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Original Article

Coexistence of Beta Thalassemia Trait and Polycythemia: Hematological Insights, Diagnostic Challenges, and Clinical Implications

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ABSTRACT

Background: The coexistence of beta-thalassemia trait (BTT) and polycythemia complicates diagnosis by lowering hemoglobin (Hb) below WHO thresholds for polycythemia vera (PV), potentially masking both disorders. Objective: To determine the frequency of beta-thalassemia trait among patients with polycythemia and evaluate whether hematocrit remains useful for recognizing masked polycythemia. Methods: This descriptive cross-sectional study was conducted at Rehman Medical Institute and the University of Haripur, Pakistan, from December 2023 to December 2024. A total of 2,000 individuals underwent screening using complete blood count, hemoglobin electrophoresis, JAK2 mutation analysis, and serum erythropoietin measurement. Relative, post-treatment, and transformed polycythemia cases were excluded. Results: Polycythemia was identified in 120 individuals, including 100 males and 20 females, with a mean age of 41.8 ± 12.3 years. Primary polycythemia was present in 20 cases and secondary polycythemia in 100 cases. Beta-thalassemia trait coexisted in 15 patients, including 5 primary and 10 secondary polycythemia cases. Coincident cases showed lower hemoglobin values of 16.2–16.4 g/dL but elevated hematocrit values of 58.1–58.5%, with microcytosis, increased red cell distribution width, and elevated HbA2. Erythropoietin remained low in primary and high in secondary polycythemia. Conclusion: Beta-thalassemia trait may mask hemoglobin-based recognition of polycythemia, while hematocrit remains elevated and clinically useful for screening. Integrated interpretation of CBC indices, HbA2, EPO, and JAK2 testing is recommended. Keywords: Beta-thalassemia trait; polycythemia; hematocrit; hemoglobin; erythropoietin; JAK2.

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INTRODUCTION

Polycythemia represents an increase in circulating red cell mass or erythrocyte concentration and may arise from primary clonal myeloproliferative disease or secondary physiological and pathological stimuli. Polycythemia vera is an acquired clonal stem-cell disorder characterized by erythropoietin-independent erythroid proliferation, increased blood viscosity, and a clinically important risk of thrombotic, hemorrhagic, fibrotic, and leukemic complications (1, 2). In contrast, secondary erythrocytosis is a non-clonal condition that develops in response to hypoxia-driven or inappropriate erythropoietin production and is commonly associated with cardiopulmonary disease, smoking, renal disorders, sleep apnea, high-altitude exposure, or idiopathic causes (3, 4). Accurate distinction between primary and secondary

polycythemia is clinically important because diagnostic work-up, risk stratification, treatment, and follow-up differ substantially across these entities.

The diagnosis of polycythemia commonly begins with hemoglobin and hematocrit assessment, followed by etiological classification using molecular and biochemical markers such as Janus kinase 2 mutation testing and serum erythropoietin concentration. However, reliance on hemoglobin alone may be problematic in individuals with coexisting red-cell disorders that alter erythrocyte indices. Beta-thalassemia trait is a heterozygous inherited disorder caused by reduced beta-globin chain synthesis and is characterized by lower hemoglobin level, microcytosis, relatively increased red blood cell count, reduced mean corpuscular volume and mean corpuscular hemoglobin, and elevated hemoglobin A2 on electrophoresis. In Pakistan, beta-thalassemia trait is relatively common, with reported population frequencies ranging approximately from 5% to 8%, making it a relevant confounder in the interpretation of hematological screening profiles (5).

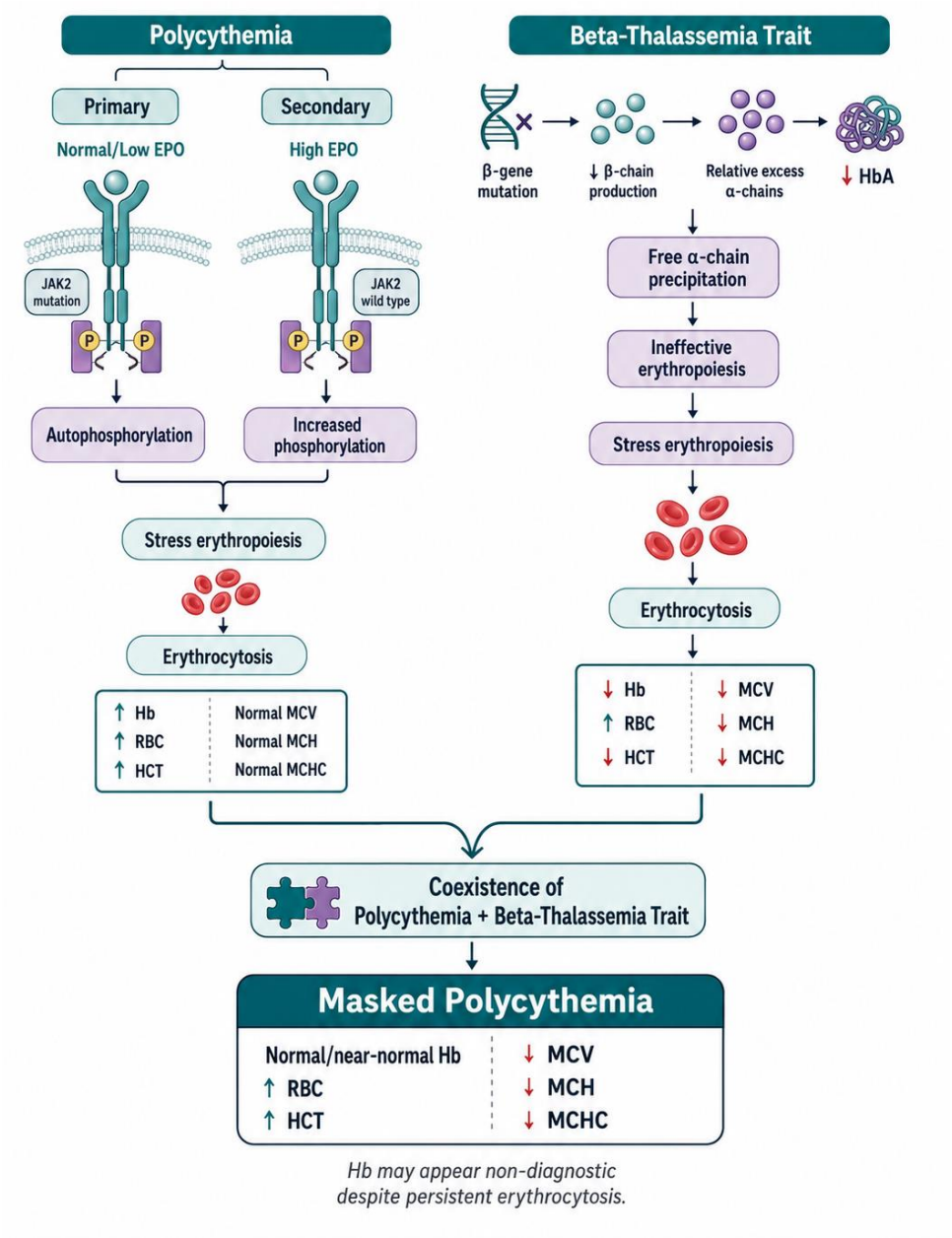

Figure 1 Pathophysiological Basis of Masked Polycythemia in Beta-Thalassemia Trait

Figure 1 illustrates the biological mechanism through which beta-thalassemia trait can mask the hematological recognition of polycythemia. The left pathway shows polycythemia arising through either primary or secondary mechanisms. In primary polycythemia, JAK2 mutation with normal or low erythropoietin promotes autonomous signaling and autophosphorylation, whereas secondary

polycythemia occurs with high erythropoietin and increased phosphorylation despite wild-type JAK2. Both pathways lead to stress erythropoiesis, erythrocytosis, increased hemoglobin, increased red blood cell count, increased hematocrit, and generally normal red-cell indices.

The right pathway demonstrates beta-thalassemia trait, where beta-globin gene mutation reduces beta-chain production, creating relative excess alpha chains, reduced HbA formation, free alpha-chain precipitation, ineffective erythropoiesis, and compensatory stress erythropoiesis. This produces erythrocytosis with reduced hemoglobin, altered hematocrit, increased RBC count, and microcytic hypochromic indices, including reduced MCV, MCH, and MCHC.

The convergence of both pathways explains masked polycythemia: when polycythemia coexists with beta-thalassemia trait, hemoglobin may appear normal or near-normal, while RBC count and hematocrit remain elevated and red-cell indices remain microcytic. This supports the central message of the study that hemoglobin alone may be insufficient for screening polycythemia in patients with beta-thalassemia trait.

The coexistence of beta-thalassemia trait and polycythemia creates a diagnostic challenge because both conditions influence red-cell parameters in different directions. Polycythemia tends to increase hemoglobin, hematocrit, and red blood cell mass, whereas beta-thalassemia trait may lower or blunt hemoglobin concentration through microcytosis despite maintaining or increasing the red blood cell count. As a result, patients with true erythrocytosis may fail to meet hemoglobin-based screening thresholds, producing a masked presentation in which hematocrit remains elevated while hemoglobin appears relatively lower. This pattern is clinically important because delayed recognition of polycythemia vera or misclassification of erythrocytosis may postpone JAK2 testing, erythropoietin assessment, risk stratification, and appropriate hematology referral (6–9).

Published literature on the coexistence of beta-thalassemia trait and polycythemia remains limited, and most available evidence consists of isolated reports or small observations rather than region-specific screening data. The issue is particularly relevant in populations where beta-thalassemia trait is common and where microcytosis may be misinterpreted as isolated thalassemia trait or iron deficiency rather than a masking factor for coexisting erythrocytosis. Previous reports have described coexistence of beta-thalassemia and polycythemia vera, but the frequency and hematological pattern of beta-thalassemia trait among patients with primary and secondary polycythemia in Pakistan have not been adequately defined (10).

Therefore, this study was conducted to determine the frequency of beta-thalassemia trait among patients identified with polycythemia and to compare hematological and biochemical profiles across primary polycythemia, secondary polycythemia, and coincident beta-thalassemia trait. The study specifically examined whether hematocrit remains a more reliable screening parameter than hemoglobin in patients with coexisting beta-thalassemia trait and polycythemia. The primary research question was whether beta-thalassemia trait masks hemoglobin-based recognition of polycythemia while preserving diagnostic elevation of hematocrit in patients undergoing hematological screening.

MATERIAL AND METHODS

This descriptive cross-sectional study was conducted to evaluate the coexistence of beta-thalassemia trait with polycythemia and to assess the hematological pattern associated with coincident disease. The study was carried out in the Department of Hematology, Rehman Medical Institute, in collaboration with the University of Haripur, Pakistan, over a one-year period from December 2023 to December 2024. A total of 2,000 individuals undergoing hematological screening during the study period were assessed for polycythemia and beta-thalassemia trait. A census-style screening approach was used, in which all eligible individuals assessed during the defined study period were considered for inclusion.

Participants were included if they underwent complete hematological evaluation for erythrocytosis and had the required laboratory investigations available for classification, including complete blood count, hemoglobin electrophoresis, JAK2 mutation testing, and serum erythropoietin measurement. Cases of relative polycythemia, post-treatment polycythemia, and polycythemia transformed into acute leukemia,

essential thrombocythemia, or myelofibrosis were excluded to avoid misclassification of erythrocytosis status and distortion of baseline hematological parameters. Clinical and demographic information was collected after written informed consent, including age, sex, and relevant clinical features used for etiological classification of polycythemia.

Polycythemia was identified using hematological evidence of erythrocytosis based on hemoglobin and hematocrit assessment, followed by classification into primary or secondary polycythemia using molecular and biochemical findings. Primary polycythemia was classified when erythrocytosis was associated with JAK2 mutation positivity and suppressed serum erythropoietin. Secondary polycythemia was classified when erythrocytosis occurred in the absence of JAK2 mutation and was supported by elevated erythropoietin concentration or clinically documented secondary causes such as smoking, hypoxia-related conditions, or idiopathic secondary erythrocytosis. Beta-thalassemia trait was identified using hemoglobin electrophoresis, with supportive red-cell indices including microcytosis, reduced mean corpuscular hemoglobin, relatively increased red blood cell count, and increased hemoglobin A2. Coincident cases were defined as patients fulfilling criteria for polycythemia who also demonstrated laboratory evidence of beta-thalassemia trait.

For each participant, 3 mL of venous blood was collected under aseptic conditions into three separate vacutainer tubes. Two lavender-top K3 EDTA tubes were used for complete blood count, hemoglobin electrophoresis, and molecular testing, while one red-top tube was used for serum erythropoietin analysis. Complete blood count was performed using a fully automated hematology analyzer, XN-1000, Sysmex, Japan. Hemoglobin electrophoresis was performed using the Capillary 2 system, Sebia, Evry, France, to identify beta-thalassemia trait through hemoglobin fraction analysis. Genomic DNA was extracted using the column method with a Viventis extraction kit, Malaysia, and JAK2 mutation analysis was performed by real-time polymerase chain reaction using the quantitative allele-specific amplification method with a Gensigue kit, United Kingdom. Serum erythropoietin concentration was measured using enzyme-linked immunosorbent assay.

The main study variables were age, sex, type of polycythemia, beta-thalassemia trait status, hemoglobin concentration, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, red cell distribution width, hemoglobin A2 percentage, JAK2 mutation status, and serum erythropoietin concentration. Hemoglobin and hematocrit were used to assess the degree of erythrocytosis, while mean corpuscular volume, mean corpuscular hemoglobin, red cell distribution width, and hemoglobin A2 were used to characterize the beta-thalassemia trait phenotype. JAK2 mutation status and erythropoietin level were used to support etiological classification of primary and secondary polycythemia.

To reduce measurement bias, all hematological and biochemical assessments were performed using standardized laboratory procedures and automated platforms. The use of a consistent diagnostic workflow for complete blood count, electrophoresis, molecular testing, and erythropoietin measurement helped minimize variation in classification. Exclusion of relative polycythemia, previously treated polycythemia, and transformed myeloproliferative disease was undertaken to reduce clinical misclassification and improve comparability of baseline hematological profiles. Potential confounding by beta-thalassemia trait was addressed analytically by separating coincident cases from non-coincident primary and secondary polycythemia groups.

Data were entered into Microsoft Excel and analyzed using SPSS version 22. Categorical variables were summarized as frequencies and percentages, while continuous variables were summarized as mean ± standard deviation. Group-wise comparisons of continuous hematological and biochemical variables were performed using analysis of variance. The diagnostic masking pattern was evaluated by comparing hemoglobin and hematocrit profiles between non-coincident polycythemia cases and coincident beta-thalassemia trait cases. Statistical significance was assessed using a p-value threshold of less than 0.05. Results were presented in tables and narrative form using group-specific denominators.

The study was conducted in accordance with the Declaration of Helsinki for research involving human participants. Ethical approval was obtained from the Ethics Committee of the University of Haripur under approval number DIR/UoH-EB/ED/0079, dated 22 August 2023. Written informed consent was obtained from all participants before data and sample collection. Participant information and laboratory data were handled confidentially and used only for research analysis.

RESULTS

Of 2,000 screened individuals, 120 were identified with polycythemia, giving an overall frequency of 6.0%. Among these 120 cases, 100 were male and 20 were female, with a male-to-female ratio of 5:1. The mean age of patients with polycythemia was 41.8 ± 12.3 years, with an age range of 19–69 years. Primary polycythemia was identified in 20 cases, while secondary polycythemia was identified in 100 cases. Among secondary polycythemia cases, smoking was reported in 45 cases, hypoxia-related causes in 35 cases, and idiopathic secondary erythrocytosis in 20 cases.

Table 1. Screening Profile and Etiological Classification of Polycythemia

Variable	Category	n	%
Screened individuals	Total screened	2,000	100.0
Screening outcome	Polycythemia	120	6.0
Screening outcome	No polycythemia	1,880	94.0
Sex among polycythemia cases	Male	100	83.3
Sex among polycythemia cases	Female	20	16.7
Polycythemia type	Primary polycythemia	20	16.7
Polycythemia type	Secondary polycythemia	100	83.3
Secondary polycythemia cause	Smoking	45	45.0
Secondary polycythemia cause	Hypoxia-related	35	35.0
Secondary polycythemia cause	Idiopathic	20	20.0

Percentages for screening outcome were calculated using 2,000 as the denominator. Percentages for sex and polycythemia type were calculated using 120 as the denominator. Percentages for secondary causes were calculated using 100 as the denominator.

The screened cohort showed that polycythemia was identified in 6.0% of individuals. Most polycythemia cases were male, representing 83.3% of identified cases. Secondary polycythemia accounted for 83.3% of polycythemia cases, while primary polycythemia accounted for 16.7%. Among secondary cases, smoking was the most frequently reported cause, followed by hypoxia-related causes and idiopathic secondary erythrocytosis. Beta-thalassemia trait coexisted with polycythemia in 15 of 120 patients, giving an overall coexistence frequency of 12.5% among polycythemia cases. Coexistence was observed in 5 of 20 primary polycythemia cases and 10 of 100 secondary polycythemia cases.

Table 2. Frequency of Beta-Thalassemia Trait Among Polycythemia Cases

Polycythemia Category	Total n	BTT n	BTT %	Non-BTT n	Non-BTT %
Primary polycythemia	20	5	25.0	15	75.0
Secondary polycythemia	100	10	10.0	90	90.0
Overall polycythemia	120	15	12.5	105	87.5

BTT: beta-thalassemia trait. Percentages were calculated within each row.

Beta-thalassemia trait was more frequent among primary polycythemia cases than secondary polycythemia cases, with coexistence observed in 25.0% and 10.0%, respectively. Overall, 12.5% of patients with polycythemia had laboratory evidence of beta-thalassemia trait, indicating that a clinically relevant minority of polycythemia cases had a coexisting microcytic red-cell disorder. Hematological and biochemical profiles differed across polycythemia categories and coincident beta-thalassemia trait subgroups. The reported mean hemoglobin was lower in coincident primary polycythemia with BTT and coincident secondary polycythemia with BTT than in the broader primary and secondary polycythemia groups. Hematocrit remained elevated in coincident groups, while microcytosis, reduced mean corpuscular hemoglobin, increased red cell distribution width, and elevated hemoglobin A2 characterized the beta-thalassemia trait phenotype.

Hb: hemoglobin; HCT: hematocrit; RBC: red blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; RDW: red cell distribution width; EPO: erythropoietin; HbA2: hemoglobin A2; BTT: beta-thalassemia trait. p-values are reported from the supplied manuscript. The source manuscript labels primary polycythemia as n=20 and secondary polycythemia as n=100 while also presenting coincident BTT subgroups. The summarized dataset does not provide recalculated means for mutually exclusive non-BTT groups.

Table 3. Hematological and Biochemical Profile Across Reported Polycythemia Groups

Parameter	Primary Polycythemia n=20 Mean ± SD	Secondary Polycythemia n=100 Mean ± SD	Primary Polycythemia + BTT n=5 Mean ± SD	Secondary Polycythemia + BTT n=10 Mean ± SD	p-value
Hb, g/dL	17.5 ± 1.2	17.8 ± 1.4	16.2 ± 1.0	16.4 ± 1.2	<0.001
HCT, %	54.8 ± 2.1	54.6 ± 2.3	58.5 ± 1.8	58.1 ± 2.0	<0.001
RBC, ×10^{12}/L	6.8 ± 0.6	6.7 ± 0.7	7.2 ± 0.5	7.1 ± 0.6	0.020
MCV, fL	88.2 ± 3.1	87.5 ± 3.4	72.4 ± 4.2	72.3 ± 4.0	<0.001
MCH, pg	29.1 ± 1.2	28.9 ± 1.3	24.1 ± 2.3	24.0 ± 2.1	<0.001
RDW, %	13.2 ± 1.1	13.5 ± 1.2	16.8 ± 1.5	16.7 ± 1.4	<0.001
EPO, mU/mL	4.2 ± 1.5	28.5 ± 10.2	3.9 ± 1.2	27.8 ± 9.5	<0.001
HbA2, %	2.1 ± 0.3	2.2 ± 0.4	4.8 ± 0.6	4.7 ± 0.5	<0.001

The coincident BTT groups showed a distinct hematological pattern. Mean hemoglobin was 16.2 ± 1.0 g/dL in primary polycythemia with BTT and 16.4 ± 1.2 g/dL in secondary polycythemia with BTT, compared with 17.5 ± 1.2 g/dL in the reported primary polycythemia group and 17.8 ± 1.4 g/dL in the reported secondary polycythemia group. In contrast, hematocrit remained higher in the coincident groups, with mean values of 58.5 ± 1.8% and 58.1 ± 2.0%. The coincident groups also demonstrated lower MCV and MCH values, higher RDW, and elevated HbA2, supporting the expected beta-thalassemia trait phenotype. EPO remained low in primary polycythemia with BTT and high in secondary polycythemia with BTT, consistent with the etiological distinction between primary and secondary polycythemia.

The manuscript-reported comparison of hemoglobin and hematocrit screening performance showed lower hemoglobin sensitivity than hematocrit sensitivity in coincident BTT cases. Hematocrit sensitivity was reported as 100% across comparisons, while hemoglobin sensitivity ranged from 80% to 85%.

Table 4. Reported Hemoglobin and Hematocrit Sensitivity for Recognition of Polycythemia

Comparison	Hb Sensitivity, %	HCT Sensitivity, %	OR	95% CI	p-value
Primary vs. Primary + BTT	85	100	0.45	0.22–0.92	0.020
Secondary vs. Secondary + BTT	82	100	0.38	0.19–0.76	0.005
Non-coincident vs. Coincident	80	100	0.42	0.25–0.71	<0.001

Hb: hemoglobin; HCT: hematocrit; OR: odds ratio; CI: confidence interval; BTT: beta-thalassemia trait. Values are reported from the supplied manuscript. The manuscript does not provide the full 2×2 diagnostic tables, threshold definitions, or reference-standard denominators needed to independently verify sensitivity, odds ratios, or confidence intervals.

The reported sensitivity pattern suggests that hemoglobin-based recognition may miss a proportion of coincident BTT cases, whereas hematocrit remained elevated across the reported comparisons. In the overall comparison, hemoglobin sensitivity was reported as 80%, while hematocrit sensitivity was reported as 100%. This supports the study's central observation that hematocrit may remain a useful screening marker when hemoglobin is relatively lowered by the microcytic phenotype of beta-thalassemia trait. However, because the source data do not provide the full diagnostic contingency tables, these diagnostic-performance estimates should be interpreted as manuscript-reported values requiring verification from individual-level or complete aggregate data. Overall, the results indicate that beta-thalassemia trait coexisted with 12.5% of polycythemia cases in the screened sample. Coincident cases showed lower hemoglobin, preserved or higher hematocrit, increased red blood cell count, microcytosis, reduced mean corpuscular hemoglobin, increased red cell distribution width, and elevated hemoglobin A2. The EPO pattern differentiated primary from secondary polycythemia, with low EPO in primary polycythemia and primary polycythemia with BTT, and high EPO in secondary polycythemia and secondary polycythemia with BTT.

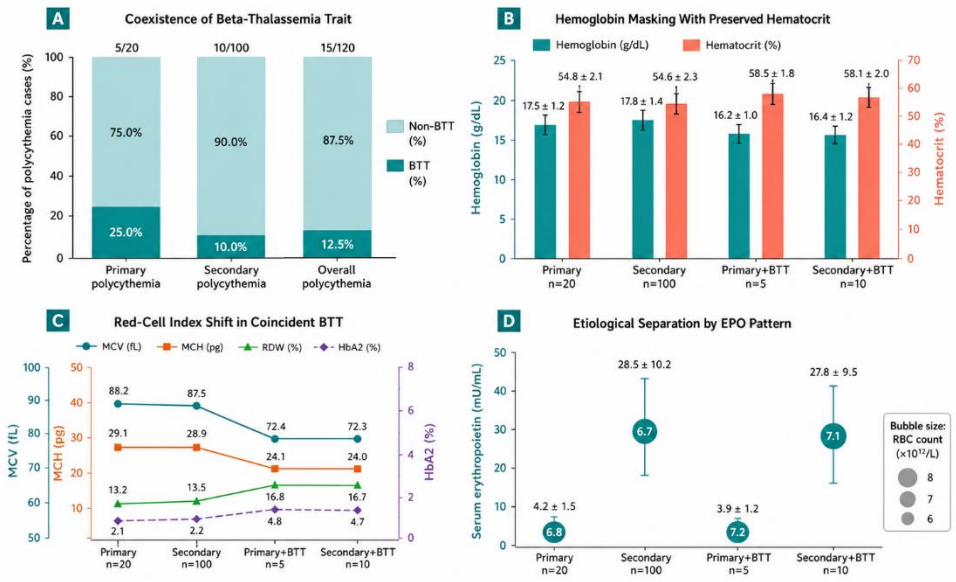

Figure 2 The multipanel figure summarizes the diagnostic masking pattern of beta-thalassemia trait among polycythemia cases.

BTT coexisted with 25.0% of primary polycythemia cases, 10.0% of secondary polycythemia cases, and 12.5% of all polycythemia cases. Coincident BTT groups showed lower mean hemoglobin values of 16.2–16.4 g/dL compared with 17.5–17.8 g/dL in the reported primary and secondary polycythemia groups, while hematocrit remained elevated at 58.1–58.5%. The red-cell index pattern showed marked microcytosis, with MCV approximately 72 fL, reduced MCH around 24 pg, increased RDW around 16.7–16.8%, and HbA2 elevation around 4.7–4.8% in coincident BTT cases. EPO values preserved etiological separation, remaining low in primary polycythemia with BTT and high in secondary polycythemia with BTT.

DISCUSSION

The present study evaluated the coexistence of beta-thalassemia trait among patients identified with polycythemia and demonstrated a clinically important hematological masking pattern. Among 2,000 screened individuals, 120 were identified with polycythemia, of whom 20 had primary polycythemia and 100 had secondary polycythemia. Beta-thalassemia trait coexisted in 15 of 120 polycythemia cases, giving an overall coexistence frequency of 12.5%. The coexistence was more frequent among primary polycythemia cases than secondary polycythemia cases, affecting 25.0% and 10.0%, respectively. This finding is particularly relevant in Pakistan, where beta-thalassemia trait is relatively common, because the microcytic phenotype may alter conventional hemoglobin-based interpretation of erythrocytosis and delay further evaluation in selected patients (5, 10).

The sex distribution showed a marked male predominance, with 100 male and 20 female patients among polycythemia cases, corresponding to a male-to-female ratio of 5:1. Male predominance has also been described in myeloproliferative neoplasms and polycythemia vera cohorts, although the ratio in the present study is higher than many previously reported series (11–13). This difference should be interpreted cautiously because the current sample included both primary and secondary polycythemia, and most cases were secondary rather than clonal polycythemia vera. The higher proportion of secondary polycythemia may reflect local exposure patterns, referral characteristics, smoking burden, hypoxia-associated conditions, or institutional screening practices. Therefore, the observed sex distribution should not be generalized as a sex-specific prevalence estimate for polycythemia vera without population-based sampling.

The principal diagnostic observation of this study was that coincident beta-thalassemia trait was associated with relatively lower hemoglobin values despite persistently elevated hematocrit. Mean hemoglobin values were lower in primary polycythemia with BTT and secondary polycythemia with BTT than in the reported primary and secondary polycythemia groups, while hematocrit remained elevated in the coincident groups. This pattern supports the biological plausibility that beta-thalassemia trait may blunt

hemoglobin concentration through microcytosis while preserving or increasing red blood cell count and hematocrit. The finding is consistent with the known hematological profile of beta-thalassemia trait, in which reduced mean corpuscular volume and mean corpuscular hemoglobin coexist with a relatively high red blood cell count and elevated hemoglobin A2. In such cases, hemoglobin alone may underestimate the degree of erythrocytosis, whereas hematocrit may provide a more reliable signal for further evaluation.

The red-cell indices in coincident cases supported the diagnosis of beta-thalassemia trait. Both primary polycythemia with BTT and secondary polycythemia with BTT showed marked microcytosis, reduced mean corpuscular hemoglobin, increased red cell distribution width, and elevated hemoglobin A2. These findings suggest that patients with erythrocytosis and unexpectedly low or borderline hemoglobin values should not be dismissed as isolated thalassemia trait or iron-deficiency-like microcytosis without assessing hematocrit, red blood cell count, hemoglobin electrophoresis, and the clinical context. Conversely, the presence of beta-thalassemia trait should not exclude concurrent primary or secondary erythrocytosis when hematocrit and red blood cell count are elevated.

Serum erythropoietin findings preserved etiological separation between primary and secondary polycythemia. EPO was suppressed in primary polycythemia and primary polycythemia with BTT, while it remained elevated in secondary polycythemia and secondary polycythemia with BTT. This distinction is important because the masking effect of BTT appears to influence hemoglobin interpretation but does not eliminate the value of EPO in differentiating primary from secondary erythrocytosis. Therefore, patients with elevated hematocrit, microcytosis, and low or suppressed EPO should undergo careful evaluation for clonal polycythemia, particularly with JAK2 testing and, when indicated, additional molecular or marrow assessment. Patients with elevated EPO require evaluation for secondary causes such as smoking, hypoxia-associated disorders, cardiopulmonary disease, renal pathology, sleep-disordered breathing, or idiopathic secondary erythrocytosis (6–9).

The reported comparison of hemoglobin and hematocrit sensitivity suggested that hematocrit remained elevated in all coincident cases, whereas hemoglobin sensitivity was lower. This supports the study's central inference that hematocrit may be a useful screening parameter for recognizing masked erythrocytosis in patients with beta-thalassemia trait. However, this finding should be interpreted as a screening observation rather than a complete diagnostic accuracy analysis. A formal diagnostic accuracy study would require clearly defined hemoglobin and hematocrit thresholds, a prespecified reference standard, complete 2×2 tables, confidence intervals for sensitivity and specificity, and analysis of both polycythemia and non-polycythemia participants. Therefore, the present data support the clinical usefulness of hematocrit in this context but should not be interpreted to mean that hematocrit alone can diagnose polycythemia vera.

The study has several limitations. First, the sampling frame requires cautious interpretation because participants were screened in a hematology-related setting rather than through a population-based design. As a result, the observed frequency of polycythemia and BTT coexistence should not be treated as a population prevalence estimate. Second, the reported aggregate tables do not provide recalculated means for mutually exclusive non-BTT subgroups, limiting precise comparison between primary polycythemia without BTT, primary polycythemia with BTT, secondary polycythemia without BTT, and secondary polycythemia with BTT. Third, CALR, MPL, and JAK2 exon 12 mutation testing were not reported, which limits full classification of JAK2-negative erythrocytosis and may underestimate uncommon clonal causes. Fourth, bone marrow morphology was not described, which may affect diagnostic certainty for polycythemia vera according to contemporary diagnostic frameworks. Fifth, the diagnostic performance estimates for hemoglobin and hematocrit require verification using individual-level data or complete aggregate diagnostic tables.

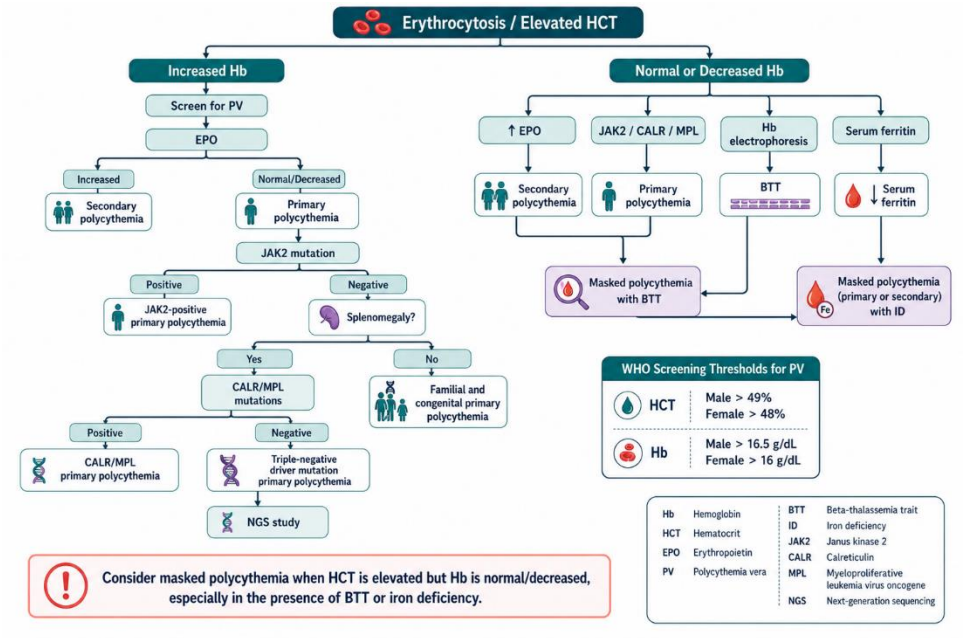

Figure 3 presents a structured diagnostic algorithm for evaluating erythrocytosis or elevated hematocrit, with special emphasis on masked polycythemia. The algorithm begins with elevated HCT or erythrocytosis and separates patients according to hemoglobin status. In patients with increased hemoglobin, the pathway follows conventional screening for polycythemia vera using EPO measurement. Increased EPO supports secondary polycythemia, while normal or decreased EPO supports possible primary polycythemia and prompts JAK2 mutation testing. JAK2-positive cases are classified as JAK2-positive primary polycythemia. JAK2-negative cases require further evaluation, including splenomegaly assessment, CALR/MPL mutation testing, consideration of triple-negative driver mutation disease, NGS testing, or familial/congenital primary polycythemia.

The right branch addresses patients with normal or decreased hemoglobin despite elevated HCT. This is the critical masked-polycythemia pathway. These patients require parallel assessment of EPO, JAK2/CALR/MPL mutations, hemoglobin electrophoresis, and serum ferritin. Elevated EPO suggests secondary polycythemia, while molecular positivity supports primary polycythemia. Hemoglobin electrophoresis identifies beta-thalassemia trait, which can lead to masked polycythemia with BTT. Low serum ferritin suggests iron deficiency, which can also mask primary or secondary polycythemia. The figure highlights that masked polycythemia should be considered when HCT is elevated but Hb is normal or decreased, especially in the presence of BTT or iron deficiency.

Despite these limitations, the study provides a clinically meaningful signal for diagnostic practice in regions with a high burden of beta-thalassemia trait. The findings suggest that patients with elevated hematocrit, high red blood cell count, microcytosis, and elevated HbA2 should be evaluated for coincident beta-thalassemia trait and polycythemia rather than being classified under a single diagnosis. A practical diagnostic pathway should include CBC review, red-cell indices, hemoglobin electrophoresis, serum erythropoietin, JAK2 mutation testing, and targeted evaluation for secondary causes. In suspected primary polycythemia with low or normal EPO and negative initial JAK2 testing, additional molecular testing and specialist hematology evaluation should be considered.

CONCLUSION

Beta-thalassemia trait coexisted with a clinically relevant proportion of polycythemia cases in this cross-sectional study and was associated with lower hemoglobin values despite persistently elevated hematocrit. The coincident phenotype was characterized by microcytosis, reduced mean corpuscular hemoglobin, increased red cell distribution width, elevated hemoglobin A2, and preserved etiological separation by serum erythropoietin pattern. These findings suggest that hematocrit, red blood cell count, red-cell indices, HbA2, EPO, and JAK2 testing should be interpreted together when evaluating erythrocytosis in regions where beta-thalassemia trait is common. Hematocrit may be particularly useful for recognizing masked erythrocytosis when hemoglobin is relatively lowered by beta-thalassemia trait, but

definitive classification of primary and secondary polycythemia requires integrated clinical, biochemical, and molecular assessment.

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