RESEARCH LETTER

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TO THE EDITOR:

Black African-American patients with primary myelofibrosis: a comparative analysis of phenotype and survival

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Racial and ethnic disparities have been documented in patients with acute myeloid leukemia through population-based surveillance, epidemiology, and end results studies in which Black patients with acute myeloid leukemia were shown to have a 12% increased risk of death compared with White patients, despite favorable cytogenetics and younger age.[1] The phenotypic or prognostic impact of the Black race on primary myelofibrosis (PMF) has not been adequately addressed.[2] In a surveillance, epidemiology, and end results–Medicare database analysis of 3364 patients with myeloproliferative neoplasms (MPNs), which included 10% non-White patients with PMF, showed that survival in Black patients, compared with their non-Black counterparts, was inferior in the setting of essential thrombocythemia and polycythemia vera but not PMF.[3] A single institution retrospective study on outcome disparities in Caucasian vs non-Caucasian patients with MPN (n = 127, PMF, n = 22, non-Caucasians with PMF, n = 11), reported an increased risk of vascular complications in non-Caucasian patients with polycythemia vera and essential thrombocythemia; however, the overall survival was similar in Caucasian and non-Caucasian patients.[4] In another study of 300 patients with MPN, including 14 non-White patients with PMF, survival was found to be inferior in non-White compared with White patients.[5] The objectives of this study were (i) to define the clinical phenotype and genotype of Black African-American (AA) patients with PMF, and (ii) to determine the long-term survival outcomes of AA patients, in comparison with their non-AA counterparts.

This multicenter study included 88 consecutive AA patients with PMF evaluated at the Mayo Clinic, Rochester MN (n = 46), Moffitt Cancer Center, Tampa, FL (n = 34), and Montefiore Medical Center, Bronx, NY (n = 8) between March 1998 and March 2022. The study patients were retrospectively recruited after institutional review board approval, with follow-ups updated in October 2022. A previously published Mayo Clinic cohort of 1266 non-Black patients with PMF (95% Caucasian) was used for comparison of phenotype and survival.[6] Race has been self-reported in the current study. The diagnosis of PMF was based on conventional criteria.[7] Screening for *JAK2*, *MPL*, and *CALR* mutations and next generation sequencing were performed in a subset of patients.[8] The dynamic international prognostic scoring system (DIPSS), DIPSS-plus, mutation enhanced international prognostic score MIPSS-70 plus version 2.0 risk stratification, and unfavorable karyotype categorization were used, as previously described.[9-12] All statistical analyses considered clinical and laboratory variables obtained at the time of diagnosis. Conventional statistical methods were applied to compare clinical characteristics and survival analysis. Survival was calculated from the time of diagnosis to the last follow-up or death. JMP Pro 16.0.0 software package (SAS Institute, Cary, NC) was used for statistical analysis.

A total of 88 AA patients with PMF (median age 61 years; range, 19-86; 52% female) were studied. Driver mutation information was available for 63 patients and included *JAK2* 68%, *CALR* 19% (type

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Data are available on request from the corresponding author, Naseema Gangat (gangat.naseema@mayo.edu).

Table 1. Comparison of clinical and laboratory characteristics at diagnosis for 1354 patients with PMF stratified based on race (Black AA vs non-AA)

Variables	Black AA patients with PMF n = 88	Non-AA patients with PMF n = 1266	*P*-value
Age in y, median (range)	61 (19-86)	65 (19-92)	**.02**
Male, n (%)	42 (48)	792 (63)	**< .01**
Driver mutation, n (%)	n = 63	n = 853	
JAK2	43 (68)	573 (67)	.74
CALR	12 (19)	169 (20)	
MPL	5 (8)	47 (6)	
Triple negative	3 (5)	64 (8)	
Type 1/like *CALR* vs others	9 (14)	136 (16)	.84
Mutations on NGS, n (%)			
TP53	1 of 34 (3)	13 of 159 (8)	.24
TET2	7 of 34 (21)	7 of 49 (14)	.45
ASXL1	8 of 34 (24)	181 of 488 (37)	.10
IDH1	0 of 34 (0)	7 of 357 (2)	.26
IDH2	0 of 34 (0)	12 of 359 (3)	.14
RUNX1	3 of 34 (9)	7 of 218 (3)	.17
N/KRAS	3 of 34 (9)	6 of 159 (4)	.24
SRSF2	5 of 34 (15)	72 of 511 (14)	.92
EZH2	1 of 34 (3)	17 of 447 (4)	.79
U2AF1	4 of 34 (12)	78 of 495 (16)	.52
Palpable splenomegaly, n (%)	37 of 86 (43)	343 of 1233 (28)	**< .01**
Transfusion-dependent, n (%)	55 (63)	854 (68)	.33
Constitutional symptoms, n (%)	55 (63)	899 (71)	.10
Arterial thrombosis at or before diagnosis, n (%)	2 (2)	134 (11)	**< .01**
Venous thrombosis at or before diagnosis, n (%)	6 (7)	91 (7)	.89
Arterial thrombosis after diagnosis, n (%)	3 (3)	68 (5)	.39
Venous thrombosis after diagnosis, n (%)	9 (10)	70 (6)	.10
Hemoglobin, g/dL, median (range)	10.1 (4.8-15.5)	10.2 (3.8-17.5)	.10
Leukocyte count × 10^9/L, median (range)	8.4 (0.9-81)	8.8 (0.8-236)	.36
Platelet count × 10^9/L, median (range)	256 (13-1193)	230 (6-2400)	.54
Circulating blasts %, median (range)	0.6 (0-15)	0 (0-18)	.28
Lactate dehydrogenase (LDH), U/L, median (range)	n = 61 493 (136-2910)	n = 995 498 (83-2530)	.28
Karyotype, n (%)	n = 70	n = 977	.21
Favorable	56 (80)	716 (73)	
Unfavorable	14 (20)	261 (27)	
DIPSS risk, n (%)	n = 88	n = 1256	**< .01**
Low	13 (15)	186 (15)	
Intermediate-1	47 (53)	462 (37)	
Intermediate-2	26 (30)	497 (40)	
High	2 (2)	111 (9)	
DIPSS plus risk, n (%)	n = 70	n = 1235	**< .01**
Low	10 (14)	150 (12)	
Intermediate-1	18 (26)	211 (17)	
Intermediate-2	32 (46)	463 (37)	
High	10 (14)	411 (33)	
Follow-up in y, median (range)	3.2 (0.1-18.6)	3.2 (0.1-30.9)	.95

95% of the cohort were of Caucasian race. Significant *P* values are in bold.
ASCT, allogeneic stem cell transplant; DIPSS, dynamic international prognostic scoring system; NGS, next generation sequencing.

Table 1 (continued)

Variables	Black AA patients with PMF n = 88	Non-AA patients with PMF n = 1266	*P*-value
Leukemic transformation n (%)	12 (14)	117 (9)	.20
ASCT, n (%)	9 (10)	67 (5)	.08

95% of the cohort were of Caucasian race. Significant *P* values are in bold.
ASCT, allogeneic stem cell transplant; DIPSS, dynamic international prognostic scoring system; NGS, next generation sequencing.

1/like *CALR*, 14%), *MPL* 8%, and triple negative 5%. Other mutations included *ASXL1* in 8 of 34 (24%), *SRSF2* in 5 of 34 (15%), and *U2AF1* in 4 of 34 (12%) evaluable patients. The karyotype was favorable in 56 of 70 (80%), unfavorable in 14%, and very high risk in 6% of the evaluable patients. The DIPSS risk distribution in the evaluable patients was low (15%), intermediate-1 (53%), intermediate-2 (30%), and high (2%). The DIPSS-plus risk distribution (n = 70) was low (14%), intermediate-1 (26%), intermediate-2 (46%), and high (14%). Mutation enhanced international prognostic score MIPSS-70 plus version 2.0 risk distribution in evaluable patients (n = 34), was very low (12%), low (18%), intermediate (24%), high (38%), and very high (9%). At the time of presentation, 43%, 63%, and 63% of AA patients demonstrated palpable splenomegaly, transfusion-dependent anemia, and constitutional symptoms, respectively. AA patients with PMF, in comparison with their non-AA counterparts, were more likely to be younger (median age, 61 vs 65 years; $P = .02$), female (52% vs 37%; $P < .01$), displaying palpable splenomegaly (43% vs 28%; $P < .01$), and belonging to the DIPSS and DIPSS-plus low/intermediate-1 risk categories (68% vs 52% and 40% vs 29%; $P < .01$). In addition, a lower incidence of arterial thrombosis at or before diagnosis was observed in AA patients (2% vs 11%; $P < .01$), which was accounted for by the younger age distribution of the AA cohort (age-adjusted $P = .13$). In contrast, the driver mutation profile and karyotype risk distribution were similar between AA and non-AA patients ($P > .1$); notably, there was a trend toward a lower incidence of *ASXL1* mutations in AA patients (24% vs 37%; $P = .1$). Table 1 provides a comparative analysis of the clinical and laboratory characteristics at diagnosis of AA vs non-AA patients with PMF.

Treatment details were available for 70 (80%) AA patients and included hydroxyurea (n = 31), ruxolitinib (n = 28), erythropoiesis stimulating agents (n = 21), thalidomide (n = 11), lenalidomide (n = 10), danazol (n = 6), interferon (n = 5), and fedratinib (n = 2). Ruxolitinib was administered for a median of 18 months (range, 0.02-197 months) and resulted in spleen and/or symptom response in 16 of 28 (57%) patients, with treatment-emergent anemia observed in 8 (29%) patients. Spleen response was documented in both patients who were treated with fedratinib. A total of 10 (11%) AA patients were enrolled in clinical trials with JAK2 inhibitors (n = 4), pomalidomide (n = 3), imetelstat (n = 2), and navitoclax (n = 1) compared with 241 (19%) of non-AA patients ($P = .06$).

At median follow-up of 3.2 years (0.1-18.6 years) for AA patients, 49 (56%) deaths and 12 (14%) leukemic transformations were recorded. The corresponding figures for non-AA patients at a median follow-up of 3.2 years (range, 0.1-30.9 years) were 887 (70%) deaths and 117 (9%) leukemic transformations. The median overall survival for AA patients was 4.8 years with 3, 5, or 10-year survival rates of 55%, 32%, or 14%, respectively, which were not significantly different from those of their non-AA counterparts (median 4.4 years; $P = .12$; Figure 1). In univariate analysis, survival in AA patients was adversely affected by DIPPS-plus intermediate-2/high risk (median, 4.3 vs 13.2 years; $P < .01$), absence of type 1/like *CALR* mutation (4.2 years vs not reached; $P = .02$), and presence of *ASXL1/SRSF2* mutations (3.4 years vs not reached; $P = .14$). Multivariable analysis, which included race as a variable, confirmed the unfavorable prognostic impact of DIPPS-plus intermediate-2/high risk ($P < .01$; hazard ratio [HR], 2.9), absence of type 1/like *CALR* mutation ($P < .01$; HR, 2.1), and presence of *ASXL1* ($P = .03$; HR, 1.3) and *SRSF2* mutations ($P < .01$; HR, 1.5); race did not have an independent impact on survival ($P = .73$). Allogeneic stem cell transplant (ASCT) was performed in 9 (10%) and 67 (5%) AA and non-AA patients, respectively ($P = .08$). All patients who received transplants had DIPSS-plus intermediate-2/high risk at the time of ASCT. Details on ASCT were available for 63 patients, and donor sources included haploidentical or mismatched, matched unrelated, and matched related in 4 (44%), 3 (33%), and 2 (22%) AA patients (n = 9), and 4 (7%), 25 (46%), and 25 (46%) for non-AA patients (n = 54), respectively ($P = .03$). Posttransplant survival was inferior in AA compared with non-AA patients (median 1.3 years vs 11.3 years; $P = .01$) (Figure 1B) and remained so when analysis was adjusted for age ($P = .02$), karyotype ($P = .02$), type 1/like *CALR* mutation ($P = .01$), and donor source ($P = .02$). Posttransplant relapse was documented in 4 of 9 (44%) AA patients vs in 10 of 67 (15%) non-AA patients ($P = .05$). In contrast, the incidence of graft-versus-host disease (GVHD) was similar between AA and non-AA patients (4 of 9 [44%] vs 41 of 67 [61%]; $P = .34$). Causes of death among AA patients who received transplants included disease relapse (n = 3), GVHD (n = 2), or sepsis (n = 1).

To our knowledge, this study is the first to describe the clinical phenotype, genotype, and outcomes of AA patients with PMF and compare them with those of their non-AA counterparts. At presentation, AA patients were younger, predominantly female, and more likely to belong to the DIPSS-plus lower risk category. In contrast, driver and other mutation distributions were similar between the AA and non-AA cohorts, albeit with a slightly lower prevalence of *ASXL1* mutations in AA patients. The higher rates of transplants in AA patients are likely a reflection of referral bias to a tertiary center. The overall survival was similar between AA and non-AA patients. On the other hand, posttransplant outcomes were inferior in the AA cohort, likely because of differences in donor sources with significantly greater use of haploidentical or mismatched transplants in AA patients. Moreover, we observed higher posttransplant relapse rates in AA patients. In our study, a limited number of AA patients underwent ASCT, which precludes definitive conclusions; however, it serves to highlight the impact of racial disparities on donor availability.[13] The limitations of this study include the comparison of a multicenter AA cohort with a single institution non-AA population, which has the potential for significant

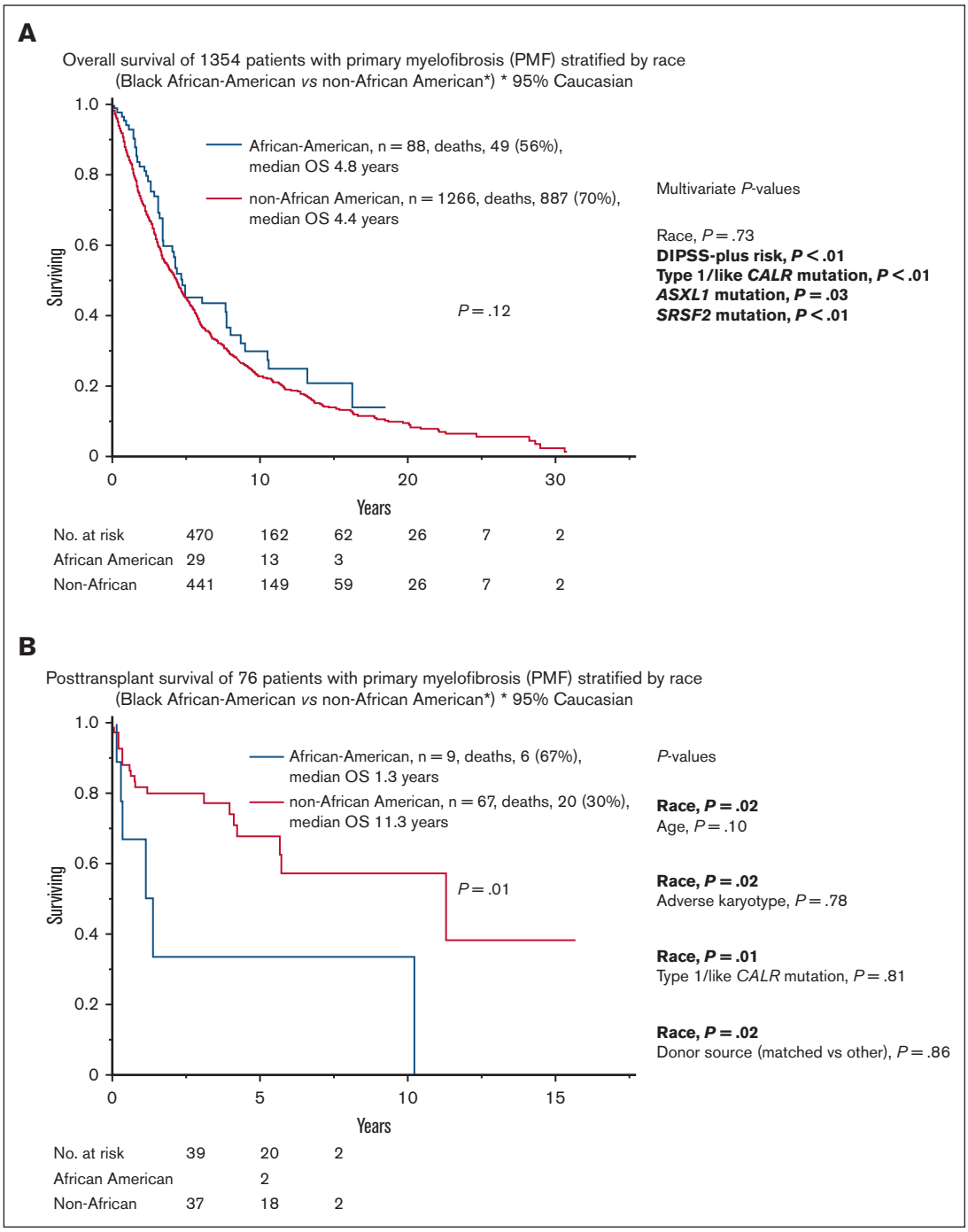

Figure 1. Comparison of overall survival and posttransplant survival of patients with primary myelofibrosis (PMF) stratified by race (Black African American vs non-African-American*). *95% Caucasian. (A) Overall survival of 1354 patients with PMF stratified based on race (Black AA vs non-AA [95% Caucasian]). (B) Posttransplant survival of 76 patients with PMF stratified based on race (Black AA vs non-AA [95% Caucasian]).

environmental confounders. Our findings require validation in a prospective series that includes AA patients evaluated at community and tertiary sites. Additional studies on race-related discrepancies in transplant outcomes with a focus on conditioning regimens, incidence of GVHD, and relapse are warranted

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