Original Study

Elevated White Blood Cell Levels and Thrombotic Events in Patients With Polycythemia Vera: A Real-World Analysis of Veterans Health Administration Data

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Abstract

Patients with polycythemia vera (PV) have a substantial risk of thrombotic events (TEs). In the present retrospective analysis using Veterans Health Administration claims data, 25% of 1565 patients experienced a TE during follow-up. We observed a positive, significant association between white blood cell (WBC) counts ≥ 8.5 × 10^9/L and TE occurrence (reference, WBC count < 7.0 × 10^9/L), supporting continued inclusion of WBC count control in disease management.

Background: Patients with polycythemia vera (PV) have a substantial risk of thrombotic events (TEs). The objective of the present analysis was to describe the association between white blood cell (WBC) levels and occurrence of TEs among patients with PV from a large real-world population. **Patients and Methods:** The present retrospective analysis using Veterans Health Administration claims data (October 1, 2005, to September 30, 2012) evaluated adult patients assigned to 4 WBC count categories (WBC count < 7.0, 7.0-8.4, 8.5 to < 11.0, and ≥ 11.0 × 10^9/L) to compare the risk of TEs (reference, WBC count, < 7.0 × 10^9/L group). Analysis was performed using a Cox proportional hazards model, considering WBC status as a time-dependent covariate. **Results:** Of the 1565 patients with PV included in the present analysis, the WBC count was < 7.0 × 10^9/L for 428 (27.3%), 7.0 to 8.4 × 10^9/L for 375 (24.0%), 8.5 to < 11.0 × 10^9/L for 284 (18.1%), and ≥ 11.0 × 10^9/L for 478 (30.5%). Of the 1565 patients, 390 (24.9%) had experienced a TE during the study period. The mean follow-up ranged from 3.6 to 4.5 years. Compared with the reference group (WBC count < 7.0 ×10^9/L), the hazard ratio for TEs was 1.10 (95% confidence interval [CI], 0.82-1.48; $P = .5395$), 1.47 (95% CI, 1.10-1.96; $P = .0097$), and 1.87 (95% CI, 1.44-2.43; $P < .0001$) for patients with a WBC count of 7.0 to 8.4, 8.5 to < 11.0, and ≥ 11.0 ×10^9/L, respectively. **Conclusion:** A positive, significant association between an increased WBC count of ≥ 8.5 ×10^9/L and the occurrence of TEs was observed in patients with PV. The potential thrombogenic role of WBCs in patients with PV supports the continued inclusion of WBC count control in disease management and evaluation of the response to therapy.

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Introduction

The primary treatment goals for patients with polycythemia vera (PV) have focused on the prevention or management of thrombotic and bleeding complications.[1] Arterial and venous thrombotic events (TEs) represent a substantial source of morbidity and mortality for patients with PV.[2] Leukocytosis has been linked to an elevated risk of vascular events in the real-world ECLAP (European collaboration on low-dose aspirin in PV) observational study.[3] This finding was

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confirmed in a post hoc subanalysis of the prospective, randomized CYTO-PV (cytoreductive therapy in polycythemia vera) study, which demonstrated a significant correlation between an elevated white blood cell (WBC) count ($\geq 11 \times 10^9$/L) and time-dependent risk of major thrombosis (hazard ratio, 3.9; 95% confidence interval [CI], 1.24-12.3).[4]

The objective of the present analysis was to describe the association between the WBC counts and the occurrence of TEs among patients with PV from a large real-world population using data from the US Veterans Health Administration (VHA). The VHA is the largest integrated healthcare system in the United States, with > 9 million enrollees and longitudinal tracking of patient care.

Patients and Methods

Study Design

This was a retrospective, observational study of longitudinal data from the VHA claims database collected from October 1, 2005, to September 30, 2012 (Figure 1). The data set included de-identified patient-level data from 21 Veterans Integrated Service Networks linking inpatient, outpatient, pharmacy, laboratory, enrollment, and vital sign databases. The present analysis complied with the Health Insurance Portability and Accountability Act of 1996 and its implementing regulations (Health Insurance Portability and Accountability Act Privacy and Security Rules) for the use of de-identified patient data.

Patients

Adult patients were included in the analysis if they had ≥ 2 claims for PV (*International Classification of Diseases, Clinical Modification* [ICD-9-CM], code 238.4) ≥ 30 days apart during the identification period (October 1, 2006, through September 30, 2007). Additional inclusion criteria were patient age ≥ 18 years at the first PV diagnosis claim (index date), continuous health plan enrollment with medical and pharmacy benefits for ≥ 12 months before the index date, and ≥ 3 WBC counts annually on average during the follow-up period. For patients with a TE, ≥ 1 WBC count before the TE was required. If no WBC count had been reported before the first TE, the patient was excluded from the analysis. Patients were also excluded from the main analysis if they had experienced a TE before the index date. The follow-up period began on the index date (date of the first PV diagnosis claim) and ended at death, disenrollment, or the end of the study period, whichever occurred first.

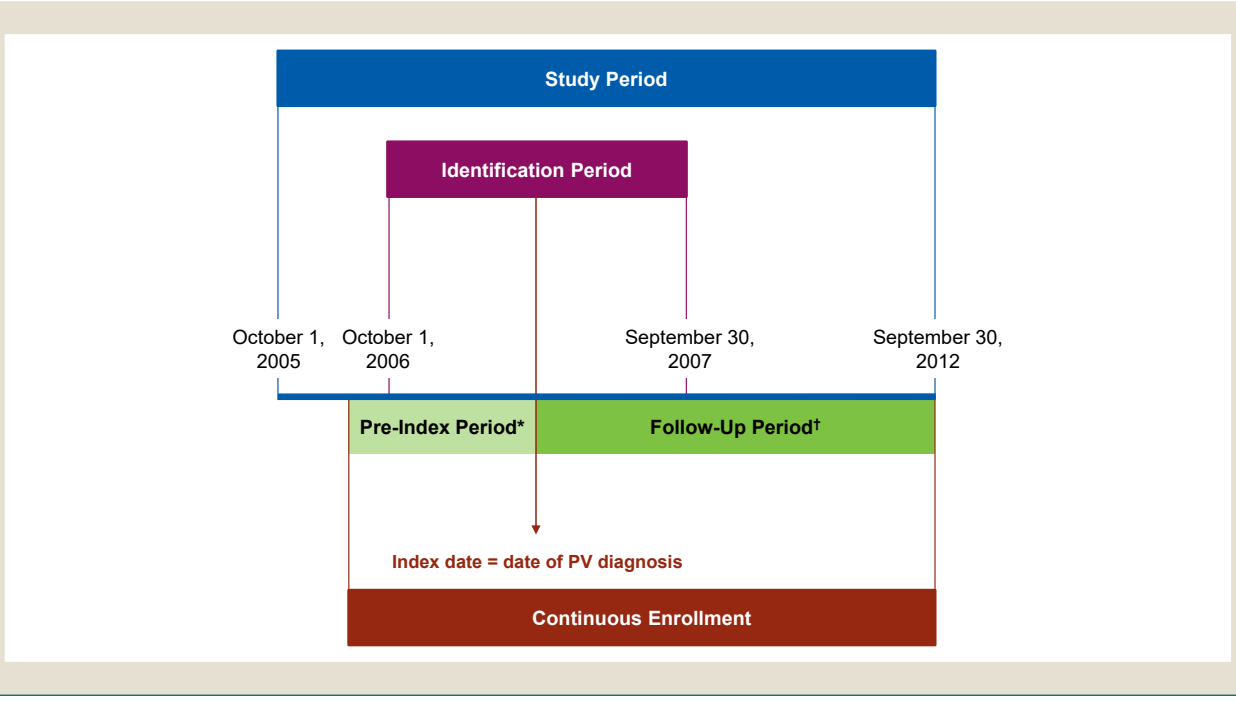
Variables

Patients were assigned to 1 of the following groups according to the last WBC measurement before the first TE or the end of the follow-up period: WBC count < 7.0, 7.0 to 8.4, 8.5 to < 11.0, and ≥ 11.0 $\times 10^9$/L. TEs were determined using ICD-9-CM codes and included ischemic stroke, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, transient ischemic attack, peripheral arterial thrombosis, and superficial thrombophlebitis.

Statistical Analysis

All demographic and baseline clinical characteristics were compared among the patients stratified by the last WBC measurement. The primary statistical analysis used a Cox proportional

Figure 1 Study Design. *Period ≥ 12 Months. †Patients Were Followed From the Index Date to the Date of the Earliest Event: Death, Disenrollment, or End of the Study Period



Abbreviation: PV = polycythemia vera.

hazards model, with the WBC count considered as a time-dependent covariate and $< 7.0 \times 10^9$/L as the reference group. This analysis was conducted using the linear interpolation approach between 2 WBC records to determine the WBC count at the time of a TE. Using this determined WBC count, the patients were designated to 1 of 4 WBC categories (separate from group allocations per primary analyses). The categorical variables were then applied for the time-dependent covariate approach. Binary variables were created for the patients within each of the 4 WBC categories (WBC count, 0-7.0, 7.0-8.4, 8.5 to < 11.0, and $\geq 11.0 \times 10^9$/L), with the WBC count $< 7.0 \times 10^9$/L category considered the reference. A second analysis included a univariate Cox proportional hazards model using the last WBC count before a TE. The purpose of this second analysis was to approximate the methods used in the CYTO-PV study and, therefore, did not consider the WBC count as a time-dependent covariate. A sensitivity analysis was performed, repeating the analysis with all patients, including both those with and without a history of thrombosis. The time from the index date to the first TE was censored at death, disenrollment, or the end of the study period.

Results

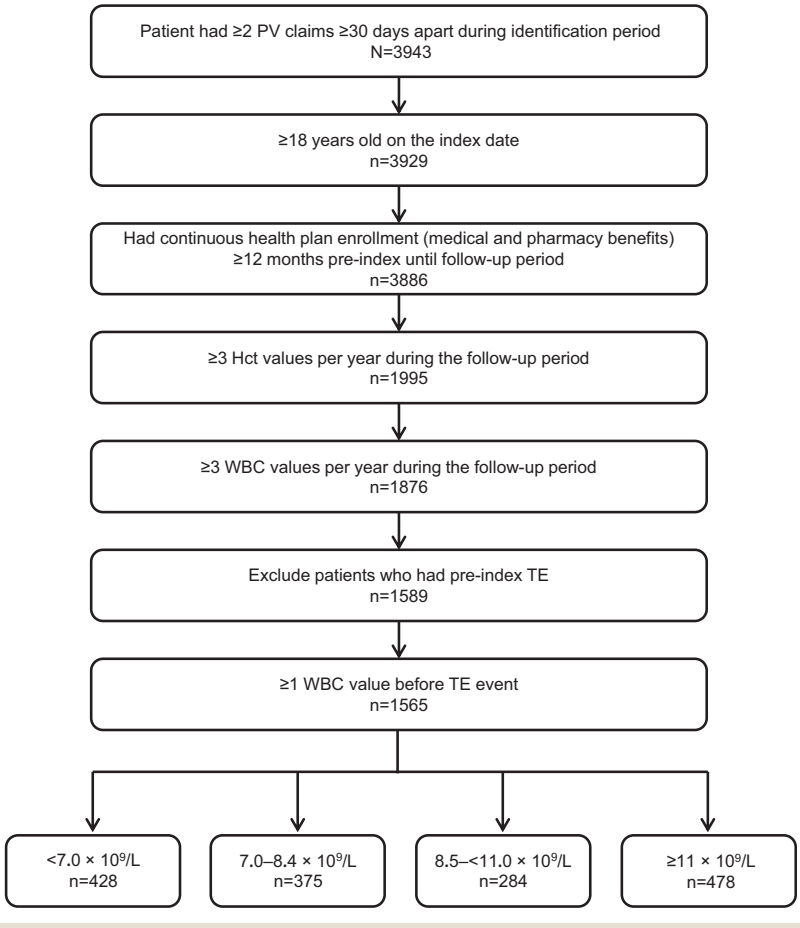
Patient Demographics and Baseline Clinical Characteristics

The analysis included a total of 1565 US veterans with PV and no history of thrombosis. The WBC count was $< 7.0 \times 10^9$/L for 428 (27.3%), 7.0 to 8.4×10^9/L for 375 (24.0%), 8.5 to $< 11.0 \times 10^9$/L for 284 (18.1%), and $\geq 11.0 \times 10^9$/L for 478 (30.5%; Figure 2). The patient demographics were similar across the 4 groups, with most patients aged ≥ 60 years (66.8%), male (98.5%), and white (65.3%; Table 1). The mean Charlson comorbidity index and chronic disease scores were similar across the 4 groups and ranged from 1.11 to 1.45 and 6.15 to 6.76, respectively. Hypertension was the most common comorbid condition across all the groups (range, 65.1%-71.5%). TEs had occurred before the index date in 278 of 1876 patients (15.3%; rate, 69.5/100 patient-years), which were used only for the sensitivity analyses.

WBC Counts and TEs During Follow-up

The mean follow-up period across the groups ranged from 3.6 to 4.5 years (Table 2). During the follow-up period, the

Figure 2 Flow Chart Showing Patient Selection



Abbreviations: Hct = hematocrit; PV = polycythemia vera; TE = thrombotic event; WBC = white blood cell.

Table 1 Patient Demographics and Baseline Disease Characteristics

Parameter	WBC Count ($\times 10^9$/L)			
	<7.0 (n = 428)	7.0-8.4 (n = 375)	8.5 to <11.0 (n = 284)	≥11.0 (n = 478)
Age, y				
Mean ± standard deviation	64.7 ± 10.8	63.7 ± 10.1	65.3 ± 10.4	67.7 ± 10.8
Median	64.0	63.0	64.0	67.0
Age group				
18-45 y	9 (2.1)	11 (2.9)	5 (1.8)	6 (1.3)
46-59 y	142 (33.2)	131 (34.9)	93 (32.8)	123 (25.7)
≥60 y	277 (64.7)	233 (62.1)	186 (65.5)	349 (73.0)
Sex				
Male	424 (99.1)	370 (98.7)	280 (98.6)	467 (97.7)
Female	4 (0.9)	5 (1.3)	4 (1.4)	11 (2.3)
Race				
Non-Hispanic white	256 (59.8)	242 (64.5)	193 (68.0)	331 (69.3)
Non-Hispanic black	44 (10.3)	23 (6.1)	15 (5.3)	27 (5.7)
Hispanic	15 (3.5)	17 (4.5)	9 (3.2)	15 (3.1)
Other	113 (26.4)	93 (24.8)	67 (23.6)	105 (22.0)
US region				
Northeast	59 (13.8)	49 (13.1)	40 (14.1)	80 (16.7)
Midwest	99 (23.1)	84 (22.4)	65 (22.9)	97 (20.3)
South	158 (36.9)	141 (37.6)	103 (36.3)	177 (37.0)
West	85 (19.9)	84 (22.4)	68 (23.9)	101 (21.1)
Other	27 (6.3)	17 (4.5)	8 (2.8)	23 (4.8)
Charlson comorbidity index score	1.11 ± 1.50	1.28 ± 1.59	1.31 ± 1.48	1.45 ± 1.73
Chronic disease score	6.15 ± 3.95	6.24 ± 4.02	6.66 ± 4.37	6.76 ± 4.13
Comorbid conditions				
Dyslipidemia	182 (42.5)	172 (45.9)	125 (44.0)	168 (35.2)
Hypertension	291 (68.0)	244 (65.1)	203 (71.5)	330 (69.0)
Diabetes	86 (20.1)	96 (25.6)	70 (24.7)	126 (26.4)
Cardiovascular events	44 (10.3)	39 (10.4)	40 (14.1)	48 (10.0)
Bleeding	33 (7.7)	29 (7.7)	31 (10.9)	47 (9.8)
Smoking[a]	101 (23.6)	116 (30.9)	88 (31.0)	119 (24.9)

Data presented as n (%) and mean ± standard deviation.
Abbreviation: WBC = white blood cell.
[a]Percentage determined from the number of patients reporting the use of smoking cessation therapy.

rates of cytoreductive treatment, including phlebotomy, were similar across the 4 groups. Cytoreductive treatment was received by 77.3% to 78.2% of patients, including 56.9% to 65.9% who had undergone ≥ 1 phlebotomy procedure. Antiplatelet agents were used by 4.4% to 5.1% of patients across the 4 groups.

Overall, 390 patients (24.9%) experienced a TE during the follow-up period, including 85 (19.9%) with a WBC count < 7.0 $\times 10^9$/L, 91 (24.3%) with a WBC count of 7.0 to 8.4 $\times 10^9$/L, 73 (25.7%) with a WBC count of 8.5 to < 11.0 $\times 10^9$/L, and 141 (29.5%) with a WBC count of ≥ 11.0 $\times 10^9$/L (Table 3, Figure 3). The mean interval between the last WBC count and the first TE in these patients was 26.3 days (median, 0 days; range, 0-758 days), with > 80% of TEs occurring within 30 days of the last WBC measurement.

Compared with the reference group (WBC count, < 7.0 $\times 10^9$/L), the hazard ratio for TEs was 1.10 (95% CI, 0.82-1.48; $P = .5395$) for the 7.0 to 8.4 $\times 10^9$/L group, 1.47 (95% CI, 1.10-1.96; $P = .0097$) in the 8.5 to < 11.0 $\times 10^9$/L group, and 1.87 (95% CI, 1.44-2.43; $P < .0001$) in the ≥ 11.0 $\times 10^9$/L group (Table 3), considering the WBC count as a time-dependent covariate. Similar results were also observed using a univariate Cox proportional hazards model with the last WBC count before a TE (in which the WBC counts were not considered time-dependent). Compared with the reference group (WBC count, < 7.0 $\times 10^9$/L), the hazard ratio for TEs was 1.22 (95% CI, 0.91-1.64; $P = .1835$), 1.39 (95% CI, 1.02-1.90; $P = .0401$), and 1.81 (95% CI, 1.39-2.38; $P < .0001$) among patients with a WBC count of 7.0 to 8.4, 8.5 to < 11.0, and ≥ 11.0 $\times 10^9$/L, respectively. A similar trend was observed when including all patients regardless of the occurrence of TEs before the index date (n = 1876). The hazard ratios for TEs compared with the reference group (WBC count, < 7.0 $\times 10^9$/L) was 1.22 (95% CI, 0.97-1.55; $P = .0959$) for the patients in the 7.0 to 8.4 $\times 10^9$/L group, 1.41 (95% CI,

Table 2 Treatment Patterns During Follow-up Period[a]

Parameter	WBC Count ($\times 10^9$/L)			
	<7.0 (n = 428)	7.0-8.4 (n = 375)	8.5 to < 11.0 (n = 284)	≥11.0 (n = 478)
Follow-up, y	4.5 ± 1.9	4.5 ± 1.9	4.2 ± 2.0	3.6 ± 2.1
Cytoreductive treatment	331 (77.3)	290 (77.3)	221 (77.8)	374 (78.2)
Phlebotomy	254 (59.4)	233 (62.1)	187 (65.9)	272 (56.9)
Phlebotomies per patient, n	11.3 ± 10.0	11.9 ± 10.9	10.9 ± 10.9	11.1 ± 12.4
Phlebotomies per patient annually, n	2.6 ± 2.3	2.6 ± 2.2	4.7 ± 26.6	3.0 ± 3.3
Hydroxyurea	141 (32.9)	79 (21.1)	71 (25.0)	198 (41.4)
Radiophosphorus	9 (2.1)	11 (2.9)	6 (2.1)	13 (2.7)
Anagrelide	7 (1.6)	10 (2.7)	7 (2.5)	47 (9.8)
Interferon	7 (1.6)	3 (0.8)	7 (2.5)	12 (2.5)
Busulfan	1 (0.2)	1 (0.3)	1 (0.4)	1 (0.2)
Pipobroman	0 (0)	0 (0)	0 (0)	0 (0)
Antiplatelet agents	22 (5.1)	19 (5.1)	14 (4.9)	21 (4.4)
Use of other medications				
Antihypertensive agents	386 (90.2)	336 (89.6)	249 (87.7)	445 (93.1)
Antilipid/anticholesterol agents	258 (60.3)	254 (67.7)	173 (60.9)	242 (50.6)
Inotropic agents	27 (6.3)	23 (6.1)	26 (9.2)	43 (9.0)
Antiarrhythmic agents	22 (5.1)	20 (5.3)	16 (5.6)	31 (6.5)

Data presented as mean ± standard deviation or n (%).
Abbreviation: WBC = white blood cell.
[a]Before the thrombotic event or at the end of follow-up if no thrombotic event had occurred.

1.10-1.81; $P = .0062$) in the 8.5 to < 11.0 $\times 10^9$/L group, and 1.53 (95% CI, 1.23-1.91; $P = .0001$) in the ≥ 11.0 $\times 10^9$/L group.

Discussion

The results from the present analysis of 1565 patients with PV in the VHA population have substantiated the findings from a post hoc subanalysis of the CYTO-PV study in a real-world setting.[4] Both studies have shown that an elevated WBC count is significantly associated with an increased risk of TEs. The strongest hazard ratio of 1.87 was observed for the patients with a WBC count of ≥ 11 $\times 10^9$/L. However, the thrombotic risk was still observed to be significantly elevated even in those with a WBC count of ≥ 8.5 $\times 10^9$/L.

Other real-world studies have reported a similar association between the WBC count and thrombotic risk in patients with PV. In a multivariate analysis of a retrospective database study of 587 patients with PV, previous TEs (hazard ratio, 1.9; 95% CI, 1.2-2.9; $P = .03$) and WBC count of ≥ 11 $\times 10^9$/L (hazard ratio, 1.3; 95% CI, 0.9-2.0; $P = .03$) were associated with an increased risk of future TEs.[5] In the ECLAP study, a significant risk of major thrombosis was observed with a WBC count > 15 $\times 10^9$/L compared with a WBC count of ≤ 10 $\times 10^9$/L (hazard ratio, 1.71; 95% CI, 1.10-2.65; $P = .017$).[3]

These findings suggest that control of the WBC count should be an important consideration in the disease management in PV. The current National Comprehensive Cancer Network clinical practice guidelines in oncology for myeloproliferative neoplasms have suggested that cytoreductive treatment should be initiated or changed in the setting of symptomatic patients with indications for cytoreductive therapy, including leukocytosis.[1]

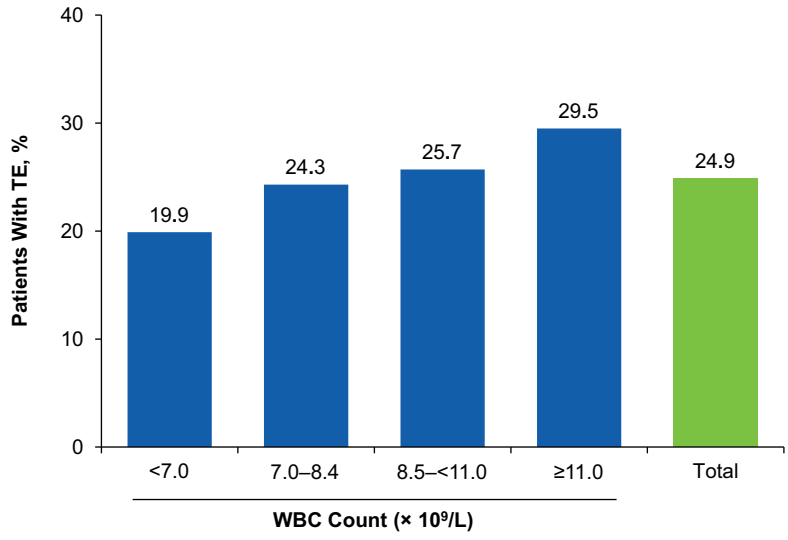
One fourth (390 of 1565) of the patients in the present study had experienced a TE during the follow-up period, indicating a substantial thrombotic burden. A previous analysis of all patients with PV (n = 7718) in this VHA population revealed a TE rate of 6.1 (arterial, 4.1; venous, 2.1) per 100 patient-years, greater than the reported rate for high-risk patients with PV in the general population.[6] Furthermore, the results from the present analysis have

Table 3 WBC Count and Thrombotic Event Occurrence Rates in US Veterans With PV, Considering WBC Count as a Time-dependent Covariate

Parameter	WBC Count ($\times 10^9$/L)			
	<7.0 (n = 428)	7.0-8.4 (n = 375)	8.5 to < 11.0 (n = 284)	≥11.0 (n = 478)
Occurrence of TE, n (%)	85 (19.9)	91 (24.3)	73 (25.7)	141 (29.5)
Hazard ratio (95% CI)	Reference[a]	1.10 (0.82-1.48)	1.47 (1.10-1.96)	1.87 (1.44-2.43)
P value	Reference[a]	.5395	.0097	<.0001

Abbreviations: CI = confidence interval; PV = polycythemia vera; TE = thrombotic event; WBC = white blood cell.
[a]WBC count < 7.0 $\times 10^9$/L served as the reference group.

Figure 3 Thrombotic Event (TE) Occurrence Stratified by White Blood Cell (WBC) Count in US Veterans With Polycythemia Vera



demonstrated that approximately one third of patients with PV in the VHA population had elevated WBC levels, compared with 25.5% in the CYTO-PV study,[4] which could also have contributed to increased thrombotic risk.

The limitations of the present study were generally related to the retrospective study design. The study included patients based on the ICD-9-CM codes within the medical claims, which have a potential for miscoding and will not capture potential confounding factors related to the occurrence of TEs. In the present study, 99% of the patients were men, which precluded analysis of the association of the WBC count and TEs in women. Additionally, the clinical data that could have influenced the thrombotic risk (eg, cytoreductive therapy, platelet count, hematocrit values) were not used in the present analysis.

Conclusion

The results from the present analysis of VHA patients with PV demonstrate a positive, significant association between elevated WBC counts and the occurrence of TEs and represent real-world confirmation of the results from the post hoc subanalysis of the CYTO-PV study. Patients with WBC counts of $\geq 8.5 \times 10^9$/L had a significantly increased risk of TE, and those with WBC counts of $\geq 11.0 \times 10^9$/L had the greatest risk. The potential thrombogenic role of elevated WBCs in those with PV provides support for the continued inclusion of WBC count control in disease management and the evaluation of the response to therapy.

Clinical Practice Points

- Leukocytosis has been linked to an elevated risk of vascular events.
- In the present retrospective, observational study of longitudinal data from the US VHA claims database, the patients were assigned to groups according to the last WBC count before the first TE or the end of follow-up (WBC count, <7.0 [reference], 7.0-8.4, 8.5 to < 11.0, and $\geq 11.0 \times 10^9$/L).
- Overall, 25% of the 1565 patients experienced a TE during follow-up, > 80% of which occurred within 30 days of the last WBC count.
- Compared with the reference group (WBC count, $< 7.0 \times 10^9$/L), patients with WBC counts of 8.5 to < 11.0 and $\geq 11.0 \times 10^9$/L had a significantly increased risk of TEs.
- The findings from the present real-world study have confirmed the potential thrombogenic role of elevated WBCs in those with PV and provide support for the continued inclusion of WBC count control in disease management and evaluation of the therapeutic response.

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Disclosure

S.P., J.Y., and D.P. are employees and stockholders of Incyte Corporation. S.S. and L.W. are employees and stockholders of STATinMED Research, as was O.B. at the time of the study, which is a paid consultant of Incyte Corporation. R.S. has served as a consultant for Incyte Corporation and has received honoraria from Gilead.

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