Causes of erythrocytosis and its impact as a risk factor for thrombosis according to etiology: experience in a referral center in Mexico City

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Background
Thrombotic events are well documented in primary erythrocytosis, but it is uncertain if secondary etiologies increase the risk of thrombosis. This study aimed to determine the causes of erythrocytosis and to identify its impact as a risk factor for thrombosis.

Methods
Data were obtained from patients with erythrocytosis between 2000 and 2017 at a referral hospital in Mexico City. Erythrocytosis was defined according to the 2016 WHO classification. Time to thrombosis, major bleeding, or death were compared among groups of patients defined by the etiology of erythrocytosis using a Cox regression model, adjusting for cardiovascular risk factors.

Results
In total, 330 patients with erythrocytosis were studied. The main etiologies of erythrocytosis were obstructive sleep apnea (OSA) in 29%, polycythemia vera (PV) in 18%, and chronic lung disease (CLD) in 9.4% of the patients. The incidence rate of thrombosis was significantly higher in patients with PV and CLD than that in patients with OSA (incidence rates of 4.51 and 6.24 vs. 1.46 cases per 100 person-years, P=0.009), as well as the mortality rate (mortality rates of 2.72 and 2.43 vs. 0.17 cases per 100 person-years, P=0.003).

Conclusion
The risk of thrombosis in CLD with erythrocytosis was comparable to that in patients with PV. Further larger-scale studies are needed to confirm these findings and evaluate the benefits of preventive management of COPD with erythrocytosis similar to PV.

Key Words  Polycythemia vera, Secondary erythrocytosis, Thrombosis, Phlebotomy
in erythrocyte mass. AE may result from the autonomous production of red blood cells (primary erythrocytosis) or as a physiological response to elevated serum erythropoietin levels (secondary erythrocytosis).

In adults, polycythemia vera (PV) is the main primary cause of erythrocytosis. It is an uncommon myeloproliferative neoplasm, with an annual incidence of 0.01 to 2.61 per 100,000 people [3] and a prevalence of 44 to 57 per 100,000 people in the United States [4]. The prevalence of secondary erythrocytosis differs according to patient population and is believed to be much higher than that of primary erythrocytosis. Secondary causes of AE are more common, with numerous possible causes, most commonly after a response to tissue hypoxia. Obstructive sleep apnea (OSA); central hypoventilation; and chronic lung disease (CLD), including chronic obstructive pulmonary disease (COPD), are among the most common causes of hypoxemia. An appropriate assessment is imperative to make a precise diagnosis and prevent complications.

Thrombotic events are well documented in PV, but it is uncertain if secondary etiologies cause an increased risk of thrombosis. A retrospective study of 172 patients with COPD revealed a higher risk of venous thromboembolism in those with erythrocytosis (20% vs. 14%), although the difference was not statistically significant [5]. Our study aimed to evaluate the association between erythrocytosis and the risk of thrombosis according to etiology in a single referral center in Mexico City.

**MATERIALS AND METHODS**

A retrospective observational cohort study was performed to evaluate all patients with erythrocytosis between January 2000 and December 2017 at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán in Mexico City. Medical history to determine the presence of baseline characteristics and cardiovascular risk factors was obtained from the electronic medical records. Eligible patients were 18 years or older with laboratory-proven erythrocytosis. Erythrocytosis was defined according to the 2016 WHO classification as a Hb concentration of >16.5 g/dL or Hct of >49% in men, and Hb concentration of >16.0 g/dL or Hct of >48% in women [6]. Patients who did not meet the 2016 World Health Organization (WHO) classification for erythrocytosis were excluded. Chronic lung disease was defined as the presence of one of the following: COPD, asthma, pulmonary fibrosis, chronic pulmonary embolism, and obliterator bronchiolitis. Thrombotic events at diagnosis and follow-up included ischemic stroke, cerebral transient ischemic attack, acute myocardial infarction, peripheral arterial thrombosis, and venous thromboembolism (deep vein thrombosis of the limbs or the abdominal vein and pulmonary embolism). Thrombosis at diagnosis considered all events that consigned to the original medical record. Postdiagnosis thrombotic events included well-documented thrombosis in the files according to the appropriate diagnostic study. Major hemorrhage consisted of any bleeding that led to hospital admission.

**Endpoints**

The primary endpoints were thrombosis, major hemorrhage, and death according to the etiology of erythrocytosis. This study was approved by the institutional ethics committee and was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and subsequent amendments.

**Study objectives**

This study aimed to determine the causes of erythrocytosis and to identify its impact as a risk factor for thrombosis.

**Statistical analysis**

Categorical variables were presented as frequencies and percentages, while numerical variables were described with median and interquartile ranges. All characteristics were described overall and within the three main etiologies: PV, OSA, and CLD. Characteristics when erythrocytosis was detected, laboratory findings during the diagnostic approach, and events during follow-up were compared among patients with PV, OSA, and CLD using the chi-square test when categorical, and analysis of variance when numerical.

Incidence rates for thrombosis, major hemorrhage, and death during follow-up and their corresponding event-free survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. The event-free survival for each patient corresponded to the time from diagnosis to the event: it was computed exactly for those who had the event and right-censored at the time of last follow-up for those who did not have the event. A Cox proportional hazards regression model was used to evaluate whether the hazard of each outcome for patients with OSA or CLD was the same as for patients with PV, adjusting for cardiovascular risk factors (age, sex, BMI, hypertension, diabetes, and smoking). P-values were 2-tailed, and P < 0.05 was considered statistically significant. Statistical analyses were performed using R version 4.0.3.

**RESULTS**

From 2000 to 2017, 330 patients with erythrocytosis were studied, of whom 72% (N=236) had a complete diagnostic approach. The main etiologies of erythrocytosis were OSA in 29% (N=96), PV in 18% (N=61), and CLD in 9.4% (N=31) of the patients. The remaining etiologies were smoking in 5.2% (N=17), renal transplantation in 3.0% (N=10), right to left cardiopulmonary shunt in 2.4% (N=8), carcinoma in 1.5% (N=5), high-affinity Hb in 1.2% (N=4), testosterone in 0.9% (N=3), and nasal airway obstruction in 0.3% (N=1) of the patients. The median time to diagnosis was 9 months in general (IQR, 2-32), 3 months in PV (IQR, 1-12), 4 months in CLD (IQR, 0-18), and 14 months in OSA (IQR, 4-44), being significantly highest in OSA (P<0.001).
Table 1 summarizes the characteristics of the studied patients: when the diagnostic approach started; overall; and in the PV, OSA, and CLD groups. The median age was 44 years (IQR, 31–58), and 76% (N=251) were men. In relation to metabolic conditions, the median BMI was 28 kg/m² (IQR, 24–32), with 38% being overweight (N=121), 36% (N=114) obese, 15% (N=50) had diabetes, 42% (N=140) had hypertension, 46% (N=145) had dyslipidemia, and 38% (N=124) had smoked. When comparing these characteristics among the PV, OSA, and CLD groups, patients with OSA were younger (P<0.001) with a higher proportion of male patients (P<0.001) and a higher median BMI (P<0.001) than patients with PV or CLD. The proportion of male patients was significantly lower among patients with PV.

Table 2 presents the clinical findings from the first evaluation. The most frequent findings were vasomotor symptoms and snoring (40% each), followed by fatigue (34%) and dyspnea (23%). When comparing the findings among patients with PV, OSA, and CLD, weight loss was more frequent in PV (26% in PV vs. 6.2% in OSA and 13% in CLD, P=0.002), dyspnea was more prevalent in CLD (52% in CLD vs. 4.9% in PV and 30% in OSA, P<0.001), snoring was more common in OSA (78% in OSA vs. 6.6% in PV and 23% in CLD, P<0.001), palpable splenomegaly and hepatomegaly were more frequent in PV (46% and 25% in PV vs. 14% and 7.3% in OSA, and 0% and 0% in CLD, P<0.001), and venous thrombosis had occurred more frequently in PV (21% in PV vs. 5.2% in OSA and 13% in CLD, P=0.007).

Findings during the diagnostic approach
Table 3 shows the laboratory findings of the diagnostic approach. When comparing these findings among patients with PV, OSA, and CLD, patients with PV had a higher leukocyte count (median of 10.2 in PV vs. 7.0 in OSA and 7.4 in CLD, P<0.001), a higher platelet count (median of 398 in PV vs. 182 in OSA and 166 in CLD, P<0.001), a higher proportion of low erythropoietin levels (63% in PV vs. 2.9% in OSA and 0% in CLD, P=0.002), a higher

Table 1. Baseline demographic characteristics when erythrocytosis was detected.

| Characteristic          | Overall (N=330) | PV (N=61) | OSA (N=96) | CLD (N=31) | P     |
|-------------------------|----------------|-----------|------------|------------|-------|
| Age (yr)                | 44 (31, 58)    | 59 (46, 66)| 38 (29, 51)| 57 (40, 64)| <0.001|
| Males                   | 251 (76%)      | 28 (46%)  | 82 (85%)   | 20 (65%)   | <0.001|
| Weight (kg) (NA=3)      | 75 (66, 90)    | 68 (57, 74)| 90 (75, 104)| 73 (64, 91)| <0.001|
| Height (m) (NA=7)       | 1.65 (1.59, 1.71)| 1.63 (1.57, 1.68)| 1.66 (1.60, 1.71)| 1.62 (1.56, 1.67)| 0.061|
| BMI (kg/m²) (NA=7)      | 28 (24, 32)    | 25 (22, 27)| 32 (28, 36)| 28 (25, 36)| <0.001|
| BMI classification (NA=7)| Normal         | 86 (27%)  | 25 (43%)   | 12 (13%)   | 6 (19%)|
|                         | Overweight     | 121 (37%) | 28 (48%)   | 24 (25%)   | 14 (45%)|
|                         | Obesity        | 116 (36%) | 5 (9%)     | 59 (62%)   | 11 (35%)|
|                         | Diabetes       | 50 (15%)  | 11 (18%)   | 14 (15%)   | 6 (19%)|
|                         | Hypertension   | 140 (42%) | 29 (48%)   | 41 (43%)   | 15 (48%)|
|                         | Smoking        | 124 (38%) | 20 (33%)   | 34 (35%)   | 15 (48%)|
|                         | Dyslipidemia   | 145 (46%) | 21 (37%)   | 49 (53%)   | 12 (44%)|

Summaries presented in median (IQR) or N (%).
Abbreviations: BMI, body mass index; CLD, chronic lung disease; NA, not available; OSA, obstructive sleep apnea; PV, polycythemia vera.

Table 2. Clinical findings when erythrocytosis was detected.

| Characteristic          | Overall (N=330) | PV (N=61) | OSA (N=96) | CLD (N=31) | P     |
|-------------------------|----------------|-----------|------------|------------|-------|
| Weight loss             | 35 (11%)       | 16 (26%)  | 6 (6.2%)   | 4 (13%)    | 0.002|
| Fatigue                 | 111 (34%)      | 18 (30%)  | 41 (43%)   | 10 (32%)   | 0.2   |
| Vasomotor symptoms      | 132 (40%)      | 32 (52%)  | 46 (48%)   | 11 (35%)   | 0.3   |
| Dyspnea                 | 75 (23%)       | 3 (4.9%)  | 29 (30%)   | 16 (52%)   | <0.001|
| Snoring                 | 133 (40%)      | 4 (6.6%)  | 75 (78%)   | 7 (23%)    | <0.001|
| Palpable splenomegaly   | 54 (16%)       | 28 (46%)  | 13 (14%)   | 0 (0%)     | <0.001|
| Palpable hepatomegaly   | 31 (9.4%)      | 15 (25%)  | 7 (7.3%)   | 0 (0%)     | <0.001|
| Arterial thrombosis     | 25 (7.6%)      | 5 (8.2%)  | 2 (2.1%)   | 1 (3.2%)   | 0.2   |
| Venous thrombosis       | 31 (9.4%)      | 13 (21%)  | 5 (5.2%)   | 4 (13%)    | 0.007|

Summaries presented in N (%).
Abbreviations: CLD, chronic lung disease; OSA, obstructive sleep apnea; PV, polycythemia vera.
Table 3. Laboratory findings during the diagnostic approach.

| Laboratory feature                  | Overall (N=330) | PV (N=61) | OSA (N=96) | CLD (N=31) | P    |
|-------------------------------------|----------------|-----------|------------|------------|------|
| Hemoglobin (g/dL)                   | 19.0 (18.1, 20.0) | 19.0 (17.7, 20.6) | 19.5 (18.4, 20.6) | 19.2 (18.0, 20.3) | 0.5  |
| Hematocrit (%)                      | 56 (54, 61)     | 59 (54, 63) | 58 (55, 63) | 58 (53, 63) | >0.9 |
| Mean corpuscular volume (fl) (NA=2) | 90 (86, 93)     | 87 (80, 91) | 91 (87, 94) | 91 (87, 95) | 0.2  |
| Mean corpuscular hemoglobin (pg) (NA=2) | 30.4 (28.5, 31.7) | 28.7 (26.2, 30.6) | 30.5 (28.8, 31.9) | 30.6 (29.0, 31.5) | 0.003 |
| Leukocyte count (×10⁹/L)            | 7.3 (6.2, 9.1)  | 10.2 (8.4, 13.9) | 7.0 (6.0, 8.5) | 7.4 (6.2, 9.0) | <0.001 |
| Platelet count (×10⁹/L)             | 200 (157, 264)  | 396 (236, 628) | 182 (143, 220) | 166 (140, 205) | <0.001 |
| EPO (mU/mL) (NA=70)                 | 10 (6, 16)      | 2 (1, 6)    | 13 (9, 18)   | 16 (9, 36)   | 0.002 |
| Low EPO                             | 43 (16%)        | 37 (63%)    | 2 (2.9%)     | 0 (0%)       |      |
| High EPO                            | 61 (23%)        | 3 (5.1%)    | 25 (36%)     | 9 (50%)      |      |
| pO2 (mmHg) (NA=51)                  | 66 (57, 73)     | 68 (58, 71) | 60 (54, 70)  | 51 (47, 61)  | <0.001 |
| SaO2 (%) (NA=51)                    | 93.2 (89.3, 95.0) | 93.4 (89.8, 95.0) | 91.9 (86.2, 94.3) | 83.7 (80.1, 91.8) | <0.001 |
| p50 (NA=168)                        | 27.0 (25.9, 28.1) | 27.0 (26.1, 27.8) | 27.3 (26.0, 28.1) | 27.6 (26.1, 29.1) | 0.8 |
| Abnormal liver function test (NA=4) | 41 (13%)        | 9 (15%)     | 13 (14%)     | 4 (13%) >0.9 |
| Elevated LDH (NA=152)               | 60 (34%)        | 29 (57%)    | 10 (21%)     | 7 (41%) 0.002 |
| Glomerular filtration rate (mL/min/1.73 m²) (NA=1) | 93 (77, 108) | 82 (64, 102) | 98 (82, 113) | 95 (83, 104) 0.003 |
| Iron deficiency (NA=167)            | 41 (25%)        | 22 (43%)    | 8 (17%)      | 2 (17%) 0.009 |

Summaries presented in median (IQR) or N (%). Abbreviations: CLD, chronic lung disease; EPO, erythropoietin; LDH, lactate dehydrogenase; NA, not available; OSA, obstructive sleep apnea; PV, polycythemia vera.

Table 4. Complementary studies during the diagnostic approach.

| Diagnostic study                  | Overall (N=330) | PV (N=61) | OSA (N=96) | CLD (N=31) | P    |
|------------------------------------|----------------|-----------|------------|------------|------|
| JAK2 test performed                | 166 (50%)      | 54 (89%)  | 38 (40%)   | 8 (26%)    |      |
| JAK2 V617F/exon12+                 | 52 (31%)       | 48 (89%)  | 2 (5.3%)a | 1 (12%)a  |      |
| BMB performed                      | 98 (30%)       | 58 (95%)  | 16 (17%)   | 3 (9.7%)   |      |
| Panmyelosis                        | 64 (66%)       | 55 (95%)  | 5 (31%)    | 1 (33%)    |      |
| Chest image performed              | 317 (96%)      | 56 (92%)  | 96 (100%)  | 29 (94%)   |      |
| Any alteration                     | 127 (40%)      | 24 (43%)  | 42 (44%)   | 24 (83%)   |      |
| Spirometry performed               | 222 (67%)      | 34 (56%)  | 76 (79%)   | 25 (81%)   |      |
| Normal                             | 150 (68%)      | 26 (76%)  | 46 (61%)   | 2 (8.0%)   |      |
| Obstructive                        | 22 (9.9%)      | 5 (15%)   | 6 (7.9%)   | 8 (32%)    |      |
| Restrictive                        | 40 (18%)       | 1 (2.9%)  | 18 (24%)   | 14 (56%)   |      |
| Obstructive+restrictive            | 10 (4.5%)      | 2 (5.9%)  | 6 (7.9%)   | 1 (4.0%)   |      |
| Polysomnography performed          | 110 (33%)      | 4 (6.5%)  | 96 (100%)  | 4 (13%)    |      |
| Apnea-hypopnea index               | 22 (9, 52)     | 30 (7, 57) | 29 (10, 64) | 6 (2, 11)  |      |
| Echocardiography performed         | 145 (44%)      | 16 (26%)  | 56 (58%)   | 21 (68%)   |      |
| LVEF (%)                           | 65 (60, 70)    | 67 (60, 70) | 66 (60, 70) | 68 (60, 70) |      |

Summaries presented in median (IQR) or N (%).

aThese three cases had the JAK2 V617F mutation but did not fulfill the diagnostic criteria for myeloproliferative neoplasm; they were classified as OSA or CLD during the diagnostic approach.

Abbreviations: CLD, chronic lung disease; LVEF, left ventricular ejection fraction; OSA, obstructive sleep apnea; PV, polycythemia vera.

The proportion of elevated lactate dehydrogenase (LDH) (57% in PV vs. 21% in OSA and 41% in CLD, P=0.002), and a higher proportion of iron deficiency (43% in PV vs. 17% in OSA and CLD). Patients with CLD had a higher proportion of high erythropoietin levels (50% in CLD vs. 5.1% in PV and 36% in OSA), lower pO2 (median of 51 mmHg in CLD vs. 68 mmHg in PV and 60 mmHg in OSA), and lower SaO2 (median of 83.7% in CLD vs. 93.4% in PV and 91.9% in OSA).

Table 4 shows the complementary studies performed during the diagnostic approach. A test for detecting the Janus kinase gene (JAK2) mutation was performed in 50%, bone marrow biopsy (BMB) in 30%, chest image in 96%, spirometry in 67%, polysomnography in 33%, and echocardiogram...
raphy in 44% of the patients. In patients with PV, 89% had a JAK2 mutation, and 95% had panmyelosis in the BMB. In patients with CLD, 83% had abnormal chest images, and 92% had abnormal spirometry results. In patients with OSA, the median apnea-hypopnea index was 29 (IQR, 10–64), and 39% had abnormal spirometry results.

**Therapies received and events during follow-up**

Concerning the treatment for erythrocytosis and its complications, 42% of the patients had at least one phlebotomy, 54% received aspirin, 16% received anticoagulants, and 24% received oxygen or continuous positive airway pressure. A quarter of the patients did not receive any specific treatment.

At the time of the last vital status update (January 31st, 2019), patients had been followed up for a median of 44 months (IQR, 20–99 mo), and there were 38 events of thrombosis, 23 significant hemorrhages, and 15 deaths. The incidence rates of thrombosis, major bleeding, and mortality were 2.32, 1.36, and 0.86 cases per 100 person-years, respectively. When comparing these incidence rates among patients with PV, OSA, and CLD, the incidence rate of thrombosis was significantly higher in patients with PV and CLD than in those with OSA (incidence rates of 4.51 and 6.24 vs. 1.46 cases per 100 person-years, \( P=0.009 \)), as well as the mortality rate (mortality rates of 2.72 and 2.43 vs. 0.17 cases per 100 person-years, \( P=0.003 \)). A detailed description of events during follow-up is presented in Table 5 and Figs. 1–3.

**Table 5. Main outcomes during follow-up.**

| Overall (N=330) | PV (N=61) | OSA (N=96) | CLD (N=31) | \( P \) |
|-----------------|-----------|------------|------------|-----|
| Time to diagnosis (mo) | 9 (2, 32) | 3 (1, 12) | 14 (4, 44) | 4 (0, 18) | < 0.001 |
| Time of follow up (mo) | 44 (20, 99) | 58 (26, 99) | 60 (28, 104) | 30 (11, 55) | 0.017 |
| Cumulative incidence | | | | |
| Thrombosis | 38 (12%) | 13 (21%) | 8 (8.3%) | 7 (23%) | 0.029 |
| Major bleeding | 23 (7.0%) | 6 (9.8%) | 9 (9.4%) | 2 (6.5%) | > 0.9 |
| Death | 15 (4.5%) | 9 (15%) | 1 (1.0%) | 3 (9.7%) | 0.001 |
| Incidence rate (cases/100 person-years) | | | | |
| Thrombosis | 2.32 | 4.51 | 1.46 | 6.24 | 0.009 |
| Major bleeding | 1.36 | 1.93 | 1.62 | 1.69 | 0.9 |
| Death | 0.86 | 2.72 | 0.17 | 2.43 | 0.003 |

Summaries presented in median (IQR) or N (%).

Abbreviations: CLD, chronic lung disease; OSA, obstructive sleep apnea; PV, polycythemia vera.

**Fig. 1.** Thrombosis free survival by final diagnosis.
Fig. 2. Major bleeding free survival by final diagnosis.

Fig. 3. Overall survival by final diagnosis.

Finally, the hazard ratios obtained by fitting the Cox regression models are provided in Table 6. We estimated that, among subjects of the same sex, age, BMI, and diabetes, hypertension, and smoking status, the adjusted hazard ratio for thrombosis, comparing patients with OSA and CLD with those with PV were 0.16 (95% CI, 0.05–0.51; \( P=0.002 \)) and 0.99 (95% CI, 0.38–2.62; \( P=0.99 \)), respectively. Similarly, the adjusted hazard ratios for major bleeding, comparing patients with OSA and CLD with those with PV were 0.99 (95% CI, 0.28–3.53; \( P=0.98 \)) and 0.79 (95% CI, 0.15–4.13; \( P=0.78 \)), respectively, and the adjusted hazard ratios for mortality comparing patients with OSA and CLD with those with PV were 0.01 (95% CI, 0.0002–0.55; \( P=0.024 \)) and 0.79 (95% CI, 0.18–3.55; \( P=0.76 \)), respectively.
DISCUSSION

We retrospectively analyzed the clinical and laboratory data of 330 patients with erythrocytosis at our institution to assess the relationship between the etiology of erythrocytosis and thrombosis. The present study is the largest cohort study on erythrocytosis in the Latin American population, and the first to provide an in-depth description regarding the assessment of this condition. Thrombotic events are a hallmark of myeloproliferative neoplasms, presenting in approximately 20% of patients, with PV as the initial manifestation. The spectrum of events includes arterial (e.g., ischemic stroke and myocardial infarction), venous (e.g., deep vein thrombosis and pulmonary thromboembolism), and unusual site thrombosis (e.g., cerebral sinuses and portal vein) [7]. In addition, they represent the first cause of morbidity and mortality in this group of patients [8, 9].

Historically, erythrocytosis has been associated with thrombotic events because of the primordial impact of erythrocyte mass on blood viscosity. In 1978, Pearson and Wetherley-Mein [10] published a retrospective analysis of 69 patients with PV correlating an Hct of >50% with an increased risk of thrombotic events. This study established an Hct of <50% and platelet count of <400×10^9/L as the goal of treatment [10]. Unfortunately, this goal was extrapolated to secondary causes of erythrocytosis, with a lack of evidence to support it.

Despite the inherent limitations, observational studies have shown that thrombosis does not accompany most forms of erythrocytosis [11]. The significant difference in the frequency of thrombotic events between PV and secondary erythrocytosis and the paradoxical increase in thrombotic events in patients with PV after phlebotomy defies the relationship between Htc, viscosity, and thrombosis [12, 13].

In particular, in cases of PV, novel insights have shown that thrombosis pathogenesis is complex and does not involve only red cells, platelets, and leukocytes [14]. The increase in the endothelial expression of cellular adhesion molecules,
the presence of neutrophil extracellular traps, and interactions between erythrocytes and platelets through the FAS-FAS ligand pathway could explain how patients experience thrombotic events before meeting the diagnostic criteria for PV or despite meeting the goals of Hct after therapy [14, 15].

Despite the comparable rates of thrombotic events observed between PV and CLD in our study, other studies have shown that COPD per se increases the risk of thrombotic events without a direct relationship with the presence of erythrocytosis [16]. The thrombotic risk could be related to factors such as cytokines, infections, and age of participants. This study does not directly address the factors involved case by case; therefore, we could not discard the potential role of these factors. In 2019, Mao et al. [17] evaluated 151 COPD patients with secondary erythrocytosis (Hb ≥17 g/dL); 23.2% were treated with phlebotomy, and there was no significant difference in the prevalence of thrombotic events between phlebotomized and non-phlebotomized patients (31.4% vs. 22.4%, P=0.28). In the group of phlebotomized patients, patients who achieved an Hct of <52% did not show any significant benefit in the prevalence of thrombosis (25% vs. 36.8%, P=0.45) [17].

The controversies previously addressed extend to clinical guidelines. The British Society of Hematology only considers PV and Chuvash erythrocytosis as significant risk factors for thrombotic events and they were established as the goals of treatment with HCT values of <45% and 52%, respectively. In hypoxic pulmonary disease with erythrocytosis, the prognostic significance of erythrocytosis is not known, and the risk of pulmonary embolism is unclear. Management with phlebotomy is advised only in the context of hyperviscosity symptoms or Hct levels of >56%. The 2020 version of the American Society of Hematology for the management of venous thromboembolism (VTE) does not consider Hct as a risk factor for VTE, although this relationship has been suggested by epidemiologic studies [7, 18, 19].

Confirming the relationship between secondary erythrocytosis and thrombosis involves the inherent risk related to treatment (e.g., hypotension and iron deficiency in the case of phlebotomy) Our knowledge of thrombotic events in this particular group has changed notably in the last decade. Nevertheless, more studies are needed to evaluate the role of Hct in thrombosis genesis and the impact of phlebotomies in specific conditions. The difference in the rate of thrombotic events could likely be explained by concomitant factors and cellular changes that modify the thrombotic risk independently of Hct.

It is noteworthy that in 28% of the patients, a final diagnosis was not accomplished, and the median Hb level for this group was 18.6 g/dL (IQR, 18.1–19.4), which was significantly lower than that in the PV, OSA, and CLD groups (P=0.005). Since this study used medical records from patients who attended a referral hospital in Mexico City, where the altitude is high (high altitude is one of the crucial factors of erythrocytosis), it is possible that in patients without a definitive diagnosis, erythrocytosis was secondary to these geographical characteristics.

The inherent limitations of this analysis include the retrospective nature of the design. The JAK2 mutation test was routinely performed until January 2014, and for patients diagnosed before 2014, the JAK2 mutation was performed in bone marrow tissue when biopsy was available. In addition, during the seventeen-year study, many great advances in medical practice were developed and more diagnostic resources were available, making a heterogeneous diagnostic assessment through time. Another limitation is that the study was performed at a high altitude; therefore, the results may not be applied directly to the general population. Nonetheless, this study provides a solid basis for future studies in Latin American populations.

In conclusion, the most frequent cause of erythrocytosis in this retrospective study was OSA, and a comprehensive assessment was frequently not accomplished. It is convenient to improve the diagnostic approach for suspected OSA with greater availability of polysomnography to achieve early treatment, avoid irreversible cardiovascular complications, and improve quality of life. The risk of thrombosis in CLD with erythrocytosis is comparable to that of PV. Further, larger-scale studies are needed to confirm these findings and evaluate the benefits of preventive management of COPD with erythrocytosis similar to PV.

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Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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