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634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Diagnostic Performance of Red Blood Cell Indices, Serum Erythropoietin, and *JAK2* Mutation Testing for the Evaluation of Polycythemia Vera at High Altitude

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Introduction:
Polycythemia vera (PV) is a clonal myeloproliferative neoplasm associated with mutation of Janus kinase 2 (*JAK2*) in virtually all patients. Patients with PV typically present with constitutional symptoms and thrombotic complications related to myeloproliferation but can present with only mild or no symptoms. In 2016, the World Health Organization (WHO) diagnostic criteria for PV were revised to use lower hemoglobin and hematocrit cut-off levels in order to avoid missing masked polycythemia. Accordingly, a hemoglobin concentration of more than 16 g/dL (HCT>48%) for females and 16.5 g/dL (HCT>49%) for males can be considered for PV evaluation (previously >18.5 g/dL for men and >16.5 g/dL for women). In conjunction, concerns arise about the unnecessary evaluation of individuals with otherwise high-normal hemoglobin levels, more so for those living at high altitude. Altitude exposure, amongst others, decreases plasma volume to increase [Hb] which may accordingly muddle the diagnosis of PV at altitude.
Nonetheless, Red Cell Mass (RCM) is seldom assessed in clinical practice. In addition, red blood cell count, related indices, and serum erythropoietin may also be affected by high altitude, and their diagnostic performance in the evaluation of PV at altitude has not been prospectively assessed.
Method: We collected lab records for all *JAK2* requests over three years (2020-2022) in two referral hospitals serving a population residing at an altitude of 2,270-3,000 meters above sea level. Indications for requests, as well as laboratory data and imaging, were gathered. Complete blood count (CBC) and other laboratory values were collected when ordered within one week of *JAK2* testing.
For CBC, EDTA anticoagulated samples were processed using Sysmex XN-3100. For *JAK2* testing, RNA isolated from peripheral blood samples (using the MagNA Pure System) was reverse-transcribed, amplified, and sequenced for any mutations involving exons 12, 13, 14, or 15 using an ABI 3730 XL genetic analyzer.
For serum EPO, frozen serum samples were outsourced to Bio Scientia Labs, Germany. Reference values for serum erythropoietin were lab generated at 4.3-29 mIU/ml and were not validated for our altitude.
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Results:Of the 208 *JAK2* tests performed during the reviewed period, 132 (63.4%) were for polycythemia (Table 1). The *JAK2* V617F mutation was found in 22 (16.7%) patients, with 10 (45.5%) of them being men. No *JAK2* mutation other than the exon 14 V617F substitution was found. *JAK2*-positive patients had a median age of 61 years, while *JAK2*-unmutated patients had a median age of 47 years. Overt polycythemia, according to the WHO 2016 classification, was identified in 15 (68.2%) , while the remainder had masked PV (defined as increased RBCs with normal hemoglobin/ HCT).
Patients with PV had significantly higher RBCs and lower MCV/MCH/MCHC compared to those with *JAK2*-unmutated polycythemia. They also exhibited significant elevation of RDW-CW and significant neutrophilia, basophilia, thrombocytosis, and splenomegaly. All PV patients with available serum EPO tests had low values (median 2 mIU/ml).

Conclusion: At altitude, patients with PV show the same age and sex characteristics as those living at low elevations. Patients with PV have higher RBCs and lower MCV/MCH/MCHC compared to those with *JAK*-unmutated (secondary) polycythemia. RDW is significantly increased in patients with PV, reflecting an associated iron deficiency. Serum EPO performed well at altitude to suggest the presence of PV.
The low rate of positive *JAK2* mutation in our high-altitude cohort may reflect poor selection of subjects and over-workup of otherwise altitude-associated erythrocytosis.
Isolated mild polycythemia at altitude remains common. Using hemoglobin/hematocrit alone to select patients for PV evaluation has a low positive predictive value and may be associated with unnecessary workup. RBC indices and RDW, along with an evaluation for iron status, might help select those more likely to have PV and could decrease unnecessary workups.

Disclosures No relevant conflicts of interest to declare.

Table 1. Characteristics of the study cohort				
Characteristic	Total	*JAK2* mutation status		*P*-value[a]
		Positive	Negative	
	132	22 (16.7%)	110 (83.3%)	
Age , years Median (IQR)	50 (37–62)	61 (50–68)	47 (36–59)	0.002
Range	17–79	17–87	18–77	
Men, No. (%)	113 (85.6)	10 (45.5)	103 (93.6)	<0.001
Splenomegaly, No. (%) (n=42)	8 (6.1)	8 (36.4)	0 (0.0)	<0.001
Erythropoietin, mIU/ml (n=65)				
Median (IQR)	7 (4.8–13)	2 (2–2.8)	8.3 (5.7–14)	<0.001
Range	1.5–27	1.5–2.8	3–27	
Complete blood count				
Red blood cells, ($x10^{12}$/L) (n=100)				
Median (IQR)	6.4 (6–7)	7.5 (7.1–8.5)	6.3 (6–6.7)	<0.001
Range	5.3–10	4.4–10	5.3–9.5	
Hemoglobin, g/dL (n=100)				
Median (IQR)	18 (18–19)	17 (15–20)	18 (18–19)	0.069
Range	13–23	13–21	14–23	
Hematocrit, % (n=100)				
Median (IQR)	54 (52–58)	56 (52–64)	54 (52–57)	0.423
Range	42–70	42–70	45–68	
Mean corpuscular volume, fl (n=100)				
Median (IQR)	86 (81–89)	74 (70–83)	87 (83–89)	<0.001
Range	56–104	56–104	70–99	
Mean corpuscular hemoglobin, pg (n=100)				
Median (IQR)	55 (32–71)	17 (5–35)	61 (44–72)	<0.001
Range	1–94	1–95	1–93	
Mean corpuscular hemoglobin concentration, g/dL (n=100)				
Median (IQR)	33 (32–34)	31 (29–32)	33 (32–34)	<0.001
Range	28–36	28–34	30–36	
Red cell distribution width–coefficient of variation, % (n=99)				
Median (IQR)	14 (13–17)	23 (20–27)	14 (13–15)	<0.001
Range	11–57	14–57	6–55	
White blood cells, ($x10^9$/L) (n=100)				
Median (IQR)	6.4 (5–8.8)	13 (8.8–18)	6 (4.7–8.1)	<0.001
Range	2.5–23	5.2–29	2.5–16	
Neutrophils, ($x10^9$/L) (n=56)				
Median (IQR)	3.7 (2–5.6)	9.8 (5–19)	3.1 (1.9–4.8)	<0.001
Range	.6–77	3.1–77	.6–33	
Lymphocytes, ($x10^9$/L) (n=56)				
Median (IQR)	2.6 (1.9–3.3)	2.1 (1.4–4.3)	2.6 (2–3.2)	0.258
Range	.5–55	.5–18	1.2–55	
Monocytes, ($x10^9$/L) (n=56)				
Median (IQR)	.6 (.47–.8)	.62 (.49–1.3)	.6 (.47–.8)	0.619
Range	.18–7.7	.18–6	.2–7.7	
Basophils, ($x10^9$/L) (n=53)				
Median (IQR)	.06 (.045–.1)	.14 (.1–.26)	.06 (.04–.085)	<0.001
Range	.003–1.2	.02–1.2	.003–.8	
Eosinophils, ($x10^9$/L) (n=38)				
Median (IQR)	.2 (.12–.42)	.49 (.2–1)	.2 (.11–.33)	0.198
Range	.06–78	.12–6.7	.06–78	
Platelets, ($x10^9$/L) (n=100)				
Median (IQR)	239 (201–298)	639 (284–894)	232 (200–270)	<0.001
Range	38–1275	133–1420	38–668	
Overt polycythemia, No. (%)	122 (92.4)	15 (68.2)	107 (97.3)	<0.001
a–*P*-values calculated using Wilcoxon rank-sum test for medians and Fisher's exact test for categorical variables.				

Figure 1

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