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Polycythemia vera disease profile in an African population—experience from a tertiary facility in Ghana

Solomon Gyabaah[1], Eunice Agyemang Ahmed[1], Adwoa Agyemang Adu-Gyamfi[1], Frederick Nkrumah Gyabaah[2], Afia Serwaa Bonsu[1], Ameyaw Prince Addo[3] and Ohene Kwaku Opare Sem[1,4]

Abstract

Objectives: The study describes the clinical and laboratory profile of the patients with polycythemia vera at Komfo Anokye Teaching Hospital in Kumasi, Ghana.

Methods and design: This was a retrospective hospital-based cohort study conducted from September 2020 to August 2022. Hematology clinic entry book was used to identify the patient's unique hospital code. Using these unique codes, retrospective data were collected using an Excel spreadsheet from the Hospital Lightwave health information management system (LHIMS) database.

Results: A total of 20 participants were recruited over the period of 2 years. The overall mean age was 51.53 ± 16.39 years. The hematological profile of the male participants revealed a mean hemoglobin of 18.25 ± 1.373 g/dl, mean hematocrit of 52 ± 3.47%, and a mean platelet of 345.5 ± 180.82. Comparatively, the mean hemoglobin, hematocrit, and platelet for the female participants were higher with figures of 19.26 ± 1.43 g/dl, 53 ± 3.61%, and 816 ± 935.32, respectively. Headache, tiredness, numbness, splenomegaly, and abnormal labs were the most common reasons why participants sought medical attention. Majority (60%) of the study participants had Janus Kinase 2 mutation. New-onset hypertension was identified in 45% of the study participants during follow-up. Thromboembolism was seen in 10% of the study population.

Conclusion: Polycythemia vera is an uncommon disease in Ghana mostly found in older males above 50 years. It is important to recognize it early to initiate therapy aimed at preventing common complications such as hypertension and thromboembolism. Polycythemia vera should be considered a differential diagnosis for patients with secondary hypertension.

Keywords

Polycythemia vera, profile, African population, Ghana

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Introduction

Polycythemia vera is a chronic myeloproliferative neoplasm that belongs to the classical BCR-ABL negative class together with essential thrombocytosis and primary myelofibrosis.[1] It is a stem cell hematopoietic disorder that is typified by erythrocytosis, leukocytosis and megakaryocytic hyperplasia with thrombocytosis, aquagenic pruritus, microvascular symptoms, and symptomatic splenomegaly.[2] Polycythemia vera is a rare condition with an estimated prevalence of 22 per 100,000 population.[3] It was first described by French doctor Louis Henri Vaquez (1860–1936) as a form of cyanosis with excessive and persistent hyperglobulinemia.[4]

In polycythemia vera, there is usually excessive red cell production with the release of pro-inflammatory cytokines which are secondary to the over-activation of the Janus

[1]Komfo Anokye Teaching Hospital, Kumasi, Ghana
[2]Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA
[3]Bridgeport Hospital/Yale New Haven Health, Bridgeport, CT, USA
[4]School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana

Corresponding author:
Solomon Gyabaah, Komfo Anokye Teaching Hospital, P.O. Box 1934, Kumasi, Ghana.
Email: solomongyabaah53@gmail.com

Kinase (JAK) 2 pathway which is a result of mutations in the *JAK2* gene.[5] Usually, the JAK pathway is tightly regulated to ensure normal blood cell production and function, but disruptions in the pathway can lead to disease states. Different experimental approaches to have been employed identify a mutation in the *JAK2* tyrosine kinase in most patients with polycythemia vera, essential thrombocythemia or primary myelofibrosis.[6]

Polycythemia vera is currently diagnosed as an increase in hemoglobin/hematocrit level above 16.5 g/dl/49% in men and 16 g/dl/48% in women, in the context of a *JAK2* mutation and characteristic bone marrow morphology.[7] There is an annual incidence of 1–3 cases per 100,000 individuals with a slight male predominance showing a ratio of 2:1.[8] The median age for polycythemia vera is 61 years with 10% of patients below 40 years of age.[9] Disease presentation includes tiredness, pruritus, epigastric discomfort, early satiety, diaphoresis, weight loss, and vasomotor symptoms such as headache, dizziness, visual disturbances, splenomegaly, symptoms of hyperviscosity, leukocytosis, thrombocytosis, microvascular symptoms (e.g., headaches, light-headedness, visual disturbances, atypical chest pain, erythromelalgia, and paresthesia), thrombotic and bleeding complications, and risk of leukemic transformation or fibrotic progression.[10,11] The hyperviscosity is due to increased cell mass and is responsible for some of the clinical manifestation and increased risk of thromboembolism.

Polycythemia vera is an important cause of major thrombotic events such as myocardial infarction, ischemic stroke, deep vein thrombosis, pulmonary embolism, and cerebral vein thrombosis.[12,13] These complications are fatal even in the setting of prompt optimal treatment. In prolonged and untreated cases of polycythemia vera, there can be transformation into myelofibrosis or acute myeloid leukemia with a poor prognosis.[14] It is therefore important that polycythemia vera is recognized early and appropriately treated.

In the 2008 WHO criteria, a hemoglobin level of greater than 18.5 g/dl in men or 16.5 g/dl in women or elevated red cell mass (RCM) >25% above mean normal predicted was a major criterion for diagnosing polycythemia vera.[15] However, in 2016 WHO revised the diagnostic criteria reducing the hemoglobin cut-offs to include a wide range of patients.[16,17] It is very important to recognize the clinical profile of patients with polycythemia vera to enable early detection and prompt treatment, especially in countries with low levels of formal education and health illiteracy where the patient usually reports late to health facilities.[18] A variation in the pattern of disease in the African population when compared to the Western population can be expected, based on significant differences in normal hematological parameters between these groups as a result of the effect of ethnic, dietary, environmental, and cultural factors.[19] The present study seeks to describe the complete clinical profile of the patients with polycythemia vera in the Komfo Anokye Teaching Hospital in Kumasi Ghana.

Materials and methods

Study design

This was a retrospective hospital-based cohort study of polycythemia vera patients seen at the Komfo Anokye Teaching Hospital from September 2020 to August 2022. Follow-up of patients was as scheduled by their attending physician according to the records. Detailed history and clinical information relating to age, sex, clinical presentations, complete blood count complications, and presence or absence of *JAK2* mutation were retrieved from case folders of eligible study participants.

Study site and population

The study was conducted at the Komfo Anokye Teaching Hospital, a 1200-bed tertiary facility in Ghana, that receives referrals from all over the country. The study population is made up of patients enrolled in the hematology clinic of Komfo Anokye Teaching Hospital with a diagnosis of polycythemia vera.

Diagnostic criteria used

1. Major criteria

- Hemoglobin >16.5 g/dl (men)
- Hemoglobin >16.0 g/dl (women)

or

- Hematocrit >49% (men)
- Hematocrit >48% (women)

or

- increased RCM

2. Bone marrow (BM) biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
3. Presence of *JAK2* or *JAK2* exon 12 mutation.

Minor criteria: Subnormal serum erythropoietin level.
Diagnosis of polycythemia vera is made by the presence of all three major criteria or the presence of two major criteria and a minor criterion.

The inclusion criteria for this study were (1) persons diagnosed with polycythemia vera, (2) hematology clinic attendant, and (3) evidence of *JAK2* mutation. Patients below the age of 18 years were excluded from this study.

Sampling method and sample size

All patients who met the inclusion criteria and were seen at the clinic from September 2020 to August 2022 were included in the study.

Data collection techniques and tools

Hematology clinic entry book was used to identify the patient's unique hospital code. Using these unique codes, retrospective data was collected using an Excel spreadsheet from the hospital LHIMS database.

Data analysis

Data was manually entered using an Excel spreadsheet. The data entered was verified, cleaned, and exported into graph pad prism for statistical analysis. Descriptive statistics were performed on variables and presented as tables and graphs.

Ethical considerations

All data collected were anonymized and not traceable to the individual participants. Gatekeeper consent for the study was sought from the hematology unit of the Komfo Anokye Teaching Hospital through the Research and Development Unit. Ethical approval was obtained from Komfo Anokye Teaching Hospital's Institutional Review Board. The ethical approval number is KATH IRB/AP/073/32.

Results

The study had a total of 20 participants diagnosed with polycythemia vera over a period of 2 years. Majority (60%) of the study participants were males. The study participants ranged in age from 25 to 81 years (mean age of 51.53 ± 16.39 years) as shown in Table 1. Among the male participants, the mean age was 52 ± 16.27 years with a maximum of 81 years and a minimum of 25 years. For the female participants, the mean age was 50.14 ± 17.80 years with a minimum of 28 years and a maximum of 77 years.

The hematological profile of the male participants revealed a mean hemoglobin of 18.25 ± 1.373 g/dl, mean hematocrit of 52 ± 3.47%, and a mean platelet of 345.5 ± 180.82. Comparatively, the mean hemoglobin, hematocrit, and platelet for the female participants were higher with figures of 19.26 ± 1.43 g/dl, 53 ± 3.61%, and 816 ± 935.32, respectively as shown in Table 2.

Headache, tiredness, numbness, and abnormal labs were the most common reasons why participants sought medical attention as shown in Figure 1. At presentation, 70% of the participants complained of headache, 40% were referred to the hematology clinic because their primary physicians found abnormal labs, 36% complained of tiredness, 20% had numbness and pruritus, and 25% were referred on account of splenomegaly. The least symptoms complained of at presentation were night sweat (5%), tinnitus (10%), and visual disturbances (10%).

Majority (60%) of the study participants were positive for *JAK2* mutation. About 13(65%) of the participants had their serum erythropoietin data recorded. Most (87.5) of the participants who were negative for *JAK2* mutation had low erythropoietin with a mean of 2.771 ± 0.616. Hypertension was the most common complication observed. An appreciable number (45%) of the study participants developed hypertension in the course of the follow-up. Thromboembolism was seen in 10% of the study population (Table 3).

Table 1. Demographic profile of the participants.

Number of patients	20
Male	12 (60%)
Female	8 (40%)
Age in years	
Mean age	51.53 ± 16.39
Minimum age	25
Maximum age	81
Male	
Mean male age (years)	52 ± 16.27
Minimum male age (years)	25
Maximum male age (years)	81
Female	
Mean female age (years)	50.14 ± 17.80
Minimum female age (years)	28
Maximum female age (years)	77

Table 2. Hematological profile of the study population.

Hematology	Mean (male)	SD	Mean (female)	SD
HB (g/dl)	18.25	1.373	19.257	1.43
HCT (%)	52%	3.47	53%	3.61
Platelet	345.5	180.82	816	935.32
WBC	6.375	2.646	7.46	4.978

SD, standard deviation; HB, hemoglobin; HCT, hematocrit; WBC, white cell count.

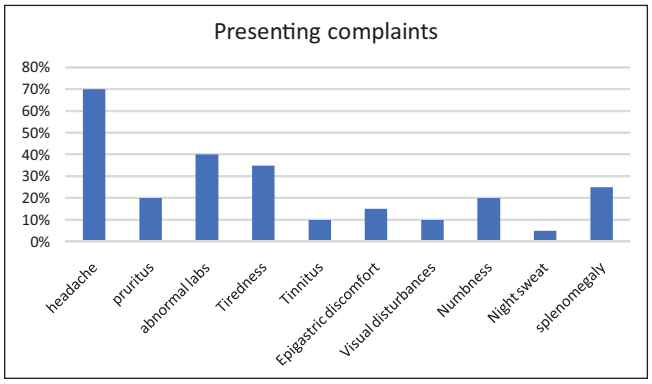

Figure 1. Shows the presenting complaints of patients with polycythemia vera.

Discussion

We found in this study that the average age of onset of polycythemia vera was 51 years with males being more affected than females. Most commonly, patients with polycythemia

Table 3. JAK2 profile, erythropoietin profile, and complications of study participants.

JAK2 mutation	Frequency (number of participants)
Positive	12 (60%)
Negative	8 (40%)
Total serum erythropoietin	13 (65%)
Number of participants with serum erythropoietin in JAK2 positive population	6 (41.7%)
Number of participants with serum erythropoietin in JAK2 negative population	7 (87.5%)

JAK2 mutation	Frequency of low erythropoietin	Mean erythropoietin
Positive	4 (33.3%)	3.300 ± 0.887
Negative	7 (87.5%)	2.771 ± 0.616

Complications of polycythemia vera	
Hypertension	45%
Thromboembolism (portal vein thrombosis and aortic valve thrombus)	10%
Angina	5%

JAK2, Janus Kinase 2.

vera present with headaches. Hypertension was the most common complication observed. Polycythemia vera affects all age groups but commonly occurs in adults, with the average age at diagnosis being around 60 years.[9,11,14] The risk of leukemic transformation of polycythemia vera increases with advanced age.[14] However, there is a highly variable interval between the time of diagnosis of polycythemia vera and the risk of leukemic transformation from a few months to as long as more than 20 years.[20–22] Incidence of leukemic transformation is estimated to be 2.3% at 10 years and 5.5% at 15 years following diagnosis.[9] In this study, there was a male preponderance to polycythemia vera with a male-to-female ratio of 3:2. Several studies have shown polycythemia to be more common in males than females with a ratio of 2:1.[8,23,24] The gender disparity in the occurrence of polycythemia vera was partly shown to be due to gender influence on *JAK2* (V617F) allele burden and this may produce phenotypic differences in the disease.[25] Palandri et al.,[5] in a review on the gender effect of polycythemia vera, acknowledging the effects of gender-specific diagnostic thresholds underscored the influence of gender on the clinical presentation, symptom burden, and pathogenesis of polycythemia vera.

The clinical presentation of polycythemia vera may be variable, such that it may be indolent without any clinical symptoms and may only be detected on routine checkups or incidentally in the course of managing other conditions.[8,13] As high as 40% of the participants in this study did not have any symptoms on presentation and were referred to the hematology clinic due to abnormal complete blood count found on routine examination. In a study by Shariq et al.,[26] it was shown that the most common presenting reason for consultation was abnormal complete blood count findings carried out as routine testing. Symptoms that are commonly reported at presentation include headache, dizziness, pruritus, numbness, epigastric discomfort, bleeding, tiredness, visual disturbances, tinnitus, and night sweats.[8,11,23,24,26] Headache has been found as the most common presenting symptom.[8,23,24] In this study, headache was found to be the most common complaint at presentation.

There is a tremendous difference in the hematologic profile as recognized by WHO in the 2008 diagnostic criteria for polycythemia compared to that of 2016. These differences have led to more patients being screened for polycythemia vera recently than before.[16] In a 5-year cross-sectional study in Pakistan, the mean hemoglobin was found to be 18.14 ± 1.9.[8] In a study in Poland, the mean hemoglobin was found to be 16.6 g/dl.[27] In Togo, the average value of hemoglobin in JAK2 positive patients was 19.8 ± 4.4 g/dl and a hematocrit of $62.7 \pm 4.4\%$ against 17.9 g/dl for those with negative *JAK2* mutation.[24] In this study, the average hemoglobin for men was 18.25 ± 1.373 g/dl and a hematocrit of $52 \pm 3.47\%$. The number was higher in females with an average hemoglobin of 19.26 ± 1.43 and a hematocrit of $53 \pm 3.61\%$.

The *JAK2* gene codes for the JAK2 protein, which participates in the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway that is important in cellular processes such as the proliferation and differentiation of red blood cells, platelets, and white blood cells in the bone marrow.[28] Detection of JAK2 mutation is an important diagnostic criterion for polycythemia vera. There has been a variable prevalence rate of *JAK2* mutation reported by different studies. The prevalence of *JAK2* mutation among polycythemia vera patients reported in the literature ranges from 46.7% to 100%.[8,24,28–31] Studies that reported low prevalence of *JAK 2* mutation used less sensitive methods. In South Africa, Shires et al.[32] showed more than 97% *JAK2* V617F prevalence among polycythemia population.[32] The proportion of *JAK2* mutation in this study was 60%. A possible reason for the low prevalence of *JAK2* mutations reported in this

Ghanaian population is the utilization of investigational methods with varying sensitivities at different private laboratories. The laboratory of the Komfo Anokye Teaching Hospital does not have the capacity to run the lab and thus *JAK2* mutation labs were done at different private laboratories which were using different methods. However, 87.5% (7/8) of those who tested negative for *JAK2* mutation had low erythropoietin. The low erythropoietin and the high hemoglobin and hematocrit were the reasons why the clinicians diagnosed them as having polycythemia vera even though they were negative for *JAK2* mutation. Polycythemia vera and erythropoietin receptor mutations are the only known conditions causing high hemoglobin and low erythropoietin.[33]

Polycythemia vera may lead to thromboembolism which can lead to some life-threatening conditions such as ischemic strokes, myocardial infarction, or pulmonary embolism.[13,34] The high hemoglobin and hematocrit levels lead to an increased viscosity of the blood, which in turn causes hemostasis and thus increased risk of thrombus formation as described in Virchow's triad.[35] Thromboembolism (portal vein thrombosis and aortic valve thrombosis) was found in 10% of our study participants. Hypertension was found to be the most common complication among our study participants. Several studies have shown that blood pressure increases in patients with polycythemia.[36–39]

Polycythemia vera is a chronic condition which has no cure. Treatment is targeted at reducing the risk of complications associated with the condition such as thrombosis, hepatosplenomegaly, hemorrhage, acute leukemia, myelofibrosis, hyperuricemia, erythromelalgia, visual disturbances, and so on. Thromboembolic phenomenon is the principal cause of mortality in polycythemia vera and thus effort should be made at reducing this risk.[1] Low-dose aspirin is given to reduce the risk of thrombosis.[10] Hematocrit level >45% is considered high risk for thromboembolic phenomenon.[40] Venesection is done to reduce the hematocrit concentration thus reducing the risk of thrombosis. Data from a randomized trial by Marchioli et al.[40] indicated that venesection of 200–500 ml of blood at tolerable intervals is capable of achieving and maintaining hematocrit levels below 45%.[40] However, this study was criticized by several published letters since patients with hematocrit below 45 received more hydroxyurea, and had a lower white count, which is an independent risk factor for thrombosis.[41]

There is a growing critique of using phlebotomy for the prevention of thrombosis. In secondary erythrocytosis, such as Eisenmenger complex or high affinity hemoglobin mutations, there is no increase in thrombosis, despite a very high hematocrit.[41] In addition, several recent studies have demonstrated hypoxia inducible factors as drivers of thrombosis in polycythemia vera and essential thrombocythemia.[42,43] Polycythemia Vera Study Group (PVSG) 01 and 05 studies demonstrated that phlebotomy was associated with a higher risk of thromboses compared to chemotherapy or radioactive 32P.[44] The European Collaboration on Low-Dose Aspirin in the Polycythemia Vera (ECLAP) study found no difference in thrombotic complications for subjects with a hematocrit within the range of 40%–55%; however, there were not enough subjects with a hematocrit >55% for evaluation.[45] In high-risk patients, it is important to add cytoreductive therapy.[41,46] Cytoreductive therapy such as hydroxyurea, ruxolitinib, and busulfan is given to reduce the risk of thrombosis and hemorrhage.[1,10] Therapies directed at both clonal suppression and anti-inflammation are important in reducing the risk of thrombosis.[47]

Limitations of the study

The sample size of the study was small. It was a record review, and thus, the information was taken as documented by the clinician. Bone marrow biopsy was not a routine practice for patients with polycythemia vera in the clinic. There was no sample size calculation for this study due to an anticipated small study population.

Conclusion

Polycythemia vera is an uncommon disease in Ghana mostly found in older males above 50 years of age. Headache is the most commonly presented complaint. It is important to recognize it early to initiate therapy aimed at preventing common complications such as hypertension and thromboembolism. Polycythemia vera should be considered a differential diagnosis for patients with secondary hypertension.

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Author contributions

SG: Conceptualization, methodology, project administration, supervision, validation, writing original draft, review, and editing. EA: Supervision, validation, visualization, writing original draft, review, and editing. AA-G: Conceptualization, methodology, validation, visualization, writing original draft, review, and editing. FG: Writing original draft, review, and editing, AB: Writing original draft, review, and editing. AA: Writing original draft, review and editing, and supervision. OO-S: Writing original draft, review and editing, supervision, and methodology.

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Ethics approval and consent to participate

Gatekeeper consent for the study was sought from the hematology unit of the Komfo Anokye Teaching Hospital through the Research and Development Unit. Ethical approval was obtained from Komfo Anokye Teaching Hospital Institutional Review Board. The ethical approval number is KATH IRB/AP/073/32. This was a retrospective record review study and thus no written informed consent was obtained.

ORCID iD

Solomon Gyabaah https://orcid.org/0000-0002-5941-9733

Availability of data and materials

Data and materials are available upon reasonable request.

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