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Myeloid neoplasms with *PHF6* mutations: context-dependent genomic and prognostic characterization in 176 informative cases

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Recent reports suggest a favorable prognosis for *PHF6* mutation (*PHF6*^{MUT}) in chronic myelomonocytic leukemia (CMML) and unfavorable in acute myeloid leukemia (AML). We accessed 176 consecutive patients with a spectrum of myeloid neoplasms with *PHF6*^{MUT}, including AML (*N* = 67), CMML (*N* = 49), myelodysplastic syndromes (MDS; *N* = 36), myeloproliferative neoplasms (MPN; *N* = 16), and MDS/MPN (*N* = 8). *PHF6* mutations were classified as nonsense (43%) or frameshift (30%) with the PHD2 domain being the most frequently (64%) affected region. Median follow-up was 25 months with 110 (63%) deaths and 44 allogeneic transplants. Our top-line observations include (a) a distinctly superior overall survival (OS; 81 vs. 18 months; *p* < 0.01) and blast transformation-free survival (BTFS; “not reached” vs. 44 months; *p* < 0.01) in patients with CMML vs. those with other myeloid neoplasms, (ii) a higher than expected frequency of isolated loss of Y chromosome, in the setting of CMML (16% vs. expected 6%) and MDS (8% vs. expected 2.5%), (iii) a significant association, in MDS, between *PHF6*^{MUT} variant allele fraction (VAF) > 20% and inferior OS (HR 3.0, 95% CI 1.1–8.1, multivariate *p* = 0.02) as well as female gender and inferior BTFS (HR 26.8, 95% CI 1.9–368.3, multivariate *p* = 0.01), (iv) a relatively favorable median post-transplant survival of 46 months. Multivariable analysis also identified high-risk karyotype (HR 5.1, 95% CI 1.2–20.9, *p* = 0.02), and hemoglobin < 10 g/dL (HR 2.7, 95% CI 1.0–7.2, *p* = 0.04), as independent predictors of inferior OS in patients with MDS. The current study provides disease-specific information on genotype and prognosis of *PHF6*-mutated myeloid neoplasms.

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INTRODUCTION

Plant homeodomain finger protein 6 (*PHF6*) gene located at the 26.2 locus of the long arm of chromosome X, encodes for a chromatin-binding protein, which contains four nuclear localization signals, and two distinct zinc finger domains known as plant homeodomain (PHD) 1, and 2 [1, 2]. The protein is postulated to regulate gene expression through chromatin modification, functioning as a tumor suppressor and impacting hematopoietic lineage differentiation [1]. *PHF6* is abundantly expressed in the central nervous and hematopoietic systems [1–4] and was first described in 2002 by Lower et al. as the gene responsible for the Börjeson-Forssman-Lehmann syndrome (BFLS). The latter is an X-linked neurodevelopmental disorder [3] characterized by short stature, mental retardation, epilepsy, distinctive facial features, hypogonadism, and obesity [2]. Somatic *PHF6* mutations have since been described in various hematological malignancies, particularly in T-cell acute lymphoblastic leukemia (16% and 38% incidence in pediatric-age and adult patients, respectively) [1, 3].

A spectrum of myeloid neoplasms, including acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), chronic myeloid leukemia (CML), myeloproliferative neoplasms (MPN), chronic myelomonocytic leukemia (CMML), and MDS/MPN have all been associated with *PHF6* mutations with incidence figures ranging between 0.7 to 5% [5–8]. Bataller et al. studied 1699

patients with myeloid neoplasms including 56 with *PHF6*^{MUT} and found no prognostic associations [6]. By contrast, Kubota et al. studied 8443 patients with myeloid neoplasms, including 147 with *PHF6*^{MUT}, and reported shortened survival in the latter versus those without the mutation (28% vs. 42% at 3 years; *p* < 0.01), especially when *PHF6*^{MUT} and *RUNX1*^{MUT} were concurrently mutated [9]. The study also suggested that *PHF6*^{MUT} was a second hit phenomenon occurring at the time of disease progression and clonal evolution [9]. In another study of 801 AML patients, including 22 with *PHF6*^{MUT}, Huang et al. identified *PHF6*^{MUT} as a predictor of poor outcome associated with poor chemosensitivity resulting in a lower complete remission (CR) rate (41% vs. 69%; *p* = 0.04) and shorter overall survival (OS; 6.0 vs. 39.0 months; *p* < 0.01) [10].

In a recent study [7], we identified *PHF6*^{MUT} in CMML to be associated with (i) superior OS and blast transformation-free survival (BTFS), (ii) thrombocytopenia, and (iii) isolated loss of Y chromosome (LoY) [7]. In the current study, we have extended the scope of our investigation by including additional informative cases with other myeloid neoplasms.

METHODS

The current study was conducted under an institutional review board approved minimum risk protocol that authorized retrospective extraction

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and analysis of data from records of patients seen across all Mayo Clinic campuses including Rochester, Minnesota; Jacksonville, Florida; and Scottsdale, Arizona sites (USA). Mutations were detected on peripheral blood or bone marrow samples by multi-gene next-generation sequencing (NGS) performed on clinical indications as per institutional protocol. Specific diagnoses were assigned in accordance with the International Consensus Classification (ICC) of myeloid neoplasms [11]. Patient demographics, co-mutations, and follow-up information were extracted from electronic medical records. Receiver operating characteristic (ROC) plots were used to identify significant cutoff levels for continuous variables. Conventional statistical methods including the Kaplan-Meier method for survival outcomes and univariate/multivariable Cox proportional hazards regression were employed to identify associations between variables and outcomes. Calculations of OS and BTFS were censored for allogeneic hematopoietic stem cell transplantation (AHSCT). All analyses were performed on JMP Pro 17.0.0 software (SAS Institute, Cary, NC, USA).

RESULTS

Overall comparative analysis

A Mayo Clinic enterprise-wide database search using the terms *PHF6*^{MUT} and morphologically annotated myeloid neoplasms identified a total of 196 patients; 20 patients were excluded because of re-assignment of mutations as variants of unknown significance (VUS; $n = 12$), diagnosis other than myeloid neoplasm ($n = 6$), or mutation detection at time of post-chemotherapy remission for AML. Specific diagnoses in the remainder 176 patients with *PHF6*^{MUT} included AML ($n = 67$, 38%), CMML ($n = 49$, 28%), MDS ($n = 36$, 20%), MPN ($n = 16$, 9%) and MDS/MPN ($n = 8$, 5%).

The clinical characteristics, laboratory parameters, and cytogenetic and mutation data are comprehensively outlined in Tables 1 and 2, stratified by the aforementioned morphologic subtype designations. The median age at the time of *PHF6*^{MUT} detection for the entire study group was 73 years (range: 22–92) with younger age distribution in patients with AML and MDS/MPN (Table 1). Several types of *PHF6* mutations were identified and classified as nonsense ($n = 61$, 43%), frameshift ($n = 43$, 30%), missense ($n = 18$, 13%) and those affecting splice sites ($n = 16$, 11%). Most mutations affected the PHD2 region ($n = 92$, 64%) followed by PHD1 region ($n = 37$, 26%). The median *PHF6* variant allele fraction (VAF) was 30%. The *PHF6*^{MUT} VAF, types and locations were similar across the disease subgroups (Table 2).

Isolated LoY was observed only in patients with CMML (16%) or MDS (8%) while complex/monosomal karyotype (MK/CK) or chromosome 7 abnormalities were most frequent in AML (22%). Ninety six percent of the patients had at least one concurrent mutation in other myeloid genes ($n = 169$; Table 2). The median number of co-mutations was 3 (range 0–7); patients with AML (42%), MPN (35%), MDS/MPN (31%) were more likely to have >3 co-mutations, compared to CMML (24%) or MDS (17%; $P = 0.04$). The most frequent co-mutations and those with significant diagnostic or prognostic relevance are shown in Table 2; *TET2* mutation was the most prevalent concurrent mutation (47%) followed by *ASXL1* (39%) and *RUNX1* (28%).

Figure 1 illustrates transplant-censored OS from time of *PHF6*^{MUT} detection, stratified by morphologic subtypes (median follow-up 25 months). OS was significantly longer in CMML (median 81 months; 3/5-year survival 70%/63%) compared to all other myeloid neoplasms including AML (median 15 months; 3/5-year survival 27%/5%, HR 5.0, 95% CI 2.7–9.4), MDS (median 26 months; 3/5-year survival 35%/0%, HR 3.4, 95% CI 1.7–6.8), MDS/MPN (median 10 months; 3/5-year survival 47%/0%, HR 4.4, 95% CI 1.6–612.1), and MPN (median 17 months; 3/5-year survival 14%/14%, HR, 3.6, 95% CI 1.6–8.4). The same was true for BTFS with corresponding BT rates of 10% in CMML, 17% in MDS, 38% in MDS/MPN, and 25% in MPN ($p < 0.01$; Fig. 2). Accordingly, CMML was excluded from subsequent univariate and multivariable analysis for OS and BTFS.

PHF6^{MUT} VAF as a continuous variable was found to have a significant unfavorable impact on OS and ROC analysis identified an optimal cut off VAF of >20%. Univariate analysis excluding patients with CMML identified hemoglobin <10 g/dl, CK/MK/chromosome 7 abnormalities, *DNMT3A*^{MUT}, *U2AF1*^{MUT}, and *PHF6*^{MUT} VAF > 20% as predictors of OS with corresponding HR (95% CI, p -value) of 1.8 (1.1–2.9, 0.03), 2.6 (1.4–4.8, <0.01), 1.9 (1.0–3.6, 0.04), 1.9 (1.1–3.4, 0.02) and 2.1 (1.2–3.6, <0.01) (Table 3). In multivariable analysis, karyotype, *PHF6*^{MUT} VAF > 20%, and *U2AF1*^{MUT} sustained their significance with corresponding HR (95% CI, p -value) of 2.5 (1.3–4.8, <0.01), 1.8 (1.1–3.1, 0.02) and 1.9 (1.1–3.5, 0.02). Another multivariable analysis excluding AML patients, identified circulating blast >2% (HR 5.9, $p = 0.01$) as the most significant predictor of BTFS (Table 3).

PHF6^{MUT} in chronic myelomonocytic leukemia

Twenty eight percent of the study cohort comprised patients with *PHF6*^{MUT} CMML ($n = 49$). In comparison to other *PHF6*^{MUT} myeloid neoplasms, taken as a comparator group, patients with CMML were more likely to have isolated LoY (16% vs. 2%, $p < 0.01$), a higher hemoglobin level (median 12 vs. 9 g/dL, $p < 0.01$), concurrent *TET2*^{MUT} (84% vs. 32%, $P < 0.01$), and were less likely to have MK/CK (0% vs. 9%, $p < 0.01$) or concurrent *DNMT3A*^{MUT} (6% vs. 18%, $p = 0.03$). According to the CMML-specific prognostic scoring system molecular (CPSS Mol) risk-model [12], patients were classified into low ($n = 6$, 15%), intermediate-1 ($n = 11$, 27.5%), intermediate-2 ($n = 19$, 47.5%), and high ($n = 4$, 10%) risk groups (Supplementary Table 1).

At a median follow up of 25 months for patients with CMML, 25 (51%) deaths, 10 (20%) AHSCTs and 7 (14%) BTs were documented; among the latter, two patients developed AML post AHSCT and were censored for survival analyses. In univariate analysis; hemoglobin <10 g/dl, CK/MK/chromosome 7 abnormalities, *DNMT3A*^{MUT}, *NRAS*^{MUT}, age ≥80 years, and *ASXL1*^{MUT} were predictive of OS with corresponding HR (95% CI, p -value) of 5.6 (1.8–16.8, <0.01), 5.9 (1.3–27.5, 0.02), 5.1 (1.1–24.8, 0.04), 0.09 (0.01–0.7, 0.02), 2.5 (1.0–6.0, 0.04) and 2.5 (1.1–5.8, 0.03) respectively. In multivariable analysis, only hemoglobin <10 g/dl, CK/MK/chromosome 7 abnormalities and *DNMT3A*^{MUT} retained their significance with corresponding HR (95% CI, p -value) of 9.8 (2.4–39.9, <0.01), 14.9 (2.3–94.8, <0.01) and 13.8 (2.1–91.8, <0.01). BTFS was independently predicted by CK/MK/chromosome 7 abnormalities (median not reached vs. 8 months, $p < 0.01$) and *ASXL1*^{MUT} ($p < 0.01$) (Table 3).

PHF6^{MUT} in acute myeloid leukemia

Five patients with *PHF6*^{MUT} mixed phenotypic/undifferentiated acute leukemia were included among the sixty-seven patients with *PHF6*-mutated AML. In comparison to other *PHF6*^{MUT} myeloid neoplasms, patients with *PHF6*^{MUT} AML were more likely to have concurrent *RUNX1*^{MUT} (39% vs. 21%, $p = 0.01$), CK/MK/chromosome 7 abnormalities (22% vs. 7%, $p < 0.01$), and concurrent *IDH2*^{MUT} (21% vs. 3%, $p < 0.01$) or *DNMT3A*^{MUT} (26% vs. 8%, $p < 0.01$). Based on the European Leukemia Net (ELN) 2022 risk stratification [13], the AML patients with *PHF6*^{MUT} were categorized into favorable ($n = 3$, 9%), intermediate ($n = 7$, 20%), or adverse ($n = 25$, 71%) risk groups (Supplementary Table 1); the prevalence of recurrent AML mutations were 12%, 7% and 6% respectively, for *FLT3*^{MUT}, *CEBPA*^{MUT}, and *NPM1*^{MUT} (Table 2). In univariate analysis, risk factors for OS in patients with *PHF6*-mutated AML included CK/MK/chromosome 7 abnormalities (HR 2.1; $p = 0.05$) and *U2AF1*^{MUT} (HR 2.8; $p = 0.04$). In multivariable analysis, ELN adverse risk stratification was the only significant risk factor (HR 5.6, $p < 0.01$).

PHF6^{MUT} in myelodysplastic syndrome

Compared to their counterparts with other myeloid neoplasms, *PHF6*-mutated patients with MDS were more likely to display

Table 1. Clinical characteristics, and cytogenetics of 176 patients with *PHF6* mutated myeloid neoplasms including acute myeloid leukemia, chronic myelomonocytic leukemia, myelodysplastic syndrome and myeloproliferative disorders.

Variables	All patients N = 176	Acute myeloid leukemia ^a N = 67	Chronic myelomonocytic leukemia N = 49	Myelodysplastic syndrome N = 36	Myeloproliferative neoplasms N = 16	Myelodysplastic/ Myeloproliferative neoplasm N = 8	P-value
Demographics:							
Age in years; median (range)	73 (22–92)	71 (22–92)	71 (35–91)	75 (58–90)	75.5 (54–87)	64 (39–77)	<0.01
Male; n (%)	134 (76)	50 (75)	36 (73)	27 (75)	14 (87.5)	7 (87.5)	0.7
Laboratory parameters:							
Leukocytes, x 10 ⁹ /L; median (range)	4.3 (0.2–385)	3.4 (0.2–385)	6.2 (2–34)	2.3 (1–13.2)	11.5 (1.1–118)	4.45 (1.5–58.4)	<0.01
Hemoglobin < 10 g/dL; n (%)	90 (52)	46 (71)	9 (19)	21 (58)	10 (63)	4 (50)	
Platelets, x 10 ⁹ /L; median (range)	57.5 (2–1208)	41 (4–514)	66 (6.4–285)	44 (2–205)	177 (19–1208)	149 (5–985)	<0.01
Platelet count < 150 × 10 ⁹ /L; n (%)	147 (85)	61 (95)	43 (90)	34 (94)	5 (31)	4 (50)	
Circulating blast %; median (range)	0 (0–97)	16 (0–97)	0 (0–5)	0 (0–2)	0.5 (0–8)	0 (0–6)	<0.01
Bone marrow blast %; median (range)	5 (0–95)	57 (12–95)	3 (0–19)	3 (0–17)	2 (0–10)	4 (1–15)	<0.01
Absolute monocyte count x 10 ⁹ /L; median (range)	0.4 (0–54)	0.15 (0–54)	1.4 (0.4–11.2)	0.2 (0–0.9)	0.43 (0–44.8)	0.35 (0.02–2.9)	<0.01
Mutations and cytogenetics							
Cytogenetics:							
Sole loss of Y chromosome; n (%)	11 (6)	0 (0)	8 (16)	3 (8)	0 (0)	0 (0)	<0.01
Abnormal; n (%)	70 (40)	36 (54)	11 (22)	12 (33)	7 (44)	4 (50)	
<i>PHF6</i> ^{MUT} Variant allele frequency; median (range) (evaluable = 168)	30 (2–100)	33 (5–100)	25.5 (4–96)	29.5 (2–98)	14 (3–99)	43 (6–84)	0.1
<i>PHF6</i> ^{MUT} Variant allele frequency > 20%; n (%) (evaluable = 168)	103 (61)	41 (66)	30 (65)	20 (55)	6 (38)	6 (75)	
Outcomes:							
Median follow up in months ^b (range)	25 (0–202)	15 (0–104)	81 (1–208)	26 (0–58)	17 (1–71)	10 (5–45)	<0.01
Deaths; n (%)	110 (63)	46 (69)	25 (51)	23 (64)	10 (63)	7 (88)	0.1
Blast transformation (excluding AML) ^b ; n (%)	18 (17)	11 (16)	5 (10)	6 (17)	4 (25)	3 (38)	0.5
Relapse of leukemia (in AML) ^b ; n (%)							
Documented Allo-SCT ^c ; n (%)	44 (25)	23 (34)	10 (20)	6 (17)	3 (19)	2 (25)	0.2

NR not reached, *MUT* mutation.^aIncluding 2 patients with myeloid sarcoma without bone marrow disease.^bCensored at the time of allogeneic hematopoietic stem cell transplantation.^cAllo-SCT: Allogeneic hematopoietic stem cell transplantation.

Table 2. *PHF6* and other concurrent mutations in 176 patients with *PHF6* mutated myeloid neoplasms including acute myeloid leukemia, chronic myelomonocytic leukemia, myelodysplastic syndrome and myeloproliferative disorders.

Mutations	All patients N = 176	Acute myeloid leukemia N = 67	Chronic myelomonocytic leukemia N = 49	Myelodysplastic syndrome N = 36	Myeloproliferative neoplasms N = 16	Myelodysplastic/ Myeloproliferative neoplasm N = 8	P-value
<i>PHF6</i> ^{MUT} location (evaluable = 144)							0.2
PHD1 only, n (%)	37 (26)	11 (21)	6 (19)	14 (39)	3 (19)	3 (38)	
PHD2 only, n (%)	92 (64)	38 (73)	23 (72)	16 (44)	11 (69)	4 (50)	
NLS only, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Combination, n (%)	15 (10)	3 (6)	3 (9)	6 (17)	2 (12)	1 (12)	
<i>PHF6</i> ^{MUT} type (evaluable = 142)							0.7
Frameshift, n(%)	43 (30)	13 (25)	12 (37.5)	12 (34)	4 (25)	2 (25)	
Missense, n(%)	18 (13)	5 (10)	2 (6)	6 (17)	3 (19)	2 (25)	
Nonsense, n(%)	61 (43)	26 (51)	13 (40)	12 (34)	8 (50)	2 (25)	
Splice site, n(%)	16 (11)	6 (12)	4 (12.5)	4 (11)	0 (0)	2 (25)	
Combination, n(%)	4 (3)	1 (2)	1 (3)	1 (3)	1 (6)	0 (0)	
Number of commutations; median (range)	3 (0-7)	3 (0-6)	3 (1-7)	2 (0-5)	3 (1-5)	2.5 (0-6)	0.04
Number of commutations > 3; n (%)	55 (31)	29 (43)	12 (24)	6 (17)	5 (31)	3 (38)	
<i>ASXL1</i> ^{MUT} ; n (%)	68 (39)	21 (31)	16 (33)	18 (50)	10 (63)	3 (38)	0.08
<i>BCOR</i> ^{MUT} ; n (%)	12 (7)	5 (7)	3 (6)	3 (8)	0 (0)	1 (13)	0.8
<i>CALR</i> ^{MUT} ; n (%)	4 (2)	0 (0)	2 (4)	0 (0)	2 (13)	0 (0)	0.02
<i>CBL</i> ^{MUT} ; n (%)	15 (9)	3 (4)	9 (18)	2 (6)	1 (6)	0 (0)	0.06
<i>CEBPA</i> ^{MUT} ; n (%)	5 (3)	5 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0.07
<i>DNMT3A</i> ^{MUT} ; n (%)	26 (15)	17 (25)	3 (6)	6 (17)	0 (0)	0 (0)	<0.01
<i>EZH2</i> ^{MUT} ; n (%)	8 (5)	4 (6)	1 (2)	1 (3)	1 (6)	1 (13)	0.6
<i>FLT3</i> ^{MUT} ; n (%)	10 (6)	8 (12)	1 (2)	1 (3)	0 (0)	0 (0)	0.09
<i>IDH1</i> ^{MUT} ; n (%)	17 (10)	9 (13)	2 (4)	3 (8)	2 (13)	1 (13)	0.5
<i>IDH2</i> ^{MUT} ; n (%)	17 (10)	14 (21)	0 (0)	2 (6)	1 (6)	0 (0)	<0.01
<i>JAK2</i> ^{MUT} ; n (%)	24 (14)	5 (7)	3 (6)	0 (0)	11 (69)	5 (63)	<0.01
<i>KRAS</i> ^{MUT} ; n (%)	6 (3)	1 (1)	4 (8)	0 (0)	1 (6)	0 (0)	0.1
<i>MPL</i> ^{MUT} ; n (%)	3 (2)	0 (0)	1 (2)	0 (0)	2 (13)	0 (0)	0.01
<i>NPM1</i> ^{MUT} ; n (%)	4 (2)	4 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0.04
<i>NRAS</i> ^{MUT} ; n (%)	16 (9)	5 (7)	8 (16)	1 (3)	1 (6)	1 (13)	0.2
<i>RUNX1</i> ^{MUT} ; n (%)	49 (28)	26 (39)	10 (20)	8 (22)	2 (13)	3 (38)	0.08
<i>SH2B3</i> ^{MUT} ; n (%)	5 (3)	1 (1)	4 (8)	0 (0)	0 (0)	0 (0)	0.1
<i>SF3B1</i> ^{MUT} ; n (%)	7 (4)	1 (1)	1 (2)	3 (8)	0 (0)	2 (25)	0.01
<i>SRSF2</i> ^{MUT} ; n (%)	33 (19)	14 (21)	11 (22)	5 (14)	2 (13)	1 (13)	0.7
<i>TET2</i> ^{MUT} ; n (%)	82 (47)	25 (37)	41 (84)	8 (22)	5 (31)	3 (38)	<0.01
<i>TP53</i> ^{MUT} ; n (%)	6 (3)	1 (1)	0 (0)	2 (6)	2 (13)	1 (13)	0.06
<i>U2AF1</i> ^{MUT} ; n (%)	25 (14)	7 (10)	6 (12)	10 (28)	1 (6)	1 (13)	0.1
<i>WT1</i> ^{MUT} ; n (%)	5 (3)	5 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0.08
<i>ZRSR2</i> ^{MUT} ; n (%)	10 (6)	2 (3)	3 (6)	1 (3)	3 (19)	1 (13)	0.2

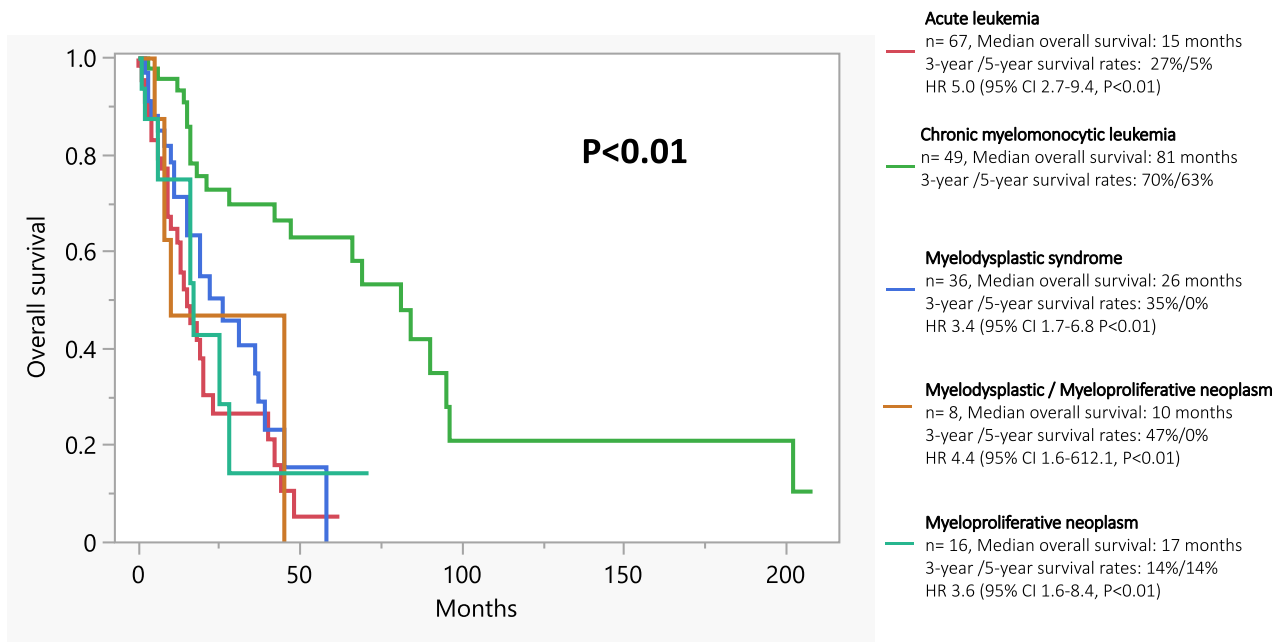


Fig. 1 Overall survival of 176 patients with *PHF6* mutated myeloid neoplasms censored at the time of allogeneic bone marrow transplant stratified by disease subtype at the time of *PHF6* mutation detection. Kaplan–Meier curve illustrates the overall survival censored at transplant of patients stratified by myeloid neoplasm subtype at the time of *PHF6* mutation detection. Patients with chronic myelomonocytic leukemia had a significantly superior survival in comparison to other myeloid neoplasms.

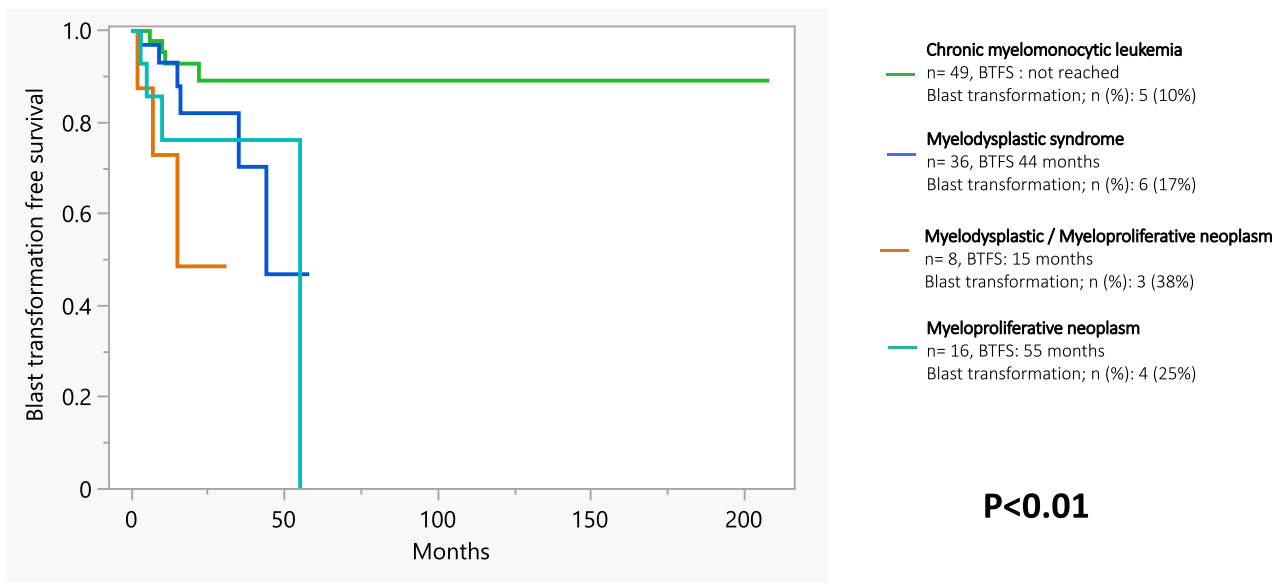


Fig. 2 Blast transformation free survival (BTFS) of 109 patients with *PHF6* mutated myeloid neoplasms censored at the time of allogeneic bone marrow transplant stratified by disease subtypes at the time of *PHF6* mutation detection. Kaplan–Meier curve illustrates the blast transformation free survival censored at transplant of patients stratified by myeloid neoplasm subtype at the time of *PHF6* mutation detection. Patients with chronic myelomonocytic leukemia had a significantly superior BTFS in comparison to other myeloid neoplasms.

concurrent *U2AF1*^{MUT} (28% vs. 11%, $p = 0.01$) and *PHF6*^{MUT} at PHD1 region (39% vs. 21%, $p = 0.01$), and less likely to co-express *TET2*^{MUT} (22% vs. 53%, $p < 0.01$). ICC designated MDS classifications [11] were MDS, NOS with single lineage dysplasia ($n = 3$, 8%), MDS, NOS with multilineage dysplasia ($n = 19$, 53%), MDS with mutated SF3B1 ($n = 1$, 3%), MDS with excess blasts (MDS-EB) ($n = 5$, 14%), and MDS/AML ($n = 8$, 22%). Based on the revised International Prognostic Scoring System (IPSS-R) [14], patients were categorized into low ($n = 9$, 28%), intermediate ($n = 11$, 34%), high ($n = 7$, 22%) or very high ($n = 5$, 16%) risk groups. In

multivariable analysis, CK/MK/chromosome 7 abnormalities, *PHF6*^{MUT} VAF > 20% (Fig. 3a) and hemoglobin <10 g/dL were associated with inferior OS with corresponding HR (95% CI, p -value) of 5.1 (1.2–20.9, 0.02), 3.0 (1.1–8.1, 0.02) and 2.7 (1.0–7.2, 0.04), while female gender was associated with inferior BTFS with HR 26.8, 95% CI 1.9–368.3 ($p = 0.01$; Supplementary Fig. 1).

PHF6^{MUT} in myeloproliferative neoplasms

Among the 16 patients with *PHF6*^{MUT} MPNs, specific diagnosis was myelofibrosis (MF; 62% secondary MF) in 13 and essential

Table 3. Impact of genetic and clinical variables on the overall survival and blast transformation free survival of 176 patients with *PHF6* mutated (*PHF6*^{MUT}) myeloid neoplasms.

Variables:	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% Confidence interval)	p-value	Hazard ratio (95% Confidence interval)	p-value
Overall survival analysis:				
<i>PHF6</i>^{MUT} chronic myelomonocytic leukemia; n = 49				
Hemoglobin < 10 g/dl	5.6 (1.8–16.8)	<0.01	9.8 (2.4–39.9)	<0.01
Complex/monosomal karyotype or chromosome 7 abnormalities	5.9 (1.3–27.5)	0.02	14.9 (2.3–94.8)	<0.01
<i>DNMT3A</i> ^{MUT}	5.1 (1.1–24.8)	0.04	13.8 (2.1–91.8)	<0.01
<i>NRAS</i> ^{MUT}	0.09 (0.01–0.7)	0.02	0.12 (0.01–1.1)	0.05
Age ≥ 80 years	2.5 (1.0–6.0)	0.04	1.8 (0.5–6.1)	0.3
<i>ASXL1</i> ^{MUT}	2.5 (1.1–5.8)	0.03	1.5 (0.6–3.8)	0.3
All <i>PHF6</i>^{MUT} myeloid neoplasms excluding chronic myelomonocytic leukemia; n = 127				
Complex/monosomal karyotype or chromosome 7 abnormalities	2.6 (1.4–4.8)	<0.01	2.5 (1.3–4.8)	<0.01
<i>PHF6</i> ^{MUT} variant allele fraction > 20%	2.1 (1.2–3.6)	<0.01	1.8 (1.1–3.1)	0.02
<i>U2AF1</i> ^{MUT}	1.9 (1.1–3.4)	0.02	1.9 (1.1–3.5)	0.02
Hemoglobin < 10 g/dL	1.8 (1.1–2.9)	0.03	1.6 (0.9–2.7)	0.07
<i>DNMT3A</i> ^{MUT}	1.9 (1.0–3.6)	0.04	1.8 (0.9–3.5)	0.09
<i>RUNX1</i> ^{MUT}	1.6 (0.98–2.6)	0.056	1.5 (0.9–2.6)	0.1
<i>PHF6</i>^{MUT} acute myeloid leukemia; n = 67				
Complex/monosomal karyotype or chromosome 7 abnormalities	2.1 (0.9–4.6)	0.05	1.9 (0.9–4.2)	0.1
<i>U2AF1</i> ^{MUT}	2.8 (1.0–7.5)	0.04	2.4 (0.9–6.6)	0.09
Hemoglobin < 10 g/dL	1.5 (0.7–3.2)	0.3	1.4 (0.6–3.2)	0.3
<i>DNMT3A</i> ^{MUT}	1.5 (0.7–3.3)	0.2	1.7 (0.7–3.9)	0.2
<i>PHF6</i> ^{MUT} variant allele fraction > 20%	1.9 (0.8–4.4)	0.1	1.6 (0.6–3.8)	0.3
<i>PHF6</i>^{MUT} myelodysplastic syndrome; n = 36				
Complex/monosomal karyotype or chromosome 7 abnormalities	4.0 (1.0–15.5)	0.04	5.1 (1.2–20.9)	0.02
<i>PHF6</i> ^{MUT} variant allele fraction > 20%	2.6 (1.0–6.9)	0.04	3.0 (1.1–8.1)	0.02
Hemoglobin < 10 g/dL	2.2 (0.9–5.6)	0.09	2.7 (1.0–7.2)	0.04
<i>DNMT3A</i> ^{MUT}	4.7 (1.0–21.3)	0.04	2.1 (0.2–21.9)	0.5
<i>U2AF1</i> ^{MUT}	1.9 (0.8–4.9)	0.1	1.9 (0.7–5.1)	0.1
<i>PHF6</i>^{MUT} myeloproliferative neoplasm; n = 16				
Complex/monosomal karyotype or chromosome 7 abnormalities				
Hemoglobin < 10 g/dL		0.4	1.9 (0.4–10.0)	0.4
<i>U2AF1</i> ^{MUT}	1.4 (0.2–11.9)	0.8	2.3 (0.2–29.0)	0.5
<i>PHF6</i> ^{MUT} variant allele fraction > 20%	1.0 (0.2–5.1)	0.9	1.1 (0.2–6.0)	0.9
<i>DNMT3A</i> ^{MUT}				
<i>PHF6</i>^{MUT} myelodysplastic / myeloproliferative neoplasm; n = 8				
Complex/monosomal karyotype or chromosome 7 abnormalities	1.7 (0.1–16.8)	0.6	0.9 (0.08–9.8)	0.9
<i>PHF6</i> ^{MUT} variant allele fraction > 20%		0.06		0.07
Hemoglobin < 10 g/dL	1.2 (0.2–8.2)	0.8	1.2 (0.2–8.7)	0.8
<i>DNMT3A</i> ^{MUT}				
<i>U2AF1</i> ^{MUT}	3.1 (0.3–34.8)	0.3	2.1 (0.2–23.7)	0.5
Blast transformation free survival analysis:				
<i>PHF6</i> mutated chronic myelomonocytic leukemia (CMML); n = 49				
Complex/monosomal karyotype or chromosome 7 abnormalities		<0.01		<0.01
<i>ASXL1</i> ^{MUT}		<0.01		<0.01

Table 3. continued

Variables:	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% Confidence interval)	p-value	Hazard ratio (95% Confidence interval)	p-value
All <i>PHF6</i>^{MUT} myeloid neoplasms excluding acute myeloid leukemia and CMML; n = 60				
Circulating blast >2%	6.0 (1.4–24.9)	0.01	5.9 (1.3–26.1)	0.01
Abnormal karyotype except isolated loss of Y chromosome	3.3 (1.1–10.3)	0.03	2.9 (0.9–9.2)	0.07
Female gender	2.9 (0.97–8.8)	0.05	2.3 (0.7–7.1)	0.1
<i>PHF6</i>^{MUT} myelodysplastic syndrome; n = 36				
Female gender	12.9 (1.4–116.5)	0.02	26.8 (1.9–368.3)	0.01
Abnormal karyotype except isolated loss of Y chromosome	2.6 (0.5–13.2)	0.2	7.4 (0.7–76.3)	0.09
Circulating blast >2%				
<i>PHF6</i>^{MUT} myeloproliferative neoplasm; n = 16				
Female gender		0.9		0.9
Abnormal karyotype except isolated loss of Y chromosome	4.0 (0.3–46.5)	0.2	5.1 (0.3–98.1)	0.2
Circulating blast >2%	9.4 (0.8–108.7)	0.07	8.4 (0.7–96.7)	0.08
<i>PHF6</i>^{MUT} myelodysplastic/ myeloproliferative neoplasm; n = 8				
Female gender	1.9 (0.2–23.6)	0.5		
Abnormal karyotype except isolated loss of Y chromosome		0.05		
Circulating blast >2%	0.9 (0.08–10.3)	0.9		

The bold values highlight the significant *p* values implying significance impact of the variable on survival.

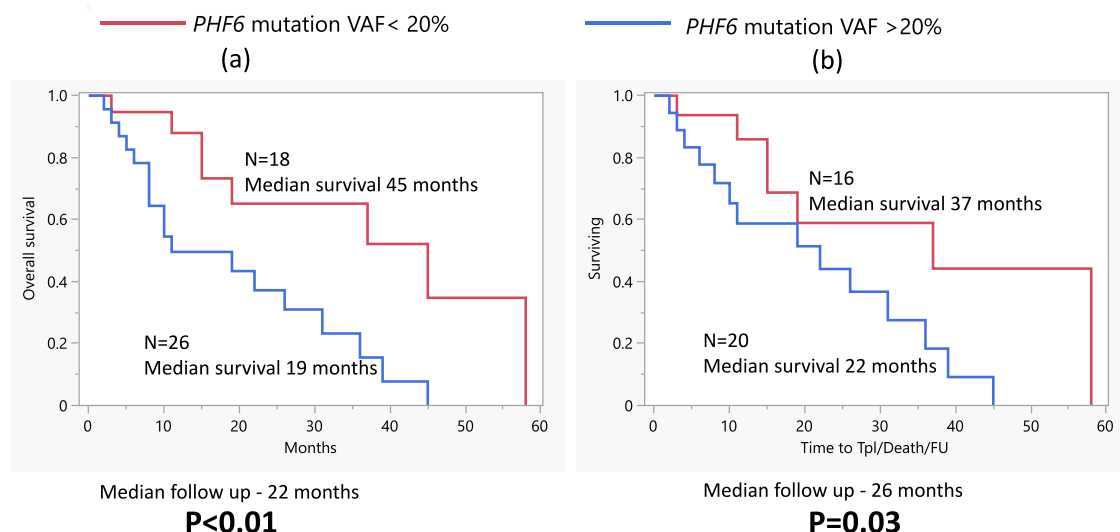


Fig. 3 Overall survival in (a) 44 patients with *PHF6* mutated myelodysplastic syndrome or myelodysplastic /myeloproliferative neoplasm, (b) 36 patients with *PHF6* mutated myelodysplastic syndrome stratified by *PHF6* mutation variant allele fraction (VAF). Kaplan-Meier curves illustrate inferior OS in patients with MDS or MDS/MPN in patients with *PHF6* mutation VAF more than 20% at diagnosis.

thrombocytopenia (ET) in 3; driver mutation distribution included *JAK2* in 68%, *CALR* 12%, and *MPL* 12%. MPN patients with *PHF6*^{MUT} were more likely to display concurrent *ASXL1*^{MUT} (63% vs. 36%, *p* = 0.04) and less likely to have a *MK/CK*/chromosome 7 abnormalities (0% vs. 14%, *p* = 0.03) or a *PHF6*^{MUT} VAF > 20% (37% vs 64%, *p* = 0.04). Among the 3 patients with ET, all were older with a median age of 79 years, none had a prior history of thrombosis, 2 had a *JAK2*^{MUT}, and 1 had *MPL*^{MUT} as the driver mutation. Interestingly, all 3 had concurrent *ASXL1*^{MUT} while 2 had a at least one known high-risk mutations [15] including *IDH2*^{MUT} and *TP53*^{MUT}. Dynamic

International Prognostic Scoring System (DIPSS) plus [16] categorized the patients with MF into intermediate-1 (*n* = 2, 15%), intermediate-2 (*n* = 6, 46%), and high (*n* = 5, 38%) risk groups. The median OS in patients with ET was 16 months like those with secondary MF (OS 17 months) and primary MF (OS 25 months, *p* = 0.3). No predictors of OS or BTFS could be identified due to small number of patients.

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Only eight patients were diagnosed with MDS/MPN, of these six were diagnosed with MDS/MPN, NOS and 2 with MDS/MPN with

thrombocytosis and SF3B1 mutation. In comparison to patients with other myeloid neoplasms they were more likely to have *SF3B1*^{MUT} (25% vs. 3%, $P = 0.02$), and *JAK2*^{MUT} (62% vs 11%, $p < 0.01$). The small number of informative cases did not allow statistically credible survival analysis but their inclusion with patients with MDS enhanced the prognostic impact of *PHF6*^{MUT} VAF > 20% (Fig. 3b).

Sequential *PHF6* mutational analysis

A repeat subsequent NGS was available in 50 patients, at a median interval of 14.5 months between the first and second NGS examination (range 1–200 months); on the second NGS testing, *PHF6*^{MUT} no longer detected in 22 (44%) patients and persisted in 28 (56%). In the former, 5 had received symptom directed therapy, 4 intensive chemotherapy, 5 low-intensity chemotherapy, 7 AHSCT, and one no treatment (Supplementary Table 2). Among the 28 patients with persistence of the mutation on repeat testing, *PHF6*^{MUT} VAF remained unchanged in 50% ($n = 14$), increased in 32% ($n = 9$, median increase 36%, range 6–60%) and decreased in 20% ($n = 5$, median decrease of 9% range 1–96%).

Post-transplant survival

A total of 44 patients underwent AHSCT including 23 with AML, 10 with CMML, 6 with MDS, 2 with MDS/MPN, and 3 with MPN; median post-transplant survival considering all 44 patients was 46 months with 3/5-year survival rate of 55%/42%. Post-transplant survival was not affected by *PHF6* VAF ($p = 0.7$) or morphologic subcategory ($p = 0.35$) with medians at 60 months for AML, 46 months for CMML, “not reached” for either MDS or MPN, and 6.5 months for MDS/MPN. Post-transplant survival was favorably affected by *ASXL1* mutation ($N = 11$; median not reached vs. 38 months in patients with wild-type *ASXL1* ($n = 33$); HR 0.13, 95% CI 0.02–1.0; $p = 0.05$).

DISCUSSION

Several observational studies have explored the clinical and prognostic correlations of *PHF6*^{MUT} in myeloid malignancies, with inconsistent observations [6–10, 17, 18]. Similarly, laboratory studies on *PHF6*^{MUT} have yielded conflicting results; knockdown mouse models have demonstrated both a tumor suppressor and an oncogenic effect of the mutation in hematological neoplasms [19–21]; suggesting a complex cell lineage and co-mutational context dependent action of the mutation [7, 20]. Kubota et al. conducted a comprehensive proteomic analysis of *PHF6* protein and reported a significant functional interaction with *RUNX1* [9]. Both co-localize to active enhancer regions and influence lineage differentiation of hematopoietic cells [9]. Another study demonstrated reduced recruitment of methyltransferase *SUV39H1* to the nucleolar region in cancer cells with *PHF6*^{MUT} that led to increased DNA transcription and proliferation. This mechanism was shown to be a potential therapeutic target to overcome cytarabine resistance [22]. However exact function and interaction with concurrent mutations remains unknown.

In the current study, the majority of the patients were males (76%), which is consistent with the described male predilection in *PHF6*-mutated neoplasms [1, 8, 9]. The observed differences in the laboratory parameters among the different disease groups were largely as expected from the underlying disease morphology; a notable exception was the higher hemoglobin levels seen in patients with CMML, similar to that reported in our recent publication [7]. Most patients had a normal karyotype; of interest, a higher-than-expected frequency of LoY occurred in the setting of CMML (16% vs. expected 6% [23]) and MDS (8% vs expected 2.5% [24]).

The PHD2 domain was the most frequently affected region across all myeloid neoplasms, consistent with previous reports [5, 7]. Nonsense and frameshift mutations were most the common mutation types. The site or type of mutation did not influence

prognosis in our patient cohort. Majority of the patients (96%) had at least one concurrent mutation in other myeloid genes, with 55% harboring 3 or more concurrent mutations, making it challenging in ascertaining mutation-specific prognostic impact. The co-mutation pattern was similar to previous reports with *TET2* [6, 7], *ASXL1* [6, 7, 9], *RUNX1* [6, 7, 9], *SRSF2* [7], *U2AF1* [6, 7, 9], and *DNMT3A* [6, 7] mutations being frequent.

Other notable observations from the current study include a significantly superior OS and BTFS in patients with *PHF6*-mutated CMML vs. in those with other myeloid neoplasms harboring *PHF6*^{MUT}. In patients with *PHF6*-mutated CMML, the CPSS-Mol risk categorization failed to predict prognosis, mandating the consideration of the *PHF6* mutation in CMML risk scoring systems [7]. We have recently elaborated on the prognostic interaction of *PHF6*^{MUT} with other mutations [7], as also shown in the current study where univariate analysis showed a favorable impact of concurrent *NRAS*^{MUT}, contrary to the adverse risk attributed with it, in previous studies [12, 25, 26].

In the current study, most patients with *PHF6*^{MUT} AML were stratified into the ELN adverse risk category (71%), with an observed median survival of 13 months vs. expected at 9 months [27]. In ELN intermediate-risk group, the observed OS was 44 months vs. expected at 16 months [27]. The frequency of *RUNX1*^{MUT} co-mutation was higher in the setting of AML [9], as previously described but, unlike the latter, the current study did not show a significant impact on prognosis. On the other hand, the favorable impact of *NPM1* mutations in AML was also recognized in the current study, in the setting of *PHF6*^{MUT}.

Another novel finding in the current study was the significant associations between *PHF6*^{MUT} VAF > 20% and inferior OS and female gender and inferior BTFS, in patients with MDS. The IPSS-R risk model performed as expected in our MDS patients with *PHF6*^{MUT}, for the risk categories of very low, intermediate, high, and very high; OS in *PHF6*^{MUT} MDS vs. expected OS, in months, were not reached vs. 90 in very low-risk [28], 36 vs. 34 intermediate [28], 19 vs. 21 high [28], and 10 vs. 13 very high-risk groups [28]. However, in patients categorized as having low-risk MDS, the observed median OS of 19 months was substantially shorter than the expected estimate at 54 months [28]. The apparent discrepancy might be partly attributed to the higher frequency of *SRSF2*^{MUT} in our cohort of *PHF6*-mutated low-risk MDS (40% vs. 4%) [29, 30]. Also, the inferior BTFS noted in female patients with MDS, could potentially be related to increased prevalence of *DNMT3A*^{MUT} which is known for its adverse prognostic impact [31].

Finally, we were encouraged by the favorable post-transplant outcome of our patients with *PHF6*-mutated myeloid neoplasms, irrespective of morphologic subcategory or *PHF6* VAF. Additional key observations from the current study, including the favorable prognostic impact in CMML which can help guide transplant decisions in these patients [7], the unique association with isolated LoY in the setting of CMML and MDS, the association between *PHF6* VAF > 20% and inferior survival in MDS all require additional studies for confirmation.

DATA AVAILABILITY

Aggregated data available by request. Patient-level data will not be shared. Please contact Ayalew Tefferi, MD for data: tefferi.ayalew@mayo.edu.

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AUTHOR CONTRIBUTIONS

All authors reviewed the final manuscript draft and approved its content. AT, SF, NG, AAS, and RH initiated the concept and study design and participated in data collection and data analysis; AT, SF, AAM, KHB, AP, NG, and AAS provided patient care; KKR, RH, and CZM provided pathology expertise and participated in the interpretation of mutation and cytogenetic reports; AT, and SF analyzed the data and wrote the paper.

COMPETING INTERESTS

SF: Nothing to disclose; AAS: Nothing to disclose; KHB: Nothing to disclose; AAM: Nothing to disclose; AP: Nothing to disclose; KKR: Nothing to disclose; RH: Nothing to disclose; CZM: Nothing to disclose; NG: Advisory board to DISC Medicine and Agios; AT: Nothing to disclose.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Institutional Review Board of the Mayo Clinic (IRB protocol number: 12-003574). All methods were performed in accordance with the Declaration of Helsinki, the relevant guidelines, and regulations.

ADDITIONAL INFORMATION

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