MPN-103

Presented at the
10th Annual Meeting of the Society of Hematologic Oncology
Houston, TX, USA • September 28-October 1, 2022

A Real-World Evaluation of the Association Between Elevated Blood Counts and Thrombotic Events in Polycythemia Vera: Analysis of Data From the REVEAL Study

Aaron T. Gerds,[1] Ruben Mesa,[2] John M. Burke,[3] Michael R. Grunwald,[4] Robyn Scherber,[5] Jingbo Yu,[5] J.E. Hamer-Maansson,[5] Stephen T. Oh[6]

[1]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [2]UT Health San Antonio MD Anderson Cancer Center, San Antonio, TX, USA; [3]Rocky Mountain Cancer Centers, Aurora, CO, USA; [4]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [5]Incyte Corporation, Wilmington, DE, USA; [6]Washington University School of Medicine, St. Louis, MO, USA

Background

- Polycythemia vera (PV) is a Ph-negative myeloproliferative neoplasm (MPN) characterized by clonal proliferation of hematopoietic progenitor cells leading to elevated peripheral blood count[1,2]
- Patients with PV have an increased risk of thrombotic events (TEs)[3]
  - Advanced age and a history of TEs are the components of the conventional risk model used to determine thrombosis risk and treatment strategy[3]
- Although the association between TEs and elevated hematocrit (HCT) levels is established,[4-9] the association between TEs and white blood cell (WBC) or platelet (PLT) counts has not been assessed in a consistent manner
- The large, real-world, p**R**ospective Obs**E**rvational Study of Patients with Polycythemia **VE**ra in US Clinic**AL** Practices (REVEAL; NCT02252159) is following patients with PV treated in both community and academic practices[10]

Objective

- To evaluate the association between elevated blood counts and occurrence of TEs in patients with PV using data from the REVEAL study

Methods

Study Design and Patients

- REVEAL is a multicenter, noninterventional, prospective observational study in patients with PV enrolled from US community practices and academic centers **(Table 1)**

Table 1. Key Patient Eligibility Criteria

Inclusion Criteria	• ≥18 years of age • Clinical diagnosis of PV per physician judgment • Under physician supervision for management of PV
Exclusion Criteria	• Life expectancy <6 months • History of/planning to undergo allogeneic hematopoietic cell transplantation • Splenectomy

PV, polycythemia vera.

- Data collection timepoints included at diagnosis, a 6-month period before, and during follow-up after enrollment (up to 3 years from last patient enrollment)
  - Data were collected between July 2014 and August 2019
- Patients included in this analysis were required to have ≥3 laboratory values (blood counts) in the post-enrollment period
- Patients were excluded if they had a post-enrollment TE but did not have a laboratory value <6 months before that TE

Model

- The association between blood count levels and TEs was assessed using a time-dependent covariate Cox proportional hazards model
- Time to first post-enrollment TE was modeled with follow-up time censored at last known visit for patients without a TE

Covariates

- Each laboratory parameter was individually modeled with sex, age, disease duration, and TE history at enrollment included as baseline covariates and treatment (hydroxyurea, other PV treatment) as a time-dependent covariate
- Blood counts at the last laboratory test prior to TE or end of follow-up were included as binary time-dependent covariates using the following thresholds[11,12]
  - HCT >45%, WBC >11×10^9/L, PLT >400×10^9/L
- Linear interpolation was used to determine laboratory values between observed laboratory values
- Alternative thresholds were also evaluated[12-14]
  - WBC: <7×10^9/L, ≥7 to <8.5×10^9/L, ≥8.5 to <11×10^9/L, ≥11×10^9/L
  - PLT: >600×10^9/L
- An analysis of the associations between WBC elevation (>11 and >12×10^9/L) and TEs at HCT ≤45% were also performed using separate interaction models to investigate if risk could be reduced by controlling WBC count alone

Statistical Analysis[11-14]

- Hazard ratios and *P* values were calculated from the Cox proportional hazards model
- All covariates were taken at baseline, except for WBC, PLT, and HCT, which were measured throughout the study
- *P* values <0.05 were considered statistically significant

Results

Patient Characteristics

- Of 2510 patients enrolled, 2271 were included in this analysis (77.9% high-risk and 22.1% low-risk) **(Table 2)**
  - Median age was 67 years (range, 22-95) and 1229 (54.1%) were male
  - Median disease duration was 4.1 years (range, 0-56.3)
  - 456 patients (20.1%) had a TE history
  - Approximately one-half of patients were on cytoreductive therapy with hydroxyurea

Post-enrollment Thrombotic Events

- Among all 2271 patients enrolled, 106 (4.7%) had TEs **(Table 3)**
  - 30 arterial TEs; 76 venous TEs
- Among the 456 patients with a previous TE, 38 (8.3%) experienced a TE during follow-up
  - 10 arterial TEs; 28 venous TEs

Table 2. Baseline Demographics

Variable	All Patients (N=2271)
Age, median (range), years	67 (22-95)
<60 y, n (%)	621 (27.3)
≥60 y, n (%)	1650 (72.7)
Male, n (%)	1229 (54.1)
Disease duration, median (range), years	4.1 (0.0-56.3)
History of thrombosis, n (%)	456 (20.1)
Risk status,* n (%)	
Low	503 (22.1)
High	1768 (77.9)
Cytoreductive therapy, n (%)	
None	920 (40.5)
Hydroxyurea	1194 (52.6)
Other†	182 (8.0)
HCT status, n (%)	
≤45%	1115 (52.5)
>45%	1008 (47.5)
WBC status, n (%)	
WBC ≤11×10^9/L	1457 (69.2)
WBC >11×10^9/L	648 (30.8)
Platelet count, n (%)	
Platelets ≤400×10^9/L	1335 (63.7)
Platelets >400×10^9/L	762 (36.3)

*Risk status was assessed based on NCCN guidelines.[13] †Other treatments: ruxolitinib (4.4%), anagrelide (2.2%), interferon (1.5%), busulfan (0.2%), and chlorambucil (0%).
HCT, hematocrit; NCCN, National Comprehensive Cancer Network; WBC, white blood cell.

Table 3. Post-enrollment Thrombotic Events

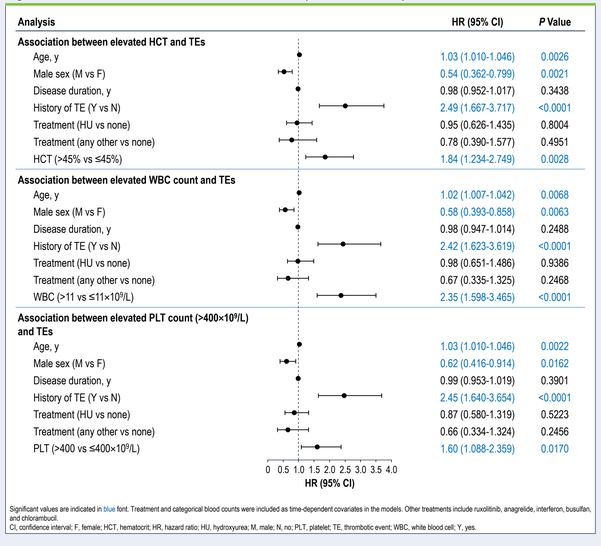
Thrombotic Event, n (%)	All Patients (N=2271)
Any	106 (4.7)
Arterial	30 (1.3)
Acute myocardial infarction	5 (0.2)
Peripheral artery thrombosis	2 (0.1)
Transient ischemic attack	15 (0.7)
Other*	8 (0.4)
Venous	76 (3.3)
Cerebrovascular accident	2 (0.1)
Deep vein thrombosis	37 (1.6)
Intracranial venous sinus thrombosis	3 (0.1)
Pulmonary embolism	14 (0.6)
Splenic vein thrombosis	2 (0.1)
Thrombophlebitis superficial	10 (0.4)
Other†	8 (0.4)

*Other arterial events include abdominal wall hematoma, acute coronary syndrome, amaurosis fugax, arterial thrombosis, atrial thrombosis, cerebrovascular accident, international normalized ratio increased, and pulmonary embolism (each, n=1). †Other venous events include aortic thrombosis, arterial thrombosis, colitis ischemic, coronary artery thrombosis, hematoma, portal vein thrombosis, retinal vein thrombosis, and thrombosis in device (each, n=1).

Associations Between Blood Count and TEs

- Significant associations were identified between blood counts and TEs based on the main thresholds of hematocrit >45%, WBC count >11×10^9/L or PLT count >400×10^9/L **(Figure 1)**

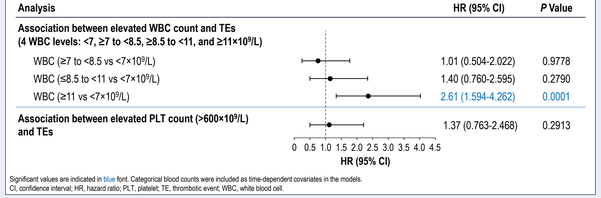
Figure 1. Association Between Blood Count and TEs (Main Thresholds)



Significant values are indicated in blue font. Treatment and categorical blood counts were included as time-dependent covariates in the models. Other treatments include ruxolitinib, anagrelide, interferon, busulfan, and chlorambucil.
CI, confidence interval; F, female; HCT, hematocrit; HR, hazard ratio; HU, hydroxyurea; M, male; N, no; PLT, platelet; TE, thrombotic event; WBC, white blood cell; Y, yes.

- Of the alternative thresholds assessed, only WBC count ≥11×10^9/L versus <7×10^9/L was significantly associated with TE risk **(Figure 2)**
  - Trends in associations between other covariates and TEs in this analysis (ie, age, male sex, disease duration, TE, and treatment history; not shown) were the same as shown previously for the main thresholds

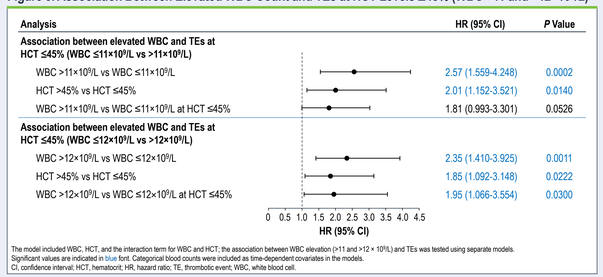
Figure 2. Association Between Blood Count and TEs (Alternative Thresholds)



Significant values are indicated in blue font. Categorical blood counts were included as time-dependent covariates in the models.
CI, confidence interval; HR, hazard ratio; PLT, platelet; TE, thrombotic event; WBC, white blood cell.

- Elevated WBC count (>12×10^9/L) is significantly associated with increased risk of TE when HCT is controlled at ≤45% **(Figure 3)**
  - Trends in associations between other covariates and TEs in this analysis (ie, age, male sex, disease duration, TE, and treatment history; not shown) were the same as shown previously for the main and alternative thresholds

Figure 3. Association Between Elevated WBC Count and TEs at HCT Levels ≤45% (WBC >11 and >12×10^9/L)



The model included WBC, HCT, and the interaction term for WBC and HCT; the association between WBC elevation (>11 and >12 × 10^9/L) and TEs was tested using separate models.
Significant values are indicated in blue font. Categorical blood counts were included as time-dependent covariates in the models.
CI, confidence interval; HCT, hematocrit; HR, hazard ratio; TE, thrombotic event; WBC, white blood cell.

Conclusions

- **This analysis of REVEAL, representing the largest real-world cohort of patients with PV to date, demonstrated significant associations individually between elevated HCT levels, elevated WBC counts, and elevated PLT counts and increased TE risk**
- **Elevated WBC count (>12×10^9/L) is significantly associated with increased risk of TE when HCT level is controlled, indicating that TE risk may be reduced by controlling WBC count as well as HCT levels**
- **These data provide evidence to support incorporation of blood count values into risk stratification and treatment strategies for patients with PV in clinical practice, thus moving beyond the conventional risk model**
- **Further studies to understand the causal relationship between elevated blood counts and TEs are warranted**
  - **Additional analyses of REVEAL are ongoing to understand the relationship between TE risk and isolated WBC elevation, as well as time-dependent risk with elevated blood counts**

Disclosures

Gerds: Consulting fees – *AbbVie, Bristol Myers Squibb, Constellation Pharmaceuticals, Novartis, PharmaEssentia, Sierra Oncology*; Research support – *Accurate Pharmaceuticals, Constellation Pharmaceuticals, CTI BioPharma, Imago BioSciences, Incyte Corporation, Kratos Pharmaceuticals*. **Mesa:** Consultancy fees – *AOP, Blueprint, Bristol Myers Squibb, Constellation Pharmaceuticals, Geron, Incyte Corporation, La Jolla Pharma, Novartis, Roche, Samus, Sierra Oncology*; Research support – *AbbVie, Celgene, Constellation Pharmaceuticals, CTI, Genentech, Gilead Sciences, Imago, Incyte Corporation, Promedior, Samus Therapeutics, Sierra Oncology*. **Burke:** Consulting fees – *AbbVie, Adaptive Biotechnologies, AstraZeneca, BeiGene, Bristol Myers Squibb, Epizyme, Gilead Sciences, Kura Oncology, Kymera Therapeutics, MorphoSys AG, Roche/Genentech, Seagen, Seattle Genetics, Verastem Oncology, X4 Pharmaceuticals*; Speaker's bureau – *BeiGene, Genentech, MorphoSys*. **Grunwald:** Consulting fees – *AbbVie, Agios, Amgen, Astellas Pharma, Blueprint Medicines, Bristol Myers Squibb, Cardinal Health, CTI BioPharma, Daiichi Sankyo, Gilead Sciences, Incyte Corporation, Invitae, Karius, Pfizer, Sierra Oncology, Stemline Therapeutics, Trovagene*; Research support – *Incyte Corporation, Janssen*; Other: *MDEdge, Med Learning Group, PER, PRIME*. **Scherber:** Employment – *Blueprint Medicines*; Former employment and stock ownership – *Incyte Corporation*. **Yu, Hamer-Maansson:** Employment and stock ownership – *Incyte Corporation*. **Oh:** Consulting fees – *AbbVie, Blueprint Medicines, Celgene/Bristol Myers Squibb, Constellation Pharmaceuticals, CTI BioPharma, Disc Medicine, Geron, Incyte Corporation, PharmaEssentia, Sierra Oncology*.

Acknowledgments

The authors wish to thank the patients, investigators, and site personnel who participated in this study. This study was sponsored by Incyte Corporation (Wilmington, DE). Medical writing assistance was provided by Simon J. Slater, PhD, CMPP, of Envision Pharma Group (Philadelphia, PA), and funded by Incyte Corporation.

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