SYSTEMATIC REVIEW

Secondary polycythemia and venous thromboembolism: a systematic review [version 1; peer review: awaiting peer review]

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Abstract

Background
Secondary polycythemia is an acquired condition characterized by an elevation in red blood cell (RBC) mass either in response to tissue hypoxia or inappropriate erythropoietin (EPO) secretion. It is proposed that the elevation of RBC mass in secondary polycythemia can lead to hyperviscosity and VTE. This systematic review aims to assess the relationship between secondary polycythemia and venous thromboembolism and discuss diagnostic strategies and management of secondary polycythemia and VTE.

Methods
This systematic review was conducted on September 2, 2022, and followed PRISMA guidelines to select and analyze relevant articles using the following databases: PubMed, ScienceDirect, and CINAHL. The queries used were “secondary polycythemia AND venous thromboembolism,” “secondary polycythemia AND deep vein thrombosis,” “secondary polycythemia AND pulmonary embolism,” “chronic obstructive pulmonary disease AND venous thromboembolism,” “chronic obstructive pulmonary disease AND deep vein thrombosis,” “chronic obstructive pulmonary disease AND pulmonary embolism,” “high altitude AND venous thromboembolism,” “high altitude AND deep vein thrombosis,” “high altitude AND pulmonary embolism,” “smoking AND venous thromboembolism,” “smoking AND deep vein thrombosis”, “smoking AND pulmonary embolism”, “hyperventilation AND venous thromboembolism”, “hyperventilation AND deep vein thrombosis”, “hyperventilation AND pulmonary embolism”, “testosterone AND venous thromboembolism”, “testosterone AND deep vein thrombosis”, and “testosterone AND pulmonary embolism.” The search duration was set from 2012–2022. Relevant publications were selected based on the inclusion and exclusion criteria.
Results
The initial search generated 5,946 articles. After narrowing the search based on inclusion and exclusion criteria, 30 articles were selected for this systematic review.

Conclusion
We found evidence to support the relationship between secondary polycythemia and VTE. Therapies targeting the factors that lead to secondary polycythemia can correct it and prevent VTE progression. If VTE occurs as a result of secondary polycythemia, anticoagulation therapy is recommended or inferior vena cava filters if contraindicated.

Keywords
Secondary Polycythemia, Venous Thromboembolism, Chronic Obstructive Pulmonary Disease, Smoking, High Altitude, Obstructive Sleep Apnea, Testosterone Therapy, erythropoietin

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Introduction

Polycythemia is an increase in red blood cell mass and can be categorized as primary or secondary polycythemia. Primary polycythemia encompasses germline mutations that cause an overproduction of red blood cells (RBCs). Germline mutations could affect hematopoietic growth factor erythropoietin (EPO) function or circulation, partial pressure of oxygen (P50), or intracellular oxygen sensing. Conversely, secondary polycythemia is acquired over a patient’s lifespan. This could result from a malignant neoplasm of hematopoietic stem cells or other organ disease states. Tissue hypoxia is one of the most frequent disease states responsible for the development of secondary polycythemia. Other causes are pulmonary disease, cyanotic heart disease, obstructive sleep apnea, renal cell carcinoma, and renal lesions. Further, acquired polycythemia can directly affect the expression of EPO, triggering a dramatic increase in EPO production. EPO is critical for starting the cascade of pathways necessary for red blood cell production. Thus, other parts of the red blood cell production pathway downstream of EPO can be impacted to lead to acquired polycythemia.

In hypoxia-induced disease states, reduced tissue oxygenation results in an upregulation of EPO as a compensatory mechanism. Red blood cell mass increases in an effort to improve tissue perfusion but does not mediate the longstanding hypoxemia. As a result, EPO, and subsequently red blood cells, are continuously produced. Blood viscosity dangerously increases to a point where unintentional blood coagulation can occur. Studies have also suggested that plasma fibrinogen plays a prominent role in the hemostatic imbalance, as it has impaired functionality in patients with secondary polycythemia. This highlights just one aspect of the complex blood profile of patients with secondary polycythemia in which there is an increased risk of thrombosis.

Due to the complex hemostatic profile of patients with secondary polycythemia, thrombosis is an outcome that must be analyzed for necessary interventions to be made; in particular, venous thromboembolism will be explored as it pertains to secondary polycythemia and its hypercoagulable state. Venous thromboembolism (VTE) encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is classified as a thrombosis originating in a deep vein, typically characterized as either an upper extremity DVT or a lower extremity DVT. PE differs from DVT in that it describes a thrombus that travels from its origin and gets lodged within the pulmonary arteries. PE may result in immediate death. Our systematic review will expand on the correlation between patients with diagnosed secondary polycythemia – excluding patients with Polycythemia Vera and other malignant neoplasms leading to secondary polycythemia – and subsequent VTE. Tissue hypoxia, chronic obstructive pulmonary disease, smoking, high altitude, obstructive sleep apnea, and testosterone therapy will be closely examined due to their association with secondary polycythemia. We will also discuss possible management methods and diagnostic interventions for patients with secondary polycythemia and VTE.

Methods

This systematic review paper strictly adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA was followed as it is a reliable method for selecting relevant publications to be included in systematic reviews and meta-analyses. A literature search for all articles about Secondary Polycythemia and VTE was conducted on September 2, 2022, using the following databases: PubMed, ScienceDirect, and CINAHL. The keywords used to identify publications were “secondary polycythemia AND venous thromboembolism,” “secondary polycythemia AND deep vein thrombosis,” “secondary polycythemia AND pulmonary embolism,” “chronic obstructive pulmonary disease AND venous thromboembolism,” “chronic obstructive pulmonary disease AND deep vein thrombosis,” “chronic obstructive pulmonary disease AND pulmonary embolism,” “high altitude AND venous thromboembolism,” “high altitude AND deep vein thrombosis,” “high altitude AND pulmonary embolism,” “smoking AND venous thromboembolism,” “smoking AND deep vein thrombosis,” “smoking AND pulmonary embolism,” “hypoventilation AND venous thromboembolism,” “hypoventilation AND deep vein thrombosis,” “hypoventilation AND pulmonary embolism,” “testosterone AND venous thromboembolism,” “testosterone AND deep vein thrombosis,” and “testosterone AND pulmonary embolism.” A focused keyword search was utilized to eliminate articles that did not contain both terms, as there were not a significant amount of studies containing both terms. The search duration was set from 2012-2022. We included case-control, cohort studies, comparative studies, clinical studies, prospective studies, retrospective studies, longitudinal studies, and observational studies. Once the search was complete, four co-authors manually screened the results and drew out relevant data from each article. We acknowledge that despite our genuine and maximal efforts, some relevant publications may have accidentally been left out. Our initial search generated 5,946 articles. After the manual screening, we narrowed the selection using our inclusion and exclusion criteria, and a total of 27 articles were ultimately included in this systematic review (Figure 1).

Inclusion criteria

The following inclusion criteria were applied: studies in English, human studies or in vivo, published over the past 10 years, primary or original research publications, full-text articles, and relevance to the research topic.
Exclusion criteria
Criteria for exclusion were as follows: animal studies or in vitro, review or systematic review articles, editorials and letters to the editor, practice guidelines, abstracts, book chapters, not full-text articles, publications with publication dates outside of the range (2012–2022), duplicates, and articles that are not relevant to our review. This information is visually presented in the PRISMA flow diagram (Figure 1).
Results
Our literature search yielded 5,946 articles: 454 from PubMed, 5,471 from ScienceDirect, and 21 from CINAHL. A total of 5,819 articles were removed based on the exclusion criteria (animal studies, reports, reviews or systematic reviews, abstracts, letters to the editor, book chapters, abstracts, articles that were not full-text, duplicates) and then 127 research articles were left to be included. Then, articles based on the content of diagnostic techniques, management, and treatment of VTE/PE/DVT and relevance to our topic were also screened and checked for eligibility. Based on this screening, an additional 97 articles were excluded, leaving 27 relevant publications to be incorporated into the systematic review (Figure 1). There were four case-control studies, 16 cohort studies, one comparative study, one clinical study, two prospective, one retrospective study, one longitudinal, and one observational study. The study characteristics are included in Table 1.

Discussion
Secondary polycythemia and VTE
RBC mass ranges from 23 to 29 mL/kg in healthy adult women and 26 to 32 mL/kg in adult men. Polycythemia is classified as an abnormal increase in red blood cell mass. Hematocrit values greater than 48% in women and greater than 51% in men, and hemoglobin values greater than 16.5 g/dL in women and 18.5 g/dL in men can be indicative of polycythemia. An elevation in RBC mass characterizes secondary polycythemia due to a physiologically appropriate response to chronic hypoxemia or due to a physiologically inappropriate secretion of factors that promote erythropoiesis. Polycythemia increases blood viscosity, which causes a diverse set of complications, including ischemia. Causes of secondary polycythemia due to chronic tissue hypoxia include COPD, smoking, high altitudes, hyperventilation syndromes such as obstructive sleep apnea and obesity, and androgens like testosterone.

Chronic hypoxemia drives erythropoiesis, which is the term used to describe the process of producing and maintaining RBC mass. Erythropoiesis is heavily regulated by various hormones, factors, and receptors, including erythropoietin (EPO). EPO’s expression is stimulated in response to hypoxia-inducible factors. The resultant physiological increase in erythrocytes enhances the oxygen-carrying capacity of the blood to facilitate adequate oxygen perfusion to hypoxic tissues. Despite this physiological process, complications may arise. Complications of secondary polycythemia can include strokes, pulmonary hypertension, blood hyperviscosity, and venous thromboembolism. In a 2016 study conducted in the USA, a diagnosis of VTE was found in 4.8% of patients with secondary polycythemia, whereas only 2.3% of patients without secondary polycythemia developed VTE. After adjusting for confounding variables like age, malignancy, strokes, previous VTEs, and pregnancies, the 2016 study concluded that patients with secondary polycythemia continued to pose a significantly greater risk in the development of VTE in comparison to patients without a secondary polycythemia diagnosis (p<0.01, OR: 1.87%; 95 CI: 1.58–2.22). Furthermore, a 2010 Serbian-based study on patients with chronic hypoxemia indicated that patients with secondary erythrocytosis had a significantly higher risk of developing pulmonary embolism in comparison to chronic hypoxemic patients without secondary erythrocytosis (p<0.001). Articles and statistical findings discussed in this review strongly associate Secondary Polycythemia and its causes, such as COPD, smoking, high altitudes, obstructive sleep apnea, and testosterone, with the development of venous thromboembolism.

COPD, secondary polycythemia, and VTE
The pathophysiology detailing the mechanisms of how COPD leads to hypoxemia, resulting in secondary polycythemia and increasing the risk of VTE, DVT, and PE, still needs to be clearly defined. This section aims to compile the currently proposed pathophysiologica mechanisms to gain further comprehension of the role of secondary polycythemia in the development of VTE. In a cross-sectional study, it was concluded that secondary polycythemia had a significant prevalence amongst COPD patients, as 10.8% or 26 out of 241 patients with COPD were also found to have secondary polycythemia.

COPD is a chronic respiratory disease with obstructive breathing patterns and is classified into emphysema and chronic bronchitis. The underlying cause of hypoxemia in mild, advanced, and acute exacerbations of COPD is a direct result of a mismatch in the ventilation/perfusion (V/Q) ratio. Emphysema is characterized by ventilation in areas of the lungs that are not properly perfused. This occurs due to the destruction of elastic fibers in the alveolar walls leading to a collapse of alveoli and obstruction of airflow; moreover, there is a loss of pulmonary capillaries and total surface area of alveoli. As a result, patients with emphysema have a high V/Q ratio leading to hypoxemia. However, chronic bronchitis results in hypoxemia in a different pathophysiological mechanism. Chronic bronchitis is characterized by decreased ventilation in perfused areas of the lungs. Obstruction of bronchi due to inflammation of the bronchial mucosa, hypersecretion of mucus, and fibrosis or edema is seen. As a result, patients with chronic bronchitis have an obstruction of airflow, leading to a low V/Q ratio and hypoxemia. As COPD progresses, worsening of the V/Q ratio mismatch and hypoxemia occurs. Rodríguez-Roisin et al. concluded that as COPD progressed, there was a worsening...
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<td>1 Park, 2016</td>
<td>Korea</td>
<td>Retrospective cohort study</td>
<td>1,375,842 outpatients</td>
<td>There were 670,258 cases of venous thromboembolism. In the general population, there was a prevalence of pulmonary embolism and deep vein thrombosis, respectively, in 113 and 138 patients. COPD patients had respective prevalence rates of 1,185 and 637.</td>
<td>Patients with COPD have a greater prevalence of PE and DVT in comparison to the general population.</td>
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<td>2 Jha et al., 2018</td>
<td>India</td>
<td>Case-control study</td>
<td>26 patients with or without DVT</td>
<td>The study consisted of healthy patients at high altitudes (&gt;3,648 meters), n=4, or with deep vein thrombosis, n=3. Likewise, there were 10 patients at sea level with deep vein thrombosis and nine healthy patients. Gene expression differed between high altitude and sea level deep vein thrombosis patients, 875 and 378 genes, respectively. Patients at high altitudes had an increased expression of hemostasis and platelet activation genes.</td>
<td>The change in hypoxia-responsive genes in high altitude patients could be responsible for the incidence of deep vein thrombosis.</td>
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<td>Algahtani et al., 2020</td>
<td>Saudi Arabia</td>
<td>Prospective study</td>
<td>234 patients at high altitudes or low altitudes</td>
<td>56.8% of deep vein thrombosis patients resided in high altitudes (2,200 meters), while 13% of patients resided in low altitudes (600 meters). High altitude patients had an increased incidence of pulmonary embolism and a significantly higher incidence of venous thromboembolisms, 81.9% compared to 21.9%. There was a significant increase in mean white blood cell count (p=0.043) and mean platelet count (p=0.005) in patients residing at high altitude.</td>
<td>Venous thromboembolism was more prevalent among people living at high altitudes.</td>
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<td>Ristić et al., 2013</td>
<td>Serbia</td>
<td>Prospective clinical study</td>
<td>842 patients with chronic obstructive pulmonary disease or respiratory failure</td>
<td>Patients identified with polycythemia, n=100, had a significant increase in the incidence of pulmonary embolism (39%) compared to those without polycythemia (11.06%), n=262 (p&lt;0.001). In addition, patients with polycythemia had a greater exacerbation of pulmonary dysfunction and pulmonary hypertension (p&lt;0.001).</td>
<td>Polycythemia is a significant risk factor for pulmonary embolism in patients with COPD or respiratory failure.</td>
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<td>Berhagaus et al., 2016</td>
<td>Germany</td>
<td>Prospective cohort study</td>
<td>106 patients</td>
<td>High-risk PE frequency was significantly greater among patients with moderate to severe obstructive sleep apnea (p=0.005).</td>
<td>OSA is a risk factor in patients with PE.</td>
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<td>Yeh et al., 2016</td>
<td>Taiwan</td>
<td>Prospective cohort study</td>
<td>70,026 patients with either chronic obstructive pulmonary disease (COPD) or asthma-COPD overlap syndrome</td>
<td>Patients with asthma-COPD (n=14,150) were at an increased risk of pulmonary embolism regardless of inhaled corticosteroid use, age, sex, comorbidity or oral steroids (adjusted HR of pulmonary embolism is 2.08, 95% CI, 1.56–2.76).</td>
<td>Asthma-COPD patients are at an increased risk of pulmonary embolism.</td>
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<td>Gregson et al., 2019</td>
<td>UK, Austria, USA, Sweden, Germany, Iceland, Australia, Denmark, Japan, Netherlands, Finland, Italy, Canada, Israel, Spain, Norway</td>
<td>Comparative study</td>
<td>731,728 patients</td>
<td>A risk factor for venous thromboembolism was smoking status (HR: 1.38 in the ERF), smoking status was associated with venous thromboembolism.</td>
<td>Smoking status is associated with venous thromboembolism.</td>
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<td>Morgan et al., 2016</td>
<td>UK</td>
<td>Case–control study</td>
<td>14,376 patients</td>
<td>COPD severity is strongly associated with venous thromboembolism but not regarding exacerbations.</td>
<td>COPD severity is strongly associated with venous thromboembolism but not regarding exacerbations.</td>
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<td>Kubota et al., 2016</td>
<td>USA</td>
<td>Prospective cohort study</td>
<td>14,654 patients</td>
<td>COPD may increase the risk of venous thromboembolism. Pulmonary emboli are more strongly associated with COPD than with DVTs.</td>
<td>COPD may increase the risk of venous thromboembolism. Pulmonary emboli are more strongly associated with COPD than with DVTs.</td>
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<td>Børvik et al., 2019</td>
<td>Norway</td>
<td>Prospective cohort study</td>
<td>9,577 patients</td>
<td>Severe respiratory symptoms, low SpO2, COPD, and COPD combined with severe respiratory symptoms are associated with increased risk of venous thromboembolism.</td>
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<td>Dong et al., 2018</td>
<td>China</td>
<td>Retrospective observational</td>
<td>551 patients with chronic obstructive pulmonary disease</td>
<td>29 patients had a venous thromboembolism, of which 18 had a pulmonary embolism, five had a deep vein thrombosis, and 6 had both. Between patients with and without venous thromboembolism, there was a statistically significant difference in GOLD grade (OR = 1.77, p=0.03) and imaging of visual emphysema (OR = 3.54, p=0.03). Smoking was positively associated with a risk of VTE in women. Visual emphysema was indicated as an independent risk factor for venous thromboembolic events, and the severity of COPD increases the risk of VTE.</td>
<td>Visual emphysema was indicated as an independent risk factor for venous thromboembolic events, and the severity of COPD increases the risk of VTE.</td>
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<td>Yuan et al., 2021</td>
<td>Sweden</td>
<td>Retrospective cohort study</td>
<td>66330 people, including men and women without VTE and cancer</td>
<td>A multivariable analysis revealed hazard ratios of 1.16 (1.03, 1.29) for past smokers, 1.09 (0.87, 1.36) for current smokers smoking 1–5 cigs/day, 1.24 (1.04, 1.48) for current smokers smoking 6–10 cigs/day, 1.47 (1.24, 1.75) for current smokers smoking 11–20 cigs/day, and 1.39 (0.80, 2.41) for current smokers smoking &gt;20 cigs/day. Smoking an additional five cigarettes per day has a constant 7% increase in the risk of venous thromboembolism in women. Smoking was positively associated with a risk of VTE in women.</td>
<td>Smoking was positively associated with a risk of VTE in women. Smoking an additional five cigarettes per day has a constant 7% increase in the risk of venous thromboembolism in women.</td>
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<td>Nair et al., 2022</td>
<td>India</td>
<td>Prospective longitudinal</td>
<td>960 healthy male soldier patients</td>
<td>Subjects residing in areas of high altitude were found to have higher rates of intrapulmonary embolism, increased levels of tissue factor pathway inhibitor (p&lt;0.003), and dampened fibrinolysis and enhanced coagulation. Patients at high altitudes are more likely to develop decreased natural anticoagulants, dampened fibrinolysis, and enhanced coagulation.</td>
<td>Patients at high altitudes are more likely to develop decreased natural anticoagulants, dampened fibrinolysis, and enhanced coagulation.</td>
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<td>Chen et al., 2015</td>
<td>Taiwan</td>
<td>Retrospective cohort study</td>
<td>1,000,000 individuals sampled from National Health Insurance Research Database</td>
<td>Deep vein thrombosis incidence in chronic obstructive pulmonary disease patients was 18.78 per 10,000 person-years in non-COPD patients and 13.36 per 10,000 person-years in COPD patients. Patients with chronic obstructive pulmonary disease had increased incidence of deep vein thrombosis compared to those without COPD.</td>
<td>Pulmonary embolism has a higher incidence in patients with chronic obstructive pulmonary disease compared to those without COPD.</td>
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<td>Chen et al., 2014</td>
<td>Taiwan</td>
<td>Retrospective cohort study</td>
<td>711,756 patients with and without chronic obstructive pulmonary disease</td>
<td>In the COPD cohort, there was a pulmonary embolism incidence of 1.23 per 10,000 persons/year (1.37/10,000 person-years). The control group had a four-times decrease in the incidence of PE (0.33/10,000 person-years). Pulmonary embolism incidence increases with age.</td>
<td>Pulmonary embolism incidence increases with age.</td>
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<td>Bertoletti et al., 2012</td>
<td>Spain, France, Italy, Israel, Switzerland, Germany</td>
<td>Prospective cohort study</td>
<td>28,920 adult patients with VTE</td>
<td>The initial most common type of VTE found in COPD patients were pulmonary embolisms with or without DVT (59%), and PE incidence was higher among COPD patients than PE patients that do not have COPD (OR 1.64, 95% confidence interval 1.49-1.80).</td>
<td>PE is seen more in COPD patients than non-COPD patients, and PE is the most common form of VTE among COPD patients.</td>
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<tr>
<td>de-Miguel-Diez et al., 2020</td>
<td>Spain</td>
<td>Retrospective cohort study</td>
<td>47,190 hospitalizations for PE</td>
<td>The incidence of PE was higher among COPD patients than non-COPD patients (IRR: 1.16, 95% confidence interval: 1.13-1.19).</td>
<td>COPD patients are more likely to have PEs than patients without COPD.</td>
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<tr>
<td>Donnally III et al., 2019</td>
<td>USA</td>
<td>Retrospective study</td>
<td>199,493 high and low-altitude patients following 1-to-2-level lumbar fusion</td>
<td>DVT and PE were examined 90 days post-operation among 31,581 patients in high altitude and 31,581 patients in low altitude. Lumbar fusions performed at low altitude hospital facilities, &lt;100 feet, resulted in significantly fewer cases of pulmonary embolism 90 days postoperatively compared to high altitude hospitals, &gt;4,000 feet (p=0.01). Deep vein thrombosis incidence 90 post-operation followed a similar trend (p=0.078).</td>
<td>Patients who underwent lumbar fusions at high altitudes developed a greater number of pulmonary embolisms 90 days postoperatively compared to those at low altitudes.</td>
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<td>Cancienne et al., 2016</td>
<td>USA</td>
<td>Case-control study</td>
<td>458,655 patients who underwent arthroscopic partial meniscectomy and/or a chondroplasty</td>
<td>Patients who had the procedure done at high altitudes (n=11,687), &gt;4,000 feet, had significantly higher rates of venous thromboembolism (P=0.0003), pulmonary embolism (P=0.0099) and deep vein thrombosis (P=0.0066) 30 days post operation compared to patients at low altitudes (n=43,936), ≤100 feet. After 90 days, the patient population displayed a similar trend.</td>
<td>High altitude was a significant risk factor for venous thromboembolism in patients who underwent knee arthroscopies.</td>
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<td>Damodar et al., 2018</td>
<td>USA</td>
<td>Retrospective cohort</td>
<td>37,819 patients with total shoulder arthroplasties</td>
<td>Patients who had their procedures done at high altitudes (n=6,948), &gt;4,000 feet, were evaluated at 30 days and 90 days post-total shoulder arthroplasty and compared to matched patients at low altitudes (n=7,016), &lt;100 feet. At the 30-day follow-up, high altitude patients had a significantly higher rate of pulmonary embolism (p&lt;0.001). This was also evident 90 days postoperatively (p=0.03).</td>
<td>High altitude patients had a significantly higher incidence of pulmonary embolism than the low altitude cohort.</td>
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<td>Broggi et al., 2021</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>68,923 patients who underwent corrective procedures of the pelvic ring and/or acetabular fracture</td>
<td>At 30 days post-operation, patients at high altitudes (n=19,181), &gt;4,000 feet, had significantly increased odds of developing a pulmonary embolism (odds ratio: 1.47, p=0.029) compared to low altitude patients, &lt;100 feet. At 90 days post-operation, patients at high altitudes had an increased risk of pulmonary embolism (p&lt;0.001) as well as deep vein thrombosis (p=0.029).</td>
<td>High altitudes were associated with increased odds of developing pulmonary embolism and deep vein thrombosis.</td>
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<td>Tyson et al., 2016</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>46,058 patients who underwent knee arthroscopy</td>
<td>Patients at high altitudes had a significantly higher incidence of venous thromboembolism compared to low elevations, &lt;1,000 feet (p&lt;0.0001). Patients at high elevations had a 3.8 times higher chance of developing a venous thromboembolism compared to low altitude patients (p&lt;0.0001).</td>
<td>Secondary polycythemia is a risk factor for VTE. Patients at high altitudes had an increased risk of developing a venous thromboembolism following knee arthroscopies.</td>
</tr>
<tr>
<td>Damodar et al., 2018</td>
<td>USA</td>
<td>Case-control study</td>
<td>87,033 patients who previously underwent knee arthroplasty</td>
<td>At both 30 and 90 days postoperatively, high altitude patients had an increased rate of pulmonary embolism compared to low altitude patients (p=0.003 and p&lt;0.001, respectively).</td>
<td>Patients at high altitudes had a higher rate of pulmonary embolism both 30 and 90 days postoperatively compared to low altitude patients.</td>
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<tr>
<td>Giri et al., 2016</td>
<td>USA</td>
<td>Retrospective cohort study</td>
<td>6,840,854 hospitalizations</td>
<td>After adjusting for confounding variables such as age, stroke, malignancy, infection, history of VTE, long bone fracture, trauma, CHF, pregnancy, mechanical intubation, nephrotic syndrome, and hospital stays &gt; 5 days, patients with secondary polycythemia had a greater risk in developing VTE when compared to patients without secondary polycythemia (p&lt;0.01, OR: 1.87%).</td>
<td>Secondary polycythemia is a risk factor for VTE. After adjusting for confounding variables, patients with secondary polycythemia had a greater risk of developing VTE.</td>
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<tr>
<td>Ory et al., 2022</td>
<td>USA, Canada</td>
<td>Retrospective cohort study</td>
<td>74 million patients</td>
<td>5,842 males with low testosterone, who received testosterone therapy and developed polycythemia, were matched to 5,842 controls with low testosterone, who did not develop polycythemia. After adjusting for confounding variables such as age, smoking, history of cardiovascular disease, malignancy, and hospital stays &gt; 5 days, patients with polycythemia had an increased risk of major adverse cardiovascular events compared to controls (OR 1.75, 95% CI 1.58-2.22).</td>
<td>Polycythemia following testosterone therapy is an independent risk factor for major adverse cardiovascular events and venous thromboembolism.</td>
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Note: Table 1. Continued
Table 1. Continued

<table>
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<tr>
<th>Author</th>
<th>Country</th>
<th>Design study</th>
<th>Study population</th>
<th>Findings</th>
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<td>26  A.Q. Alkhedaide, 2019</td>
<td>Saudi Arabia</td>
<td>Prospective study</td>
<td>80 people who are either tobacco smokers or controls</td>
<td>Patients who were tobacco smokers had significantly increased red blood cell counts, hemoglobin concentrations, hematocrit, and neutrophils following a complete blood count. They also had a significant reduction in erythropoietin, 35%, and interleukin 7, 65%. Gene expression of RAG-1, RAG-2, and EPOR-1 were upregulated.</td>
<td>Tobacco smoking may lead to secondary polycythemia.</td>
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<td>27  Berghaus et al., 2016</td>
<td>Germany</td>
<td>Prospective cohort study</td>
<td>206 patients</td>
<td>A 3.75-fold risk of acute PE was observed in patients with moderate OSA compared to patients with milder OSA (p&lt;0.001).</td>
<td>Acute PE manifestation increases with the severity of OSA.</td>
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of the V/Q ratio mismatch as well as irregularities in the pulmonary blood gasses; however, in Global Initiative for Obstructive Lung Disease (GOLD) stage IV, there was only a modest worsening of the V/Q ratio mismatch when compared to GOLD stage I.\textsuperscript{19,20} A low V/Q ratio and a decreased mixed venous oxygen tension (PvO\textsubscript{2}) are also seen in acute exacerbations of COPD (AE–COPD) due to the accumulation of mucus, inflammation of bronchi, and broncho-spasm.\textsuperscript{17} Therefore, hypoxemia occurs during acute exacerbations in COPD patients.\textsuperscript{17} Overall, COPD places patients in a state of chronic hypoxemia due to the persistence of airflow obstruction, leading to an upregulation of the hypoxia-inducible transcription factor-1 (HIF-1) and the release of EPO.\textsuperscript{18} This release of EPO results in secondary polycythemia, therefore, increasing the levels of hematocrit and red blood cell mass.\textsuperscript{21} As stated previously, an increase in hematocrit results in an increase in blood viscosity and promotes a state of hypercoagulability, increasing the risk of developing a VTE.\textsuperscript{2,10,22} Ristić \textit{et al.}, in a prospective study, found that 39\% of patients with severe exacerbations of COPD or pulmonary failure developed PE as opposed to only 11.06\% of patients with severe exacerbations of COPD or pulmonary failure developed PE.\textsuperscript{23} Therefore, this study concluded that polycythemia is an important risk factor for developing PE in patients with chronic hypoxemia, including those with severe exacerbations of COPD or pulmonary failure.\textsuperscript{23}

Numerous studies have concluded that an association between COPD and the development of VTE, DVT, and PE exists. Chen \textit{et al.} found that patients with COPD had an increased incidence of deep vein thrombosis, 18.78 per 10,000 person-years, compared to the non-COPD patients, 13.36 per 10,000 person-years.\textsuperscript{24} A retrospective cohort study with over a million participants revealed that patients with COPD had a greater prevalence of DVT and PE than the general population.\textsuperscript{25} In the general population, there were 138 participants with DVT and 113 participants with PE; however, in COPD patients, there were 637 patients with DVT and 1,185 patients with PE.\textsuperscript{25}

Despite the prevalence of DVT, many studies concluded that pulmonary embolisms are more prevalent in COPD patients. A clinical study revealed that the common initial VTE in COPD patients is PE with or without DVT (59\%).\textsuperscript{26} Bertoletti \textit{et al.}, in a prospective cohort study, stated that pulmonary embolisms are the most common type of VTE amongst COPD patients, and the incidence of PE is higher in comparison to patients who do not have COPD (OR 1.64, 95\% confidence interval, 1.49–1.80).\textsuperscript{20} In a retrospective cohort study, de-Miguel-Diez \textit{et al.} also concluded that COPD patients are more likely to experience PE than patients with COPD because the study found that patients with COPD had a higher incidence of PE than patients without COPD.\textsuperscript{27} Another clinical study found that COPD patients had a higher incidence of PE (1.37/10,000 persons/year) when compared to the control group who did not have COPD and had a four-times decrease in the incidence of PE (0.35/10,000 person/year).\textsuperscript{28} Kubota \textit{et al.} also concluded that pulmonary embolisms are associated stronger with COPD than with DVTs and discovered that the risk of VTE was increased in patients with respiratory symptoms and normal spirometry (hazard ratio: 1.40) or COPD (hazard ratio: 1.33).\textsuperscript{29} Pulmonary embolisms are also the common type of VTE seen in patients with asthma–COPD overlap syndrome (ACOS) as opposed to patients without ACOS (adjusted HR of pulmonary embolism is 2.08, 95\% CI, 1.56–2.76).\textsuperscript{30}

The risk of VTE is typically increased as COPD severity increases.\textsuperscript{31–33} In a retrospective clinical study with 551 COPD patients, the severity of COPD described by the GOLD staging system revealed an increased risk of VTE as the severity of COPD increased (OR = 1.77, p=0.035).\textsuperscript{33} Likewise, Børvik \textit{et al.} found the HR for VTE in patients with stage I and stage II COPD was 1.09, while the HR for VTE in patients with stage III and IV COPD was 1.92.\textsuperscript{32} Børvik \textit{et al.} findings also show an increased risk of VTE as the COPD severity increased.\textsuperscript{32} However, Morgan \textit{et al.} discovered that although there is a 17\% increase in the risk of VTE from GOLD Stage 1 to Stage 2 (OR =1.17; 95\% CI: 1.03–1.33), there was no increase in odds of developing a VTE in GOLD Stages 3 and 4 when compared to GOLD Stage 1 (OR: 1.16; 95\% CI: 1.02–1.33).\textsuperscript{31} As mentioned above, the lack of increased odds of developing a VTE can be attributed to only a modest worsening of the V/Q ratio mismatch in GOLD Stage IV compared to GOLD stage I.\textsuperscript{19}

An increased risk of developing VTE can be identified by noticing the signs and symptoms of COPD. Dong \textit{et al.}, in a retrospective clinical study, noted that visible emphysema is an independent risk factor for the development of VTE events in patients with COPD (OR: 3.54, p=0.03).\textsuperscript{34} Similarly, COPD patients with severe respiratory symptoms such as dyspnea, phlegm, and cough had more than a 1.4–2-fold risk of developing VTE.\textsuperscript{32}

The current pathophysiological mechanisms of how COPD results in secondary polycythemia can be associated with the prevalence of VTE patients with COPD. As a result, it is probable that an increased risk of developing VTE is correlated to developing secondary polycythemia in COPD patients.

\textbf{Smoking, secondary polycythemia and VTE}

The pathophysiology describing how cigarette smoking leads to hypoxemia, resulting in secondary polycythemia and increasing the risk of venous thromboembolism (VTE), has not been clearly defined or investigated. This section aims to assemble proposed pathophysiological mechanisms to understand further the role of secondary polycythemia in developing VTE.
Smoking results in chronic hypoxemia leading to a type of secondary polycythemia known as smoker’s polycythemia.\(^1\)\(^,\)\(^2\)\(^,\)\(^10\) Smoker’s polycythemia is identified as a combination of secondary polycythemia and relative polycythemia due to a decrease in the plasma volume as a result of exposure to chronic tobacco smoke.\(^3\)\(^,\)\(^22\) Cigarettes contain over seven thousand different chemicals from which nicotine and carbon monoxide have been identified to result in smoking-related hypoxia.\(^23\) Nicotine acts as a peripheral vasoconstrictor, resulting in decreased delivery of oxygen to the peripheral tissues, leading to hypoxia.\(^23\) Additionally, the carbon monoxide in cigarettes impairs the body’s normal gas exchange, further contributing to the hypoxia seen in cigarette smokers.\(^9\) Carbon monoxide has a higher affinity for hemoglobin than oxygen; as a result, carbon monoxide binds with hemoglobin more preferentially, resulting in the formation of carboxyhemoglobin.\(^34\) This formation of carboxyhemoglobin increases hemoglobin’s affinity for oxygen, causing a left shift of the carboxyhemoglobin dissociation curve, and decreases oxygen release from hemoglobin, causing a reduced delivery of oxygen to the kidneys and the release of erythropoietin.\(^2,\)\(^34\) In a clinical study, cigarette smoking was found to reduce subcutaneous tissue oxygen tension for approximately fifty minutes following a cigarette; therefore, a person smoking one cigarette pack a day would experience tissue hypoxia for approximately 15–20 hours each day.\(^35\) Thus, chronic smokers experience sustained hypoxemia, leading to erythropoietin (EPO) release and erythropoiesis resulting in an increase in red blood cell plasma concentration.\(^2,\)\(^34\) Despite this, some studies concluded that smoking and EPO levels have an inverse relationship, indicating that the secondary polycythemia which develops is not a result of increased EPO.\(^36\)\(^,\)\(^37\) In a clinical study with 40 smokers and 40 non-smokers, the smokers lacked elevated EPO; however, an increase in EPO receptor mRNA expression was found, which supported the increase in RBC count, hemoglobin, and hematocrit levels seen.\(^37\) In addition to the changes in EPO levels and erythropoiesis, smoker’s polycythemia also causes hemoconcentration, which is a shrinkage of the plasma volume leading to a relative increase in hematocrit.\(^2,\)\(^34\)\(^,\)\(^38\) Overall, cigarette smoking increases the hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentration, which in turn increases the hematocrit levels in the plasma.\(^10\) The resulting elevation in hematocrit levels directly increases blood viscosity.\(^2,\)\(^22\) Hematocrit levels and blood viscosity share a non-linear relationship in which minute increases in hematocrit generate disproportionate increases in blood viscosity.\(^22\) The resulting blood hyperviscosity precipitates a hypercoagulable state increasing the risk of developing a VTE.\(^2,\)\(^10\)\(^,\)\(^34\)

Several studies have concluded that an association between smoking and the development of VTE exists. In a prospective cohort study, the cohort with chronic hypoxemia and secondary erythrocytosis had a statistically significantly (p<0.001) higher incidence of pulmonary embolism (39%) when compared to the cohort with chronic hypoxemia without secondary erythrocytosis (10%).\(^24\) Additionally, a comparative study investigating cardiovascular risk factors for VTE concluded that smoking status is associated with a higher risk of venous thromboembolism (HR: 1.38 in the Emerging Risk Factors Collaboration) with similar hazard ratios for deep vein thrombosis and pulmonary embolism in the UK Biobank (HR: 1.23, 95% CI).\(^39\) A meta-analysis of 13 studies found a relative risk of 1.30 for venous thromboembolisms in current smokers after adjusting for body mass index (BMI), concluding an increased risk of VTE in current cigarette smokers.\(^40\) Another prospective cohort study found that current smoking and the incidence of VTE were positively associated with hazard ratios of 1.52 and 1.32 in women and men, respectively.\(^41\) Moreover, cigarette smoking and the risk for VTE were found to be positively correlated as a dose-response relationship. A systematic review and meta-analysis of 21 studies found a dose-response relationship between the number of cigarettes smoked per day (1–14, 15–24, and >25 cigarettes) and the relative risk of VTE (RR: 1.20, 1.33, and 1.63), respectively.\(^42\) In women, smoking an additional five cigarettes per day has a 7% increase in the risk of venous thromboembolism in women revealing a positive association between smoking and VTE.\(^43\)

The current proposed pathophysiological mechanisms of how smoking leads to secondary polycythemia can be linked to the incidence and prevalence of VTE/DVT/PE in current smokers. Therefore, it is plausible that the development of secondary polycythemia increases the risk of developing VTE.

**High altitude, secondary polycythemia, and VTE**

Venous thromboembolism development has been studied extensively among orthopedic surgeons to minimize the risk factors contributing to pulmonary emboli and deep vein thrombosis development.\(^34\) Several orthopedic procedure studies have identified higher altitudes as a modifiable risk factor predisposing individuals to develop VTEs.\(^44\) For example, a 2016 case–control study indicated high altitude as a significant risk factor in the development of VTE among patients undergoing knee arthroscopies.\(^45\) In a study conducted in 2006, the risk of developing DVT increased 24.5-times among lowland residing soldiers in higher altitudes for an extended period compared to lowland soldiers residing in low altitudes for an extended period.\(^46\) In an American-based retrospective study evaluating DVT and PE development 90 days after lumbar fusion surgery, it was noted that fusions performed at altitudes below 100 feet resulted in fewer reported cases of PE and DVT in comparison to fusions conducted at altitudes above 4,000 feet (p=0.01, p=0.078).\(^47\) Another retrospective cohort study conducted in 2018 on patients with total shoulder arthroplasties supports the notion that high altitude is a risk factor for VTEs.\(^44\) The evidence provided in the 2018 study highlighted that higher altitude patients had a higher rate of
PE both 1 month (p<0.001) and 3 months (p<0.03) after total shoulder arthroplasty operations in comparison to lower altitude patients receiving the same operation. Moreover, a case–control study performed in 2018 on patients undergoing total hip arthroplasty denoted that patient residing in higher altitudes had an increased rate of PE development when compared to patients at low altitudes at both 30 and 90 days postoperatively (p=0.003 and p<0.001). Another orthopedic study that evaluated VTE risks at varying altitudes indicated that high altitude patients had significantly increased odds of developing PE 30 days and 90 days postoperatively in comparison to lower altitude patients (OR: 1.47, p=0.029 and p<0.001). Similarly, a retrospective cohort study on patients who underwent knee arthroplasty highlighted patients at high elevation centers were at a significantly increased risk of VTE in comparison to low elevations (p<0.0001).

In addition to the extensively documented research that suggests higher altitudes as a modifiable risk factor in the development of VTE following orthopedic procedures, a prospective study on individuals residing at varying altitudes showcased a 56.8% and an 81.9% incidence of DVT and PE among higher altitude residents. The same study indicated a 13% and a 21.9% incidence of DV and PE among lower altitude residents.

The body’s compensatory mechanisms, when at higher altitudes, are believed to be a critical factor in the predisposition of patients to VTE. Hypoxia exposure at high altitudes leads to compensatory changes in blood oxygen affinity to aid in survival. Erythrocytosis, or the increased production of erythrocytes, is a thoroughly documented physiologically compensatory response to hypoxia found in populations living in higher altitude regions. The hypoxic environment stimulates hypoxia-inducible factors that act on the kidney and erythroid progenitor cells to secrete EPO. The EPO-stimulated red blood cell production improves tissue oxygenation and carrying capacity. Despite this improvement, the hematocrit can exceed 45% leading to hyperviscosity and complications such as thromboembolism.

A prospective study that evaluated thrombosis as a complication of extended stays at high altitudes associated a 30 times higher risk of vascular thrombosis with extended stays at higher and extreme altitudes. Some studies suggest that factors contributing to Virchow’s Triad predispose individuals living at high altitudes to develop VTE. Virchow’s triad includes blood stasis, hypercoagulability of blood, and vessel or endothelial damage. Individuals at high altitudes are exposed to environmental conditions such as hypoxia, hemoconcentration, low temperature, dehydration, severe weather, and thermally constrictive clothing. These exposures promote blood stasis and endothelial damage. In addition, the secondary polycythemia experienced by individuals residing in higher altitudes contributes to the hypercoagulable state of blood. Thus, VTE may occur due to the presence of all three factors leading to Virchow’s triad at high altitudes.

Some literature suggests that VTE development in high altitude environments is attributed to the activation of the coagulation cascade leading to an increased risk of thrombosis. Other studies suggest that subjects living in areas of higher altitude have higher rates of thrombosis due to decreased levels of anticoagulants such as tissue factor pathway inhibitor (p<0.001), thrombomodulin (p=0.016), enhanced coagulation (FXa: p<0.001) (PVIIa: p<0.001), and dampened fibrinolysis. The enhancement of coagulation and dampening of anticoagulant factors could promote thrombus formation and subsequent VTE development in high altitude patients. In addition, other studies postulate that high altitude induced VTEs are caused by increased expression of platelet activation genes and elevated mean platelet count (p=0.005). Moreover, another study suggests that elevated VTE rates in high altitude patients are caused by a thrombotic milieu achieved by an agglomeration of erythrocytosis, elevated platelet count, increased plasma activation, raised fibrinogen levels, dehydration and hypoxia.

Obstructive sleep apnea, secondary polycythemia, and VTE

Obstructive sleep apnea (OSA), a sleep-breathing disorder, is caused by recurrent episodes of complete or partial collapse of the airway during rest. OSA leads to sleep fragmentation and hypoxia, which results in polycythemia. The notion that OSA can lead to the development of secondary polycythemia was made evident in a 2015 study. Within this study, 77,518,944 discharges were analyzed, and a statistically significant association was made between OSA and secondary polycythemia (OR: 5.90, 95% CI or CI 5.64–6.17). Moreover, growing evidence suggests obstructive sleep apnea may be a risk factor for VTE. This is highlighted in a German-based prospective cohort study that stated high risk pulmonary embolism frequency was significantly greater among patients with moderate to severe sleep apnea (p=0.005). Further, research suggests that the severity of OSA may be indicative of acute pulmonary embolism manifestation. This phenomenon can be explained by increased hypoxia-inducible factor-1 (HIF-1) expression to compensate for the hypoxic environment created by the recurrent episodes of airway collapse in obstructive sleep apnea. Hypoxia-inducible factors act on the kidney and erythroid progenitor cells to upregulate the secretion of erythropoietin (EPO). EPO then stimulates erythrocyte production, resulting in polycythemia, to improve tissue oxygenation and O2 carrying capacity. The elevated hematocrit, blood viscosity, and hypercoagulability created by secondary polycythemia increase the risk of VTE.
Testosterone therapy, secondary polycythemia and VTE

The pathophysiological mechanisms describing the role of testosterone in secondary polycythemia and VTE development are not entirely understood. This section aims to gather proposed pathophysiological mechanisms to comprehend the role of secondary polycythemia in developing VTEs. Testosterone replacement therapy (TRT) is a treatment commonly used to increase testosterone levels in aging men experiencing symptomatic hypogonadism. 

TRT has many benefits, including increasing libido, sexual function, muscle strength, bone density, and bone strength. Despite these benefits, a common adverse effect seen in TRT is a remarkable increase in hematocrit and hemoglobin levels, indicating either polycythemia or erythrocytosis. TRT increases hematocrit and hemoglobin levels by increasing the set point of EPO for higher physiological hemoglobin levels and by increasing the bioavailability of iron by decreasing ferritin and hepatic levels. 

Osterberg et al. concluded that using testosterone can increase hemoglobin levels by 5–7% and that more than 20% of men treated with TRT develop polycythemia. The prevalence of secondary polycythemia developing while using testosterone varies from 2.5% to greater than 40%, depending on the testosterone formulation and dose. Moreover, studies have noted that testosterone increases the risk of polycythemia by four-fold in men who are androgen deficient. Another issue of concern with using testosterone is the development of VTE. In 2014, the US Food and Drug Administration (FDA) mandated warning labels to be added to testosterone, stating that testosterone may increase the risk of developing VTE. This risk of VTE may be linked to the increases in hemoglobin and hematocrit in secondary polycythemia. Ory et al., in a retrospective cohort study found that men who were being treated with testosterone and had secondary polycythemia experienced an increased risk of developing VTE (OR: 1.35, p<0.001). As a result, this study concluded that during the first year of testosterone therapy, testosterone is a risk factor for developing VTE. As previously discussed, an increase in hematocrit results in hyperviscosity of the blood, which places the person in a hypercoagulable state, increasing the risk of VTE.

Diagnosis of secondary polycythemia

Secondary polycythemia can develop from various conditions and situations, including smoking, chronic obstructive pulmonary disease, high altitudes, hypoventilation syndromes, and testosterone therapy. As a result, a detailed history and physical examination are the first tools to diagnose secondary polycythemia. A physician should also aim to ask many questions to elicit the etiology of the secondary polycythemia, such as a history of smoking, COPD, recently moved or stayed in an area of higher altitude, shortness of breath or snoring, and testosterone therapy or use of anabolic steroids. Additionally, patients with secondary polycythemia may have symptoms such as headache, dizziness, fatigue, and pruritus, which are also essential to elicit from patients. During a physical examination, fingernail clubbing, cyanosis, staining of nails and teeth due to nicotine, high body mass index, or scratch marks may be seen.

Moreover, the use of diagnostic and laboratory tests are vital and supplementary to diagnosing secondary polycythemia. Secondary polycythemia is defined as an abnormal increase in red blood cell (RBC) mass which can be evaluated by a complete blood count (CBC) or using chromium-51. Patients with increased hemoglobin and hematocrit levels typically have an increase in RBC mass; therefore, a CBC can be used as it can evaluate both hemoglobin and hematocrit levels. In a healthy adult, the RBC mass is 26–32 mL/kg in males and 23–29 mL/kg in females; as a result, values higher than 32 mL/kg and 29 mL/kg are seen as elevations in RBC mass. Hemoglobin and hematocrit values greater than 185 g/L and 51% and 165 g/L and 48% for males and females, respectively, are typically associated with elevated RBC masses. Another method to assess RBC mass is using chromium-51; however, due to its limited supply, it is rarely utilized. Secondary polycythemia usually has increased serum levels of EPO, while primary polycythemia has decreased serum levels of EPO. Therefore, it is vital to check the levels of serum EPO to differentiate between primary and secondary polycythemia. However, it is imperative to note that normal levels of EPO can be seen in patients with secondary polycythemia. One of the primary causes of secondary polycythemia is hypoxia. Oxygen saturation can be checked using pulse oximetry, and oxygen saturation lower than 92% indicates hypoxia. Renal, hepatic, neurological, and genetic etiologies may also result in secondary polycythemia. As a result, a renal ultrasound and computed tomography (CT), hepatic ultrasound and CT, brain CT, and genetic mutation testing for hypoxia inducible factor-2 alpha (HIF2A) and erythropoietin receptor may be necessary depending upon each patients presentation.

Treatment of secondary polycythemia

Correction of precipitating factors that lead to secondary polycythemia is the first line of management. If smoking precipitates hematologic abnormalities, it is recommended that the patient quit smoking and offer supportive, pharmacological, and psychological interventions. Low-flow O2 therapy to correct hypoxia is recommended in COPD-induced secondary polycythemia. However, oxygen toxicity and respiratory depression may develop from O2 therapy. Acute oxygen toxicity can manifest as central nervous system effects such as disorientation, dizziness, fatigue, paresthesias, tinnitus, and hyperventilation. Thus, it is imperative to monitor low O2 flow therapy administration. Phlebotomy, the removal of blood from a patient, can provide temporary relief in patients with secondary polycythemia. However,
phlebotomy is contraindicated in patients who develop secondary polycythemia due to high altitude living. In patients who reside in high altitudes, secondary polycythemia is a physiologically appropriate compensation mechanism instilled to maintain proper tissue oxygenation. When managing patients with secondary polycythemia induced by high-altitude living, a continuous evaluation is necessary to maintain a balance between circumstantial tissue oxygenation and hyperviscosity. The management of secondary polycythemia varies based on the development of complications, such as thromboembolic episodes. Although not extensively studied in patients with secondary polycythemia, aspirin may be useful in preventing thromboembolic episodes as per data extrapolated from studies involving polycythemia vera. Additionally, venesection, a technique performed to decrease cardiovascular death and thrombosis in polycythemia vera, may be useful in managing severe secondary polycythemia complications.

**Diagnosis of VTE**

Venous thromboembolisms are classified into two types: deep vein thrombosis and pulmonary embolism. Although DVTs and PEs share some diagnostic tests, some available tests are used only for either DVTs or PEs. Before imaging and laboratory tests are run, physicians first must suspect a DVT or PE based on the patient’s symptoms. Some symptoms of DVT are unilateral leg pain, tenderness, warmth, swelling, and redness, whereas some symptoms of PE are chest pain, dyspnea, hemoptysis, tachycardia, hypotension, and syncope. Once VTE is suspected, a physician must delegate the pretest probability (low, intermediate/moderate, or high) of a VTE in the patient so that a proper diagnostic plan can be chosen. The Wells model can determine the pretest probability for DVT, while the Wells model or the revised and modified Geneva rule can be used for PE. D-Dimer testing is a diagnostic test for DVT and PE. If the D-Dimer levels are higher than 500 ng/mL, it suggests that a patient has a PE; however, the age-adjusted D-Dimer threshold levels to rule out DVT are currently in progress. However, the American Society of Hematology (ASH) guidelines recommend against using positive results for D-dimer testing as the sole diagnostic test for VTE and suggests using additional diagnostic tests to diagnose VTE. Grégoire Le Gal et al., in the ASH 2018 guidelines, found that the sensitivities and specificities of D-Dimer testing for PE and DVT varied: PE (0.97, 0.39), upper extremity DVT (0.96, 0.47), and lower extremity DVT (0.96, 0.35), respectively.

Compression ultrasonography is a commonly used diagnostic test for DVT and is beneficial for first-time DVTs. Compression ultrasonography has a sensitivity of 0.90 and a specificity of 0.99 for diagnosing lower extremity DVT. Moreover, Doppler can be added to compression ultrasonography when needed to identify blood vessels precisely and when doubt arises regarding the compressibility of a specific segment of a blood vessel. Duplex ultrasound is used to diagnose upper extremity DVT and has a sensitivity of 0.87 and a specificity of 0.85. Another test that can be used to diagnose DVT is magnetic resonance venography which is typically used as an alternative when ultrasonography provides inconclusive results and when DVT is unable to be ruled out.

Computerized tomographic pulmonary angiography (CTPA) and V/Q lung scans are the two most commonly used diagnostic tests for PE. CTPA is preferred over V/Q scans because it diagnoses roughly 33% more PE and is readily available. However, CTPA exposes patients to ionizing radiation and utilizes a contrast medium. The contrast medium in CTPA can result in allergic reactions, can be toxic to the kidneys, and is contraindicated in patients who have severe renal impairment. The sensitivity and specificity of CTPA in diagnosing PE are 0.93 and 0.98, respectively. Magnetic resonance imaging (MRI) can be used in patients who cannot undergo CTPA as no intravenous contrast, and ionizing radiation is used. V/Q scans are also commonly used to diagnose PE because it does not use intravenous contrast, expose the patients to significantly lower amounts of radiation, and have similar sensitivity and specificity to CTPA. Lastly, compression ultrasonography can also be used, and its sensitivity and specificity are 0.49 and 0.96, respectively.

**Treatment of VTE**

VTE is categorized as deep vein thrombosis and pulmonary embolism and is a potentially critical consequence of secondary polycythemia. The general goal of VTE therapy is to prevent the extension of a thrombus and PE formation and to relieve symptoms while simultaneously preventing thromboembolic events in the future. The general management of VTEs includes three months of anticoagulant therapy such as low molecular weight heparins (LMWH), vitamin K antagonists, or direct factor Xa or direct factor IIa inhibitors. Regarding outpatient management of VTEs, LMWH and Vitamin K antagonists are generally employed.

In patients with an acute phase of VTE, prompt initiation of full-dose anticoagulation with LMWH, UFH, fondaparinux, apixaban, or rivaroxaban is recommended to prevent morbidity and mortality. LMWH or UFH can be continued as monotherapy or transitioned to vitamin K antagonists, edoxaban, or dabigatran therapy. Thrombolytic therapies such as alteplase and reteplase are reserved for patients with severe VTE, massive PE, or DVT coupled with threatened limb loss. They are reserved for critical cases as thrombolytic drugs have the potential to worsen life-threatening
conditions such as disseminated intravascular coagulation (DIC) and heparin-induced thrombocytopenia (HIT). In circumstances where anticoagulation therapy is contraindicated or has failed in patients with acute VTE, insertion of vena cava filters may be employed. Studies have shown that low intensity treatments are less effective at preventing recurrent thrombosis when compared to standard anticoagulation. Moreover, standard anticoagulation is as effective as high intensity treatments. However, if a patient refuses higher intensity and standard intensity treatment, lower intensity treatment is better at preventing recurrent thrombosis than an absence of therapy.

VTE recurrence risk can be classified into an abundance of categories. If a patient has never reported a VTE but receives one due to trauma or surgery, the recurrence rate is low. However, patients with malignancy have an elevated risk of recurrent thrombosis. Thus, it is recommended that these patients receive anticoagulation therapy for six months with LMWH if renal function is not impaired. In pregnant women who develop DVTs, LMWH is recommended. Additionally, inferior vena cava filters may be considered in pregnant women who develop PE near term due to the risk of hemorrhage.

Conclusion
In conclusion, compelling evidence exists to support the relationship between secondary polycythemia and the development of VTEs. Secondary polycythemia is a hematologic condition classified by an increase in RBCs driven by chronic hypoxia. We found evidence that supports the notion that secondary polycythemia can be precipitated by underlying hypoxic and pro-inflammatory conditions such as COPD, smoking, high altitude living, obstructive sleep apnea, and testosterone therapy, ultimately leading to VTE. The aforementioned conditions generate environments that elevate the expression of erythropoietin, causing a state of erythrocyte proliferation which leads to polycythemia. If erythrocyte proliferation exceeds a certain viscosity, unintentional blood coagulation can occur, leading to thrombotic and thromboembolic conditions. History taking and physical examination are pivotal in determining the underlying cause of secondary polycythemia. However, to accurately diagnose secondary polycythemia, elevated hematocrit, hemoglobin, serum EPO, and hypoxia must be observed. Further, if VTE is suspected, a pretest probability is recommended via the Wells model or Geneva criteria. D-dimer and compression ultrasonography can also be performed to diagnose VTE. PE specific diagnostic strategies include CTPA and V/Q scans. Furthermore, the treatment of secondary polycythemia begins with the correction of precipitating factors that lead to the development of the condition. Low oxygen flow therapy may be employed but must be monitored closely to avoid complications of oxygen toxicity. Repeated monitoring of high-altitude patients with secondary polycythemia is strongly advised, as erythrocytic compensation is necessary for survival at higher altitudes. If VTE develops as a consequence of secondary polycythemia, anticoagulation therapy must be employed. In patients wherein anticoagulation therapy is contraindicated, inferior vena cava filters may be considered. Finally, polycythemia vera management strategies such as aspirin therapy in the prophylaxis of thromboembolic episodes and venesection should continue to be explored in terms of efficaciousness in secondary polycythemia management.

Ethical statement
Not applicable. No patient data or animal studies were used in this review.

Consent from patients
In this review, no patient information was used. Consent is not applicable.

Data availability
Underlying data
No data are associated with this article.

Reporting guidelines
Panjwani, Amelia; Burle, Venkata Sathya; Raj, Rhea; Thomas, Sneha; Gorantla, Vasavi (2023): Secondary Polycythemia and Venous Thromboembolism: A Systematic Review. figshare. Figure. https://doi.org/10.6084/m9.figshare.22535791.v1

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