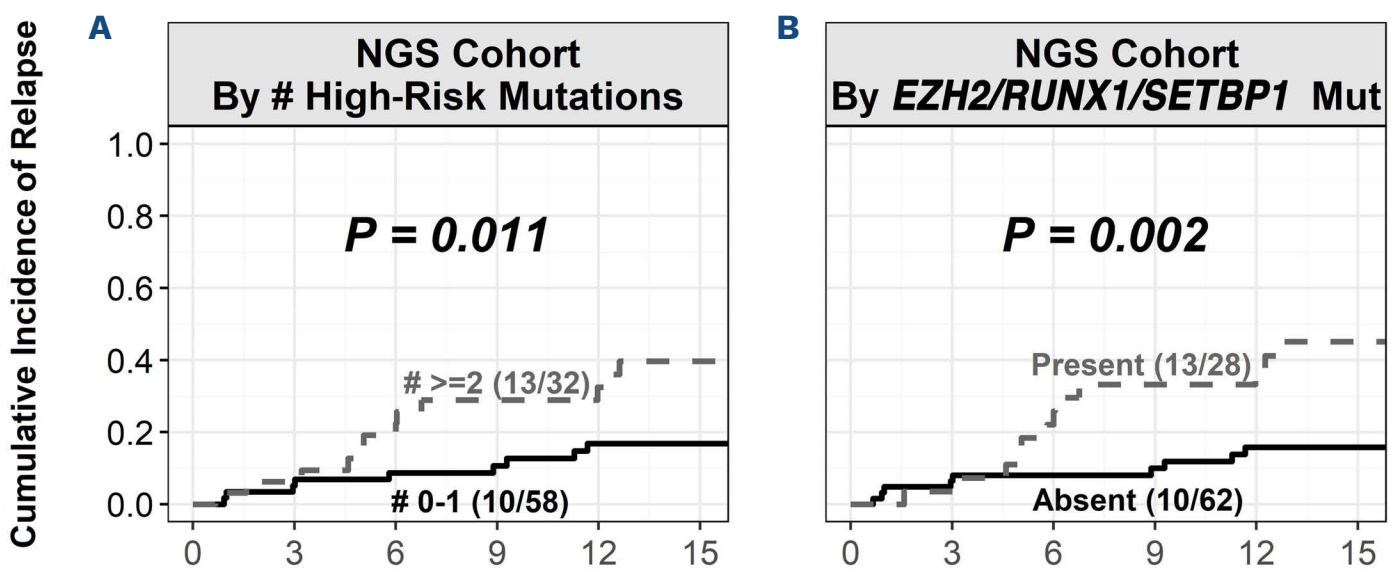

Figure 4. Difference in relapse by high-risk mutations in the cohort of 90 patients with next-generation sequencing data. (A) Relapse by number of high-risk mutations. (B) Relapse by *EZH2*, *RUNX1*, or *SETBP1* mutations (Mut). NGS: next-generation sequencing.

Table 3. Multivariable analysis for non-relapse mortality, relapse, progression-free survival and overall survival (N=90).

	NRM		Relapse		PFS		OS	
	sdHR (95% CI)	*P*	sdHR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at HCT (10-year increment)	3.28 (1.30-8.25)	0.01	1.11 (0.67-1.81)	0.69	1.98 (1.13-3.45)	0.02	2.01 (1.11-3.63)	0.02
HCT year (2019-2021 *vs.* 2011-2018)	0.39 (0.10-1.47)	0.16	0.71 (0.28-1.80)	0.48	0.55 (0.28-1.10)	0.09	0.53 (0.25-1.13)	0.10
R-IPSS (intermediate/high/very high *vs.* very low/low)	2.53 (0.84-7.68)	0.10	0.82 (0.32-2.12)	0.68	1.44 (0.74-2.81)	0.28	1.35 (0.66-2.75)	0.42
E/R/S mutation (presence *vs.* absence)	0.43 (0.14-1.33)	0.14	2.61 (1.06-6.44)	0.04	1.24 (0.64-2.40)	0.52	0.88 (0.42-1.82)	0.73
Spleen size at HCT (enlarged/splenectomy *vs.* normal)	1.19 (0.34-4.14)	0.78	1.70 (0.74-3.87)	0.21	1.78 (0.91-3.51)	0.09	2.20 (1.04-4.65)	0.04
Donor age (10-year increment)	1.36 (0.87-2.12)	0.18	1.09 (0.68-1.77)	0.71	1.17 (0.85-1.63)	0.34	1.14 (0.79-1.62)	0.49
Conditioning intensity (RIC/NMAC *vs.* MAC)	0.37 (0.12-1.16)	0.09	3.90 (1.32-11.49)	0.01	1.51 (0.75-3.05)	0.25	1.20 (0.57-2.52)	0.64

NRM: non-relapse mortality; PFS: progression-free survival; OS: overall survival; sdHR: subdistribution hazard ratio; ATG: anti-thymocyte globulin; *E/R/S*: *EZH2/RUNX1/SRSF2*; HCT: hematopoietic cell transplant; R-IPSS: revised-International Prognostic Scoring System; MAC: myeloablative conditioning; NMAC: non-myeloablative conditioning; RIC: reduced-intensity conditioning.

sociated with higher NRM. RIC/NMAC and presence of *E/R/S* were significantly associated with higher relapse rate (sdHR=3.90; 95% CI: 1.32-11.49; *P*=0.01 for RIC/NAMC and HR=2.61; 95% CI: 1.06-6.44; *P*=0.04 for *E/R/S* mutations).

Inferior PFS and OS were noted with advanced age at HCT (HR=1.98; 95% CI: 1.13-3.45; *P*=0.02 for PFS and HR=2.01; 95% CI: 1.11-3.63; *P*=0.02 for OS), and splenomegaly at HCT or a splenectomy prior to HCT (HR=1.78; 95% CI: 0.91-3.51; *P*=0.09 for PFS and HR=2.20; 95% CI: 1.04-4.65; *P*<0.04 for OS). As a result of the counterpoise of lower NRM and higher relapse, conditioning intensity did not show a significant association with PFS or OS (HR=1.51; 95% CI: 0.75-3.05; *P*=0.25 for PFS and HR=1.20; 95% CI: 0.57-2.52; *P*=0.64 for OS). Notably, the choice of myeloablative conditioning, over RIC/NMAC, was statistically significantly correlated with younger age at HCT in this analysis, corroborating observations from clinical practice (*Online Supplementary Figure S1*).

Discussion

Our study provides a comprehensive description of the outcomes of haplo-HCT in MDS/MPN in a cohort of 120 patients in this multi-institutional collaboration. The potentially curative role of HCT in high-risk CMML was recently elucidated in comparison to non-HCT options.[6] We demonstrate that haploidentical donors can be used with HCT outcomes similar to what has been historically reported with matched donors, in the rare diagnosis of MDS/MPN. This is particularly important for populations who are less likely to find a fully matched donor in the unrelated donor registry. Graft failure rate was under 10% and OS was 70% at 1 year and 56% at 3 years in our study. In the recent international analysis of CMML patients without AML transformation, HCT resulted in OS of about 30-35% at 3 years, with a majority (~75%) of donors being HLA-matched siblings or unrelated donors.[6] Japanese nationwide registry data reported an OS of 48.5% at 3 years in MDS/MPN-NOS, using a variety of related, unrelated, and cord blood donors.[30] Notably, 40% patients in this study were under 50 years of age at HCT. In a Mayo Clinic cohort of 17 CMML and eight MDS/MPN-NOS patients without antecedent blast transformation, HCT with matched donors resulted in a graft failure of 6% and 0%, and OS of 47% and 41%, at 2 years, respectively.[7] Among 14 patients with MDS/MPN with neutrophilia, the Japanese registry study reported 54% OS at 1 year, using predominantly matched donors and select cord blood donors.[4] While the timeline of HCT in all these studies varies, outcomes in our study are comparable to the limited reports presented above, underscoring that donor availability should not preclude consideration of HCT for patients with MDS/MPN whose outcomes remain poor in the absence of the HCT.

This study also explores modifiable disease-related features, in the form of spleen size control and blast reduction, which can possibly be optimized prior to HCT to allow for superior disease control and survival following HCT. We previously demonstrated the role of enlarged spleen size in negatively impacting relapse outcomes in myelofibrosis.[9,31] As demonstrated previously, splenomegaly is an indicator of aggressive disease biology and is not addressed with splenectomy, which did not appear to correlate with improved outcomes.[31] JAK inhibitors have shown meaningful spleen size reduction in myelofibrosis[32-34] and have an emerging role in the management of CMML by targeting JAK-STAT dependent GM-CSF signaling in CMML.[35,36] Hence, JAK inhibitors may address spleen size reduction prior to HCT in MDS/MPN as in myelofibrosis, an evaluation warranted in future studies. While MDS/MPN (except CMML) were not included in the pivotal VIALE-A trial, retrospective studies have demonstrated disease control with a combination of hypomethylating agents with BCL-2 inhibitor, venetoclax, in select patients with elevated blasts in MDS/MPN.[37] We cannot identify an optimal bridging therapy in this study due to the variable availability of drugs over the years and various factors guiding bridging therapy selection in the real-world, including individual center practices. However, a systematic evaluation of the role of JAK inhibitors and BCL-2 inhibitors for disease control and as a bridge to HCT in MDS/MPN is warranted.

Intensity of conditioning regimen is often a matter of discussion in planning HCT, especially in chronic myeloid malignancies where average age of diagnosis or HCT is often over 60 years. As is noted in our study, decisions on conditioning intensity are commonly driven by age and the comorbidity status of an individual patient, in that younger or fitter patients are enriched in the myeloablative cohort. In myelofibrosis, MDS and other myeloid malignancies, retrospective studies of higher intensity conditioning demonstrate the possibility of better disease control but at the expense of higher NRM,[38-41] similar to what we note in this study. Ultimately, OS is not statistically different. Hence, patient selection remains a critical confounder to consider when interpreting the role of intensity of conditioning in a retrospective manner.

A growing body of evidence has uncovered the role of the genomic landscape in the overall prognosis as well as response to hypomethylating agent therapy in MDS/MPN.[12,14,42] Our study further elaborates on the role of somatic mutations in MDS/MPN, including previously defined high-risk mutations, in prognosticating outcomes of haploidentical donor HCT. In two cohorts of CMML patients, mutations in *ASXL1, CBL, RUNX1, NRAS*, and *SETBP1* were associated with adverse survival.[16,42] We also demonstrated higher prevalence of high-risk mutations, specifically *EZH2*, in

men with MDS/MPN, which may be responsible for inferior overall outcomes when compared to women.[15] *E/R/S*, and *ASXL1* mutations have also been associated with a lower risk of response to non-HCT therapy, especially hypomethylating agents, in MDS/MPN.[12,43] In the context of HCT, somatic mutation data has historically been limited to CMML. Mutations in *DNMT3A, TP53, ASXL1*, and *NRAS* correlated with inferior survival in two different studies.[13,44] The presence of high-risk mutations, specifically *E/R/S*, or the presence of ≥2 high-risk mutations significantly increased the risk of relapse in our study. Collectively, these data suggest that MDS/MPN harboring high-risk mutations identified in the non-transplantation context also influence relapse following HCT. Notably, the difference was significant for relapse, but not OS in our study, which possibly suggests that some of these patients can be salvaged after relapse following BMT with DLI or other novel therapeutic strategies.

MDS/MPN is a rare, yet consequential, disease entity. This extensive report of haploidentical donor HCT in MDS/MPN was feasible due to our robust multi-institutional collaboration. The present analysis nevertheless remains limited by its retrospective nature and heterogenous practice across centers. We combined the four entities within MDS/MPN for this analysis given the high-risk nature of all four entities when considered for HCT and because our initial analysis demonstrated no statistical difference in OS among CMML, MDS/MPN-NOS, MDS/MPN with neutrophilia, and MDS/MPN with *SF3B1* mutation and thrombocytosis. The strategy of combining diseases for analyses increases the sample size but introduces the confounding effect of variable nuances of these entities.

Conclusion

We demonstrate feasibility and comparable outcomes with haplo-HCT and PTCy in MDS/MPN with reference to previously published data, in a multi-institution study. Given the otherwise incurable diagnosis of MDS/MPN, this study provides a rationale for expanding the potential donor pool to include haploidentical donors in patients undergoing transplant evaluation. Optimization of disease-related factors such as spleen size and blast percentage reduction prior to HCT should be explored in future studies. The mutation landscape associated with MDS/MPN can guide outcomes with HCT. Future studies are needed to explore pre-HCT therapies and their impact on modifying mutational burden and post-transplantation outcomes.

Disclosures

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Contributions

TJ conceptualized the study, acquired data, interpreted the data analysis, wrote the first draft of the manuscript, and approved the final draft. HLT and RV conducted the data analysis, edited the manuscript draft, and approved the final draft. HE, PV, TK, SAW, LPG, AB, AK, RT, MRG, SA, KVGN, MI, ATG, AV, SRM, MAM, DA, VG and SO acquired data, interpreted the data analysis, edited the manuscript draft, and approved the final draft. RJJ conceptualized the study, interpreted the data analysis, edited the manuscript draft, and approved the final draft.

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Data-sharing statement

De-identified patient data will be made available upon a reasonable request to the corresponding author after publication.

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