ORIGINAL RESEARCH REPORT

Does Race Play a Role in Complications and Outcomes of Philadelphia Chromosome-Negative Myeloproliferative Neoplasms?

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Abstract

Background: **Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) are a group of hematologic malignancies with known vascular complications. The role race and ethnicity play in these complications is less defined. We aimed to further evaluate the role of race in patients without a history of previous thrombotic or hemorrhagic events.**

Methods: **In this retrospective study, 300 adult patients with MPN were included; 270 (90.0%) were White and 30 (10.0%) were non-White. The non-White group primarily consisted of African American or Black (26 patients), followed by others. Median age at diagnosis was 58 years for White patients and 61.5 years for non-White patients. The interaction between outcomes and vascular events with race was evaluated using multivariate logistical regression models.**

Results: **The incidence of thrombotic events was inversely correlated with age at diagnosis, with younger patients demonstrating a higher rate of thrombotic events over time ($p < .001$). The incidence of thrombotic or hemorrhagic events did not differ between White and non-White patients. A statistically significant difference in median survival was observed between White and non-White patients: 29 years (95% confidence interval [CI]: 21.8—not reached) versus 13 years (95% CI: 5.7—22.7), respectively ($p = .016$).**

Conclusion: **This study did not find a significant difference in the rate of thrombotic or hemorrhagic events between White and non-White patients with MPN but suggested that non-White patients had significantly shorter median survival than White patients. Such observations may inform future studies to further characterize racial disparities in outcomes.**

Keywords: Essential thrombocythemia, Myelofibrosis, Polycythemia vera, Race, Vascular outcomes

1. Introduction

Philadelphia chromosome-negative myeloproliferative neoplasms (MPN)—essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF)—are a group of hematologic malignancies characterized by an overproduction of differentiated hematopoietic cells [1—3]. Previous studies have established the association of MPN with both thrombotic and hemorrhagic complications [4—11]. These vascular complications are associated with an increase in morbidity and mortality [4—7]. Thrombotic complications have been correlated with age greater than 60, elevated white blood cell count (WBC), *JAK2 V617F* mutation, and previous history of thrombosis [4—11]. Hemorrhagic complications noted in MPN are thought to be due to acquired von Willebrand factor insufficiency, thrombocytopenia secondary to bone marrow involvement, as well as antiplatelet and anticoagulant medications [4,12]. The timing of vascular complications in relation to diagnosis has not been well studied. A Swedish population-based study by Hultcrantz et al. [5] in 2018 reported higher

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odds of thrombosis at the time of MPN diagnosis, with the rate decreasing during the first year after diagnosis [5]. The MPN registry by the German Study Alliance Leukemia (SAL) similarly showed a higher risk of thrombosis at diagnosis [4]. Interestingly, this same German SAL-MPN study showed a higher risk of bleeding after diagnosis, reflecting MPN complications or treatments leading to hemorrhage [4]. Some studies looking at the vascular complications in Philadelphia chromosome-negative MPN have suggested a trend of disparity in outcomes among patients of different racial backgrounds [13]. The data in that arena remain limited. A single-institution retrospective study by Khan et al. [13] in 2016 suggested that non-Caucasian race was associated with increased risk of thrombotic and hemorrhagic events in patients with PV and ET. Our single-institution retrospective study aimed to further evaluate the role of race and sex in patients without a history of previous thrombotic or hemorrhagic events.

2. Materials and methods

This study looked at data from patients seen at Indiana University Simon Cancer Center from January 1992 to January 2019. The study was approved by the Indiana University Institutional Review Board. Patients were 18 years of age or older with a diagnosis of Philadelphia chromosome-negative MPN. Patients with a prior history of any thrombotic event or a hemorrhagic event requiring transfusion of at least 1 unit of packed red blood cells or requiring hospitalization were excluded. In total, 300 patients were included in the study.

Based on 2016 WHO classification of MPN, patients were grouped into PV, ET, or PMF. The study analyzed data based on initial diagnosis for each patient; therefore, in the occasional patient whose disease may have transformed along the course from ET or PV to PMF, the original diagnosis was considered. Patients within each category were further stratified by self-identification of race and ethnicity. The main categories were White and non-White with the latter comprising African American or Black, Middle Eastern, Asian, South Asian, and multiracial patients. Due to limitations in documentation in the electronic medical record, further stratification of ethnicities was unable to be preformed.

Other data obtained included patients' age, sex, family history of MPN, active smoking at time of diagnosis, diabetes history, hypertension history, medical insurance status, and the presence of constitutional symptoms at the time of diagnosis. Medical insurance status was considered as an element that could influence adequate and timely access to care. Further laboratory data was extracted with regard to WBC count, hemoglobin (Hgb) level, and platelet count at the time of diagnosis and at first thrombotic or hemorrhagic event. Erythropoietin level, marrow blast count, splenomegaly (defined by abdominal imaging or by physical exam), and data regarding disease-related genetic mutations were additionally collected.

The main clinical outcomes studied were thrombotic and hemorrhagic events. A hemorrhagic event was defined as a bleeding event requiring at least 1 unit of blood transfusion or immediate medical care including evaluation by a medical provider or hospitalization. Thrombotic events included microvascular or macrovascular thrombotic complications such as ischemic cerebrovascular accident, transient ischemic cerebrovascular attack, myocardial infarction, pulmonary embolism, deep vein thrombosis, abdominal thrombosis, peripheral arterial thrombosis, retinal vein occlusion, dural sinus thrombosis, or splenic infarct. Additionally, data on anticoagulation, antiplatelet therapy, cytoreductive therapy, transfusion therapy, or any other MPN-directed therapies were collected. Other outcomes considered were disease progression to myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), transformation to myelofibrosis, splenectomy, hematopoietic stem cell transplantation, and mortality.

2.1. Statistical analysis

Baseline characteristics, clinical features, and outcomes were summarized using frequency and percentages for categorical variables with median and range for continuous variables. The comparison between White and non-White was executed using chi-square test or Fisher exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Covariates of interest were analyzed to assess if there was an effect for target outcomes. Logistic regression was used to determine if covariates of interest had an impact on the incidence of thrombotic, hemorrhagic, or any event with all MPNs combined for this analysis. If more than one variable was found to be significant in the univariable analysis, a multivariable analysis was completed.

The Kaplan-Meier method was used for overall survival (time from diagnosis until death or censored at the time of last follow-up), time to thrombotic event, and time to hemorrhagic event stratified by race. A log-rank p value was used to

compare White versus non-White. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) with $p < .05$ indicating statistical significance.

3. Results

3.1. Patient characteristics

Of the total 300 patients studied, 270 (90%) were White and 30 (10%) were non-White (Table 1). The non-White subset consisted of 26 African American or Black (9%), two Middle Eastern (0.66%), one Asian (0.33%), one South Asian (0.33%), and no multiracial patients. Looking at each subtype of MPN, there were 101 PV, 105 ET, and 94 PMF patients. The average age at diagnosis was 58 years for White patients and 61.5 years for non-White patients within all types of MPN. Women comprised 57.4% of White and 46.7% of non-White patients. Among all patients, 98.3% were found to have medical insurance. No significant difference was found between White and non-White patients with regard to medical insurance coverage.

3.2. Clinical outcomes

In this cohort of 300 patients, we recorded a total of 104 unique vascular events in 91 patients, of which 73 were thrombotic while 31 were hemorrhagic. Characteristics of the total MPN cohort showed a statistically significant difference in platelet count at diagnosis between White and non-White patients (473×10^9/L vs. 618×10^9/L, respectively; $p = .026$). This was largely driven by the PMF cohort of patients. Hgb and WBC count at diagnosis were similar between races in all subtypes of MPN. No statistically significant difference was found regarding spleen size or constitutional symptoms at the time of diagnosis.

3.3. Thrombotic complications

Of the total thrombotic events, 50 were arterial while 23 were venous in nature. The status of antiplatelet therapy in three patients is unknown, but 21 of 70 patients (40%) were on antiplatelet agents at the time of first thrombotic event with no statistically significant difference between White and non-White patients (28.8% vs. 40%, respectively; $p = .26$). There was no significant difference in the incidence of thrombotic events between White and non-White patients ($p = .3$). Moreover, the length of time from diagnosis to first thrombotic event was not significantly different between White and non-White

Table 1. Clinical features and outcomes in myeloproliferative neoplasms (MPNs) stratified by race.

Variable label	PV ($N = 101$)			ET ($N = 105$)			PMF ($N = 94$)			All MPNs ($N = 300$)		
	Non-White	White	p	Non-White	White	p	Non-White	White	p	Non-White	White	p
	$N = 7$	$N = 94$		$N = 9$	$N = 96$		$N = 14$	$N = 80$		$N = 30$	$N = 270$	
Age at diagnosis (yr)	67 (20–76)	59 (24–88)	0.6931	41 (29–81)	53 (25–89)	0.5904	61.5 (46–86)	63 (33–92)	0.4634	61.5 (20–86)	58 (24–92)	0.4426
Sex (female)	4 (57.1)	54 (57.4)	0.99	3 (33.3)	64 (66.7)	0.0687	7 (50.0)	37 (46.3)	0.7953	14 (46.7)	155 (57.4)	0.2605
Race			NA			NA			NA			NA
White	0	94 (100)		0	96 (100)		0	80 (100)		0	270 (100)	
African American or Black	7 (100)	0		7 (77.8)	0		12 (85.7)	0		26 (86.7)	0	
Asian	0	0		0	0		1 (7.1)	0		1 (3.3)	0	
Middle Eastern	0	0		2 (22.2)	0		0	0		2 (6.7)	0	
South Asian	0	0		0	0		1 (7.1)	0		1 (3.3)	0	
Active smoker	1 (14.3)	15 (16)	0.99	2 (22.2)	14 (14.6)	0.6240	2 (14.3)	9 (11.3)	0.6661	5 (16.7)	38 (14.1)	0.7829
Diabetes	2 (28.6)	9 (9.6%)	0.1674	1 (11.1)	13 (13.5)	0.99	2 (14.3)	12 (15)	0.99	5 (16.7)	34 (12.6)	0.5653
Preexisting hypertension	4 (57.1)	41 (43.6)	0.6970	5 (55.6)	39 (40.6)	0.4865	7 (50)	37 (46.3)	0.7953	16 (53.3)	117 (43.3)	0.2956
Medical insurance coverage	7 (100)	90 (95.7)	0.99	9 (100)	96 (100)	NA		14 (100)	0.99	30 (100)	265 (98.1)	0.99
WBC at diagnosis	12.7 (7.5–26.5)	11.0 (3.8–107.5)	0.4262	7.8 (3.9–27)	10.0 (2.6–48)	0.0808	8.4 (1.9–137.3)	9.9 (0.7–252.8)	0.6517	8.5 (1.9–137.3)	10.2 (0.7–252.8)	0.6690

Hgb at diagnosis	16.3 (13.8−20.1)	16.2 (6.0−23)	0.4868	12.9 (9.6−18.3)	12.8 (6.9−18.5)	0.5631	10.4 (6.5−13.9)	10.6 (6.4−22)	0.7500	12.9 (6.5−20.1)	13.1 (6−23)	0.5323
PLT at diagnosis	604.0 (338−788)	429.5 (73−1300)	0.0907	959.0 (541−4173)	698.5 (109−2370)	0.0751	478.5 (70−1748)	249.5 (13−1036)	**0.0379**	618.0 (70−4173)	473.0 (13−2370)	**0.0256**
JAK2 V617F mutation	6 (85.7)	70 (88.6)	0.99	3 (37.5)	53 (67.9)	0.1207	7 (77.8)	31 (62)	0.4687	16 (66.7)	154 (74.4)	0.4161
CALR mutation	0	0	NA	0	4 (5.1)	0.99	1 (11.1)	5 (10.0)	0.99	1 (4.2)	9 (4.3)	0.99
Thrombotic event	1 (14.3)	26 (27.7)	0.6713	2 (22.2)	27 (28.1)	0.99	2 (14.3)	14 (17.5)	0.99	5 (16.7)	68 (25.2)	0.3023
Antiplatelet at thrombotic event			NA			NA			NA			0.2576
None	1 (100)	16 (61.5)		1 (50)	19 (70.4)		1 (50)	10 (71.4)		3 (60)	45 (67.2)	
Aspirin	0	7 (26.9)		0	3 (11.1)		0	2 (14.3)		0	12 (17.9)	
Anagrelide	0	0		1 (50)	3 (11.1)		0	1 (7.1)		1 (20)	4 (6)	
Two of the above	0	2 (7.7)		0	1 (3.7)		1 (50.0)	0		1 (20.0)	3 (4.5)	
Unknown	0	1 (3.8)		0	1 (3.7)		0	1 (7.1)		0	3 (4.5)	
Hydroxyurea at thrombosis	0	6 (22.2)	NA	0	5 (18.5)	NA	1 (50)	1 (7.1)	NA	1 (20)	12 (17.6)	NA
Hemorrhagic event	0	4 (4.3)	0.99	2 (22.2%)	14 (14.6)	0.6240	3 (21.4)	8 (10)	0.3605	5 (16.7)	26 (9.6)	0.2149
Antiplatelet at hemorrhagic event			Not done			Not done			Not done			0.99
None	0	2 (50)		2 (100)	8 (57.1)		1 (33.3)	4 (50)		3 (60)	14 (53.8)	
Aspirin	0	1 (25)		0	4 (28.6)		2 (66.7)	3 (37.5)		2 (40)	8 (30.8)	
Anagrelide	0	1 (25)		0	2 (14.3)		0	1 (12.5)		0	4 (15.4)	
Hydroxyurea at hemorrhagic event	0	1 (25)	NA	0	5 (35.7)	0.99	1 (33.3)	1 (12.5)	0.4909	1 (20)	7 (26.9)	0.99
Progression to AML/MDS	0	3 (3.2)	0.99	0	3 (3.1)	0.99	3 (21.4)	12 (15)	0.6915	3 (10)	18 (6.7)	0.4523
Progression to myelofibrosis	1 (14.3)	10 (10.6)	0.5656	2 (22.2)	22 (22.9)	0.99	0	3 (3.8%)	0.99	3 (10)	35 (13)	0.7798
Progression to myelodysplasia	0	2 (2.1)	0.99	0	1 (1)	0.99	0	0	NA	0	3 (1.1)	0.99
Death	1 (14.3)	10 (10.6)	0.2337	2 (22.2)	15 (15.6)	0.8017	5 (35.7)	18 (22.5)	0.5043	8 (26.7)	43 (15.9)	0.1608

Data are presented as *N* (%) or median (range).

AML = acute myeloid leukemia; ET = essential thrombocythemia; Hgb = hemoglobin; MDS = myelodysplastic syndrome; PLT = platelet; PMF = primary myelofibrosis; PV = polycythemia vera; WBC = white blood cell.

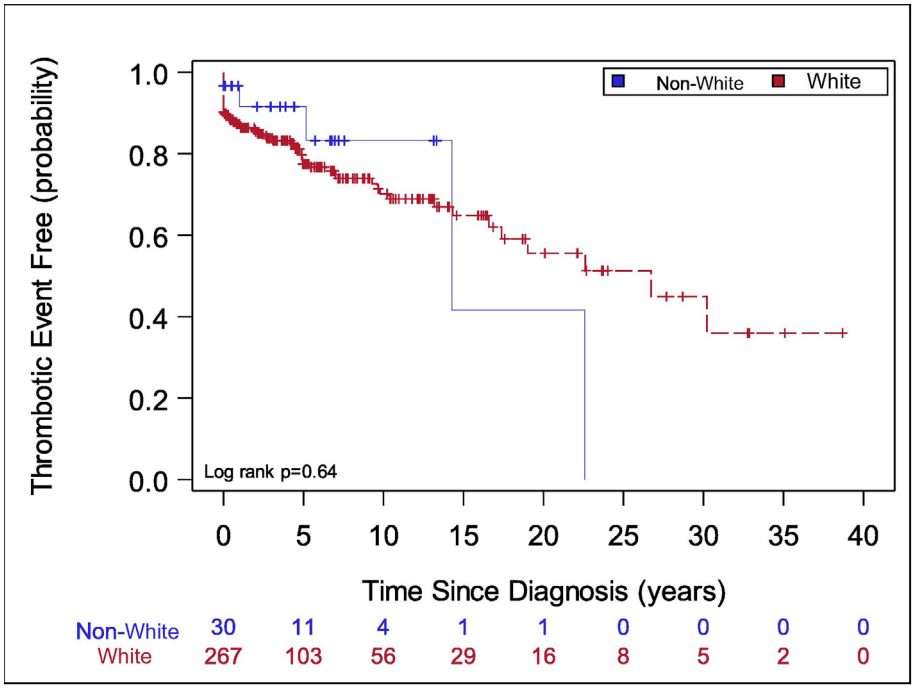

Fig. 1. Kaplan-Meier curve for time until thrombotic event by race.

patients for all MPNs ($p = .64$; Fig. 1) or any individual subtype. Among White patients who had an event of any type, thrombosis appeared to be more frequent than hemorrhage (82.9% vs. 31.7%, respectively), while for non-White patients, this proportion was equal (55.6% for both event types). Multivariable analysis which included age at diagnosis and hypertension revealed that the incidence of thrombotic events was correlated significantly with age at diagnosis ($p < .001$). Patients diagnosed at a younger age had a higher incidence of thrombotic events over time. When analysis was dichotomized at 60 years of age, patients younger than 60 years were more likely to have an incidence of a thrombotic event over time (odds ratio of 2.6). Using univariable analysis, patients with hypertension demonstrated lower incidence of thrombotic events (odds ratio of 0.57, $p = .048$), a finding that did not hold statistical significance when the above multivariable analysis was conducted. The study also found that patients with hypertension had a longer time to thrombosis than patients without hypertension (hazard ratio [HR]: 0.6, $p = .042$).

3.4. Hemorrhagic complications

A total of 31 hemorrhagic events were found among the study patients. Of 31 patients, 14 (45%) were on antiplatelet agents at the time of hemorrhagic event. Similar fraction of White (45.2%) and non-White (40%) patients were on antiplatelet agents. There was no significant difference in the incidence of hemorrhagic events between White and non-White patients ($p = .2$). The time from diagnosis to first hemorrhagic event appeared to be shorter in non-White patients but did not reach statistical significance ($p = .07$; Fig. 2). No significant correlation was found between hemorrhagic events and age or baseline hypertension. Although not statistically significant, incidence of hemorrhagic events appeared to have a correlation with Hgb at the time of diagnosis; a lower Hgb was associated with lower incidence of hemorrhagic events (odds ratio of 0.90, $p = .067$). A lower Hgb at diagnosis, however, was associated with shorter time to first hemorrhagic event (HR: 1.14, $p = .043$).

3.5. Progression of disease and mortality

Progression (from ET and PV) to myelofibrosis, MDS, and AML was similar between races without a statistically significant difference. When analyzing overall survival by race, the median survival time was 29 years (95% confidence interval [CI]: 21.8–Not reached) for White patients and 13 years (95% CI: 5.7–22.7) for non-White patients ($p = .016$; Fig. 3). Among patients who had any event, a larger proportion of non-White patients (44.4%) died compared with White patients (20.7%); however, the difference did not reach statistical significance ($p = .08$).

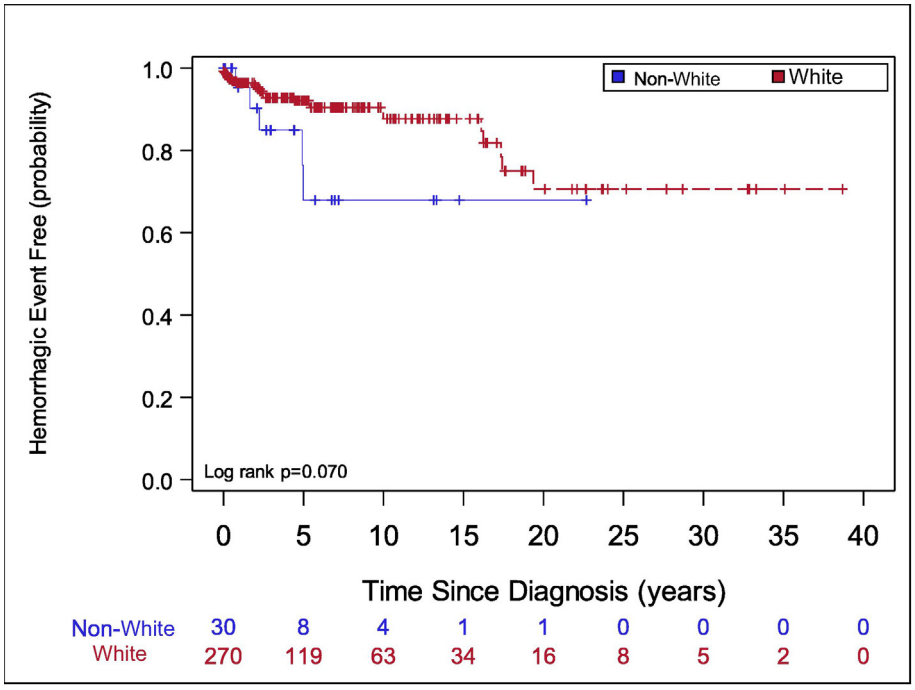

Fig. 2. Kaplan-Meier curve for time until hemorrhagic event by race.

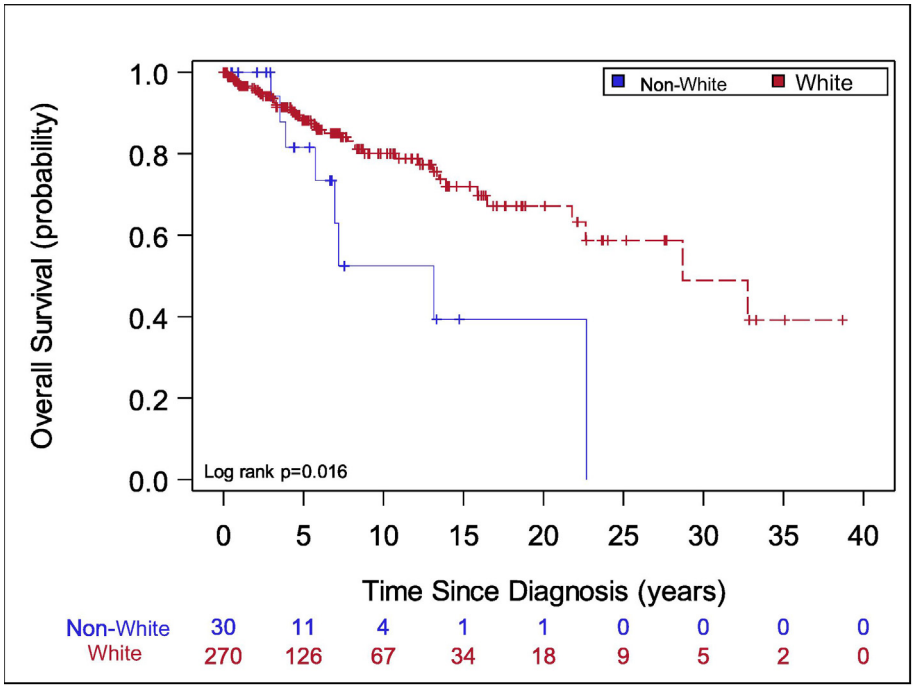

Fig. 3. Kaplan-Meier curve for overall survival by race.

4. Discussion

Vascular—thrombotic and hemorrhagic—complications in Philadelphia chromosome-negative MPN have been well studied. The role of racial influence on such complications has not been systematically addressed. Our study investigated possible associations between race and incidence of vascular complications or other clinical outcomes in MPN. Regardless of race, studied patients had equal access to medical care.

In the cohort of 300, patients diagnosed with MPN without a preceding thrombotic or hemorrhagic event at a younger age demonstrated a higher incidence of thrombotic events than patients diagnosed with MPN at an older age. Such correlation held valid when we dichotomized the cohort into age groups below and above 60 years. A possible explanation is that younger patients naturally have longer exposure to the detrimental effects of MPN or perhaps demonstrate a more aggressive disease over time [14]. This finding is contradictory to some previous studies stating younger patients with MPN are thought to have a lower risk of thrombosis [7,8,15]. In fact, additional studies have shown that MPN diagnosis at a younger age leads to a higher chance of cardiovascular and cerebrovascular disease and subsequent mortality [14,16,17].

Contrary to the study by Khan et al. [13], we did not find a statistically significant association between race and incidence of hemorrhagic or thrombotic events in PV and ET patients, or all MPNs together ($p = .35$, $p = .55$, $p = .99$, respectively). Our findings showed potentially shorter time from diagnosis to the first hemorrhagic event in non-White patients when compared with White patients, a difference that did not reach statistical significance ($p = .07$). In our study, 28.4% of White and 20% of non-White patients were taking antiplatelet agents at the time of first event ($p = .26$). Khan et al. [13] did not report regarding the number of patients with an event on antiplatelet therapy but among all patients in that study. In their study, there appears to be a higher fraction of Caucasians (70%) on aspirin than non-Caucasians (55%), although the difference did not reach statistical significance ($p = .07$). Moreover, an important distinction between the studies is that Khan et al. [13] included patients with a history of hemorrhagic or thrombotic events prior to diagnosis of MPN, whereas we excluded such patients. These patients were excluded since they would be at higher risk of another vascular event, while we intended to capture events most attributable to MPN.

The significant difference in median overall survival between White and non-White patients in our study is an important finding; White patients lived significantly longer than non-White patients (29 years vs. 13 years, respectively). This finding indicates that there is potential for race-related differences in long-term outcomes of MPN patients. As it is difficult to ascertain true association in a retrospective study, this finding illuminates the following questions: (a) Are there race-related social disparities and higher susceptibilities contributing to more advanced disease? (b) Do non-White patients avoid seeking medical attention in earlier phases of their disease when they are less symptomatic due to a mistrust in the medical community? (c) Are non-White patients less likely to be referred to tertiary academic centers? Furthermore, our data do not suggest an association between the shorter survival in non-White patients and vascular events. The time from diagnosis to first hemorrhagic event appeared to be shorter in non-White patients ($p = .07$)—an observed trend that cannot easily explain the significant difference in median survival between the races.

Interestingly, we found in this study that a history of hypertension at the time of diagnosis of MPN was associated with longer time to thrombotic events regardless of race (HR: 0.6, $p = .042$). Possible explanations could be potential protective effect of antihypertensive medications or preventive benefit of stricter blood pressure control. We also found that patients with a lower Hgb level at diagnosis had a shorter time to first hemorrhagic event (HR: 1.14, $p = .043$). This finding may be explained by the severity of disease in patients who are more anemic at presentation.

Lastly, our data demonstrated that in White patients with any event, thrombosis was more frequent than hemorrhage (82.9% vs. 31.7%, respectively). However, in our non-White patients with any event, rates of both hemorrhagic and thrombotic events were similar (55.6%). Similar rates of antiplatelet use were noted at the time of vascular complications. The data for our cohort of White patients was consistent with a recent meta-analysis demonstrating higher events of thrombosis than hemorrhage in MPN patients [12]. However, it should be noted that this meta-analysis did not document race, making it difficult to derive firm conclusions on the impact that race may have on vascular complications.

One limitation of our study was that the majority of the patients in our cohort were White. Among non-White patients, the most common race was African American or Black. Thus, the results may be generalizable to the African-American or Black population but not necessarily other races or ethnicities. Additionally, our patients represent the general population in the state of Indiana due to our referral base in a single-center and single-state experience. Our cohort populations are supported by the most recent census of 2010, which reports that White individuals comprised 85% of the population within the state of Indiana, African American or Black individuals represented 10%, and Asian individuals represented 2% [18]. Despite similar demographics to the census in our study,

under-representation of minorities in MPN reports has been evident since being brought to light by Modan [19] when investigating the prevalence of PV in the greater Baltimore metropolitan region. This initial report from Modan [19] showing lower rates of PV in the non-White subgroup was again noted in recent studies looking at epidemiological report in the United States from 2001 to 2012 [20]. The consistently lower prevalence of MPN in the non-White subset reiterates the question of inherent disparities or more challenging access to care and lower likelihood of referral and diagnosis.

5. Conclusion

In this single-institution retrospective study, we did not find a statistically significant difference in the rate of vascular complications between White and non-White patients with Philadelphia chromosome-negative MPN. However, the study demonstrated a significantly longer survival in the White cohort. Although our study had limitations with the size of the non-White cohort, such observations may inform future studies to further characterize disparities in outcomes at the socioeconomic level. Future efforts should focus on multicenter collaborations to evaluate the possible role of race or ethnicity in complications and outcomes of patients with MPN and to investigate the underlying causes of any potentialdisparities.

Ethics approval

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee of Indiana University approved this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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