Original Article

Profile of Polycythaemia Vera in South Western Nigeria

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Abstract

Background: Polycythaemia vera (PV) is the most common myeloproliferative neoplasms (MPNs), others include essential thrombocytosis and primary myelofibrosis. PV is a Philadelphia chromosome-negative MPN, it is a rare haematologic disorder seen primarily in adults aged 60 years and older, with a higher prevalence in men. **Aim:** The aim of this study is to record the prevalence and explain the epidemiological, clinical, and biological PV in teaching hospital in South Western Nigeria. **Materials and Methods:** Case notes of all patients with a diagnosis of polycythaemia vera managed at the University of Medical Sciences Teaching Hospital, Ondo state, over a 3-year period between January 2018 and November 2021 were reviewed. The clinical and laboratory findings were extracted from the case records. SPSS-16 (SPSS Inc., USA) and Microsoft Excel statistical software packages were used for statistical calculations. **Results:** A total of 26 cases of PV were managed at University of Medical Sciences, Ondo state, during the period of the review. There were 20 male and 6 female, with the mean age for males 41.61 ± 18.1 and 32.33 ± 0.52 for females. Majority of the patients in the study (53.8%) had headache and fatigue, 54.5% of the patients experienced dizziness, itching and visual disturbance, hypertension, weight loss, and subconjunctival haemorrhage were found in 6 (23.08%), 5 (19.20%), and 4 (15.40%), respectively, night sweat, dyspepsia, and splenomegaly accounted for (1) 3.85%. None of the patients experienced thrombosis and bleeding. Six of the patients were able to pay for Janus Kinase 2 (JAK2) mutation in which 4 of the results were positive for JAK2 mutation while 2 patients were able to afford to pay for serum erythropoietin; the results were below the normal value. All the patients were able to pay for full blood count, peripheral blood film, and bone marrow aspirations. The average packed cell volume for males was 59.7 ± 2.3 and 55.22 ± 4.9 for females while the mean blood and platelets count in our study was 11.19 ± 1.23 and 486 ± 122.3 × 10^9/l. **Conclusion:** The study showed a low prevalence of PV in Nigeria although most cases of PV were seen among the young adults < 60 years of age affecting their life expectancy because it has a detrimental effect on their work productivity, family life, and social life.

Keywords: Myeloproliferative neoplasm, Philadelphia, polycythaemia vera

Introduction

Polycythaemia vera (PV) is the most common myeloproliferative neoplasms (MPNs), others include essential thrombocytosis and primary myelofibrosis. They are unique haematopoetic stem-cell disorders that share common mutations which activate signal-transduction pathways responsible for haematopoiesis.[1,2] PV is characterized by uncontrollable, myeloid proliferation with predominant erythrocytosis.[3] It is characterized by erythrocytosis and mutation activation in Janus Kinase 2 (JAK2) with marrow trilineage myeloproliferation.[4]

PV is a rare haematologic disorder seen primarily in adults aged 60 years and older, with a higher prevalence in men.[5] Study by Bolarinwa and Durosinmi shows that PV accounts for just 0.03% of all the haematologic cancers seen and the middle-aged are commonly affected while Mehta *et al.* in the United States observed the prevalence to be 45–57/100,000 people.[6,7]

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The prevalence of PV has been reported by several studies to be higher among American but lower among African Americans.[6] The incidence of PV is higher among men than women in all races with rates of 2.8/100,000 men and 1.3/100,000 women.[5] Globally, PV is a rare occurrence in children and young adults (ages <40 years) although few cases have been seen in them[7] but more common among people 60–65 years of age.[5]

Patients with PV have a mutation in the non-receptor tyrosine Kinase JAK2 with the majority of patients harboring the classic

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JAK2 (V617F). This mutation inactivates the pseudokinase domain, which causes constitutional enzymatic activity and intracellular signal transduction, this will eventually lead to uncontrolled cell production.[8] The *JAK2*V617F mutation is present in more than 95% of PV cases but is also found in 50%–60% of essential thrombocytosis and primary myelofibrosis cases.[9] The classification scheme for myeloid neoplasms by the World Health Organization shows PV as a BCR-ABL1-negative MPN.[10] Common features shared between MPN include; clonal involvement of a multipotent haematopoetic progenitor cell, thrombotic and haemorrhagic diathesis, potential evolution to myelofibrosis, as well as to acute myeloid leukaemia (AML), marrow hypercellularity with effective haematopoiesis as compared to ineffective haematopoiesis seen in myelodysplastic syndrome.[3,11]

PV itself is often asymptomatic but symptoms such as weakness, pruritus, headache, light-headedness, visual disturbance, fatigue, painful paresthesias of the hands and feet (erythromelalgia), atypical chest pain, hepatosplenomegaly, thrombotic and bleeding complications, and risk of leukaemia transformation (AML) or fibrotic progression.[11] The three major criteria of the World Health Organization (WHO) are met before the diagnosis of PRV can be made (1) haemoglobin of more than 16g/dl and 16.5g/dl in females and males, respectively, or hematocrit of more than 49% or 48% in man and woman, respectively, or increased in red cell mass, (2) bone marrow trilineage proliferation with pleomorphic mature megakaryocytes, and (3) presence of a JAK2 mutation (JAK2V617F) or a mutation at exon 12 of JAK). It can also be diagnosed by meeting the first two major criteria and a minor criterion which is having a subnormal erythropoietin level.[3]

The aims of treatment for PV are to alleviate symptoms by maintaining the value of packed cell volume <45% and to reduce the risk of thrombosis.[12] The available medications do not prolong survival or change the natural history of the disease but rather prevent thrombosis.[13] Treatment modalities depend on the risk stratification of patient either as low or high risk based on age (< or >60 years) and presence or absence of thrombotic events.[14] Patients are grouped into high risk if they are older or equal to 60 years or with a thrombosis history, while low-risk patients are <60 years and no previous history of thrombosis.[14] The recommendation for the low risk is phlebotomy with a hematocrit target of 45% and aspirin therapy and also cytoreductive therapy if they are symptomatic. The high-risk patients in addition to aspirin and phlebotomies also require cytoreductive therapy with hydroxyurea as first-line however, interferon is considered as an alternative therapy to hydroxyurea in a younger person, women of childbearing age, intolerance or resistance to hydroxyurea therapy and on situation where the disease is not well controlled by phlebotomy alone. The second-line drugs are busulfan for older patients and ruxolitinib which is a JAK inhibitor used for patients resistant to hydroxyurea, and who have protracted pruritus.[14-17] Survival in PRV is relatively long with a low risk of leukaemia transformation. Studies from clinical trials have shown that PRV patients treated with chlorambucil, radiophosphorus, and pipobroman have a high risk of transforming into acute leukaemia.[18]

The overall survival in PRV and the other MPNs is lower than that of age- and sex-matched general populations.[19] The median survival age for PV is approximately 14 years for those >60 years; and 24 years for those <60 years.[20] An international study conducted by Tefferi and Barbui in Mayo clinic among 1545 patients with PV, shows that the risk factors for overall survival include age, leukocytosis, thrombosis, and abnormal karyotype.[18]

In Nigeria, there is a paucity of studies on PV. There have been a paucity of studies on the clinical and biological features on PV in Nigeria. Therefore, the study is carried out to explain the clinical and biological PV in teaching hospital in South Western Nigeria.

Materials and Methods

Case notes of all patients with a diagnosis of polycythaemia vera managed at the Department of Haematology and Blood Transfusion, University of Medical Sciences Teaching Hospital, Ondo state over a 3-year period between January 2018 and November 2021 were reviewed. The clinical and laboratory findings were extracted from the case records. The diagnosis of the PV was based on history, clinical examination, results of bone marrow aspiration and/or biopsies, full blood count (FBC), JAK 2 mutation, and serum erythropoietin.

Patients that presented with polycythaemia were managed as PV based on the WHO diagnostic criteria. Haemoglobin >16.5 g/dL in men and >16 g/dL in women, or hematocrit >49% in men and >48% in women, or red cell mass >25% above mean normal predicted value.[21] Patients were recruited into low-risk patients (aged <60 years and with no prior history of thrombosis) and high-risk patients.

All these patients fulfilled at least two of A1 (raised red cell mass), A2 (normal arterial oxygen saturation), A3 (Splenomegaly) category, and at least one of B category (platelet count) of the WHO diagnostic criteria. Patients' follow-up period was calculated from the date of diagnosis to the last day of follow-up. SPSS-11 (SPSS Inc., USA) and Microsoft Excel statistical software packages were used for statistical calculations.

Results

A total of 26 cases of PV were managed at the University of Medical Sciences, Ondo state, for over a period of 3 years.

Table 1 shows the frequency distribution, mean value, and median values of patients' age and gender. A total of 26 patients were recruited into this study, 20 (76.9%) male and 6 (23.1) female. The age range was 17–77 years. The mean age was 41.6 ± 18.1 for males and 32.33 ± 0.52 for females.

Table 2 shows the clinical finding on the first presentation. More than half of the patients with PV, 14 (53.8%) complained of headache and fatigue, 13 (50%) of the patients presented with dizziness, visual disturbances, and itching. Hypertension, weight loss, and subconjunctival haemorrhage were found in 6 (23.08%), 5 (19.20%), and 4 (15.40%), respectively. Night sweats, dyspepsia, and splenomegaly accounted for (1) 3.85%. Thrombosis and bleeding were not observed in any of the patients at the time of presentation.

Table 3a and b shows the laboratory investigations and treatment modality. All (100%) the patients were able to carry out the following investigation- FBC, peripheral blood film, bone marrow aspiration, and biopsy, only 6 (23.07%) were able to pay for JAK2 mutation and 4 (66.7%) were positive and (2) 33.3% were negative. Only 2 (7.7%) patients were able to do serum erythropoietin and the results were below the normal range (3.5–31.5mLU/mL). All the patients had phlebotomy and 96% were on aspirin or clopidogrel while 7.69% were on hydroxyurea.

Table 4 shows the mean values of the FBC results. The mean PCV for males was 58.70 ± 2.3 and that of the females was 55.22 ± 4.5. The mean values for TWBC and platelet count were 11.19 ± 1.23 and 486.20 ± 122.3 × 10^9/L, respectively. The PCV, TWBC, and platelet count were crossed with the gender of the patients and $P < 0.005$ showed a significant association between these variables.

Table 1: Frequency distribution, mean value, and median values of patient's age and gender

Parameters	Frequency, *n* (%)	Mean age value±SD	Median age value	Age range
Male	20 (76.9)	41.6±18.1	38.50	19-77
Female	6 (23.1)	32.33±0.52	32.00	32–33
Total	26 (100)	39.46±16.3	33.00	17-77

SD: Standard deviation

Table 2: Clinical finding at first presentation

Clinical features	Number of cases (*n*=26) (prevalence [%])
Headaches	14 (53.8)
Weakness (fatigue)	14 (53.80)
Visual disturbance	13 (50.00)
Dizziness	13 (50.0)
Itching	13 (34.60)
Hypertension	6 (23.08)
Weight loss	5 (19.20)
Sub-conjunctiva haemorrhage	4 (15.40)
Numbness	2 (7.70)
Tinnitus	2 (7.70)
Splenomegaly	1 (3.85)
Dyspepsia	1 (3.85)
Night sweats	1 (3.85)
Thrombosis	0
Bleeding	0

Discussion

Nigeria, a low-middle-income nation with scarce resources has long struggled with a lack of proper medical treatment and services for the management of a variety of medical conditions, including haematological neoplasms. This study comprises a report of 26 patients with PV, their haematological changes and clinical features using available resources at our disposal.

In this study, it was observed that PV was found to affect adolescents, middle-aged and the elderly, which was in keeping with other studies.[21,22] This is because $JAK2^{V61F}$ expression is age independent.[23] The median age at diagnosis in this study was early adulthood, which was in keeping with a study done in Italy[21] and Togo,[24] however, Bolarinwa and Durosinmi[6] in Nigeria showed a higher age group of PV patients. Passamonti *et al*.[21] and Deadmond and Smith-Gagen[25] in their studies using a cancer registry the risk of developing PV is higher at a lower age in female, this was also similar to the finding in this study. Studies by Deadmond and Smith-Gagen[25] and Bolarinwa and Durosinmi[6] have shown a higher male-to-female ratio, which was also observed in this study. A study by Stein *et al*.,[26] demonstrated that females have a significantly lower $JAK2^{V617F}$ allele burdens than males, this probably could account for a higher incidence of PV in males than in females. Gender discrepancies are also observed in terms of incidence, response to therapies, and prognosis in malignancies including haematological disorders such as acute lymphoblastic leukaemia, chronic lymphocytic leukaemia, and multiple myeloma.[27] The actual aetiology is unclear, but the following may be contributing factors: deranged immune system, sex hormones, gene molecular pattern, and medications.[27,28]

Majority of the patients were symptomatic which necessitated their presentation in the clinic, however, some were incidental discoveries following medical checkups. A significant percentage (>50%) of the patients presented with headache, generalized body weakness, dizziness, visual disturbances, and pruritus, which correlate with finding by other authors.[18] However, many studies have shown that symptoms have a negative impact on the quality of life which equally affect daily activities, family life, social life, and work productivity leading to low quality of life.[29,30] Thus Majority of the patients in this study are young adults and middle age, who are part of the working force, which implies that their contribution at work may be reduced, this, therefore, have a negative macroeconomic impact.[31]

The WHO criteria for making the diagnosis of PRV is three major criteria or the first two major and one minor,[10] however, <10% of the patient were able to pay for the requested investigations as a majority of them have severe financial constraints or have exhausted their little income in peripheral centers or traditional homes before presenting at the teaching

Table 3a: Laboratory investigations done by patients with polycythaemia rubra vera

Investigations	Frequency (%)	Finding
Full blood count	26 (100)	Mild-to-moderate leukocytosis, mild-to-moderate thrombocytosis, and erythrocytosis
Peripheral blood film	26 (100)	Leukocytosis, thrombocytosis, and erythrocytosis
Bone marrow aspirations/biopsy	26 (100)	Trilineage hyperplasia
JAK2V1676	6 (23.7)	4 (66.7%) positive and 2 (33.3%) negative
Serum erythropoietin	2 (7.7)	100% low (<1.50 mLU/mL)

Table 3b: Treatment modality for patients with polycythaemia rubra vera

Treatment modality	Frequency (%)
Phlebotomy	26 (100.00)
Aspirin/clopidogrel	25 (96.00)
Hydroxyurea	2 (7.69)
Interferon	0
JAK inhibitors	0

JAK: Janus kinase

Table 4: Mean values of full blood count of patient

Parameter	Mean±SD	Reference values	*T*-test	*P*
PCV				
Male	59.70±2.3	40-50	18.89	0.000*
Female	55.22±4.5	38-42	7.23	0.001*
TWBC ($\times 10^9$/L)	11.19±1.23	2.8-9.0	9.108	0.000*
Platelet count ($\times 10^9$/L)	486.20±122.3	95-4000	1.33	0.001*

*Where significant *P*=0.005. PCV: Packed cell volume, TWBC: Total white blood cell count, SD: Standard deviation

hospitals. FBC and peripheral blood film were in keeping with erythrocytosis, leukocytosis, and thrombocytosis. Bone marrow aspiration showed age-adjusted trilineage hyperplasia with pleomorphic megakaryocytes, which was inconsistent with another finding.[21] JAK2 mutation was found to be positive among four of the patients out of six (66.6%) were who were able to pay for the investigation, thus meeting the WHO major criteria, which is in keeping with the study that shows the majority of the patient with PRV are JAK2 mutation positive.[9] The patient's socioeconomic status played a significant role in their inability to fund some of the recommended investigations most especially the JAK2-V617F mutation or serum erythropoietin test. This emphasizes how patient's social status and wealth affect their care and compliance which is worsened by overreliance of the Nigerian health-care system on an out-of-pocket payment system.

The treatment modality was based on risk-adapted classification, they were divided into two groups; low-risk and high-risk

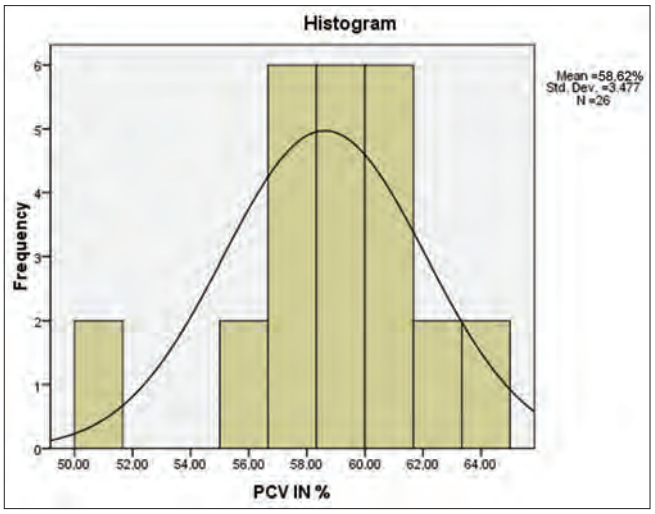

Figure 1: Histogram showing the frequency distribution of the packed cell volume

based on the patient's age and thrombotic history in agreement with the study by Tefferi and Barbui,[11] Most of our patients were low risk as majority of them were <60 years with no thrombotic phenomenon and were therefore on aspirin/clopidrogel and phlebotomy while those with high risk were placed on cytoreduction therapy (hydroxyurea) in addition to phlebotomy and antiplatelet therapy. A significant number of the patients are well and alive, few were however lost to follow-up. This is in line with a study done by Bolarinwa and Durosinmi.[6]

Figure 1 shows the frequency distribution of the packed cell volume. Majority of the patients had PCV of 59%. The mean PCV in this study is 58.62%.

Limitation

The low number of cases of PV seen in our study has been traced to the issue of patient accessibility to well-equipped hospitals as well as problem of patient adherence to long-term medical monitoring and poor referral and diagnosis by the physicians. Furthermore, not all cases of PV are being managed by the haematologists as physicians and other health-care providers attend to patients using their laboratory findings (elevated PCV) and blood donation as a way of management without the knowledge of a haematologist. Furthermore, some of the patients were lost to follow-up, hence clinical information about these patients were incomplete.

Conclusion

The study has shown the clinical features of patients with PV in Nigeria with most cases seen among the low-risk patients. Despite the fact that PV is linked to a higher mortality rate, many patients have a lengthy median survival time, emphasizing the necessity of efficient and well-tolerated treatment. Patients have few treatment alternatives, and many are forced to use ineffective medications that cause unpleasant side effects and put them at risk of developing MF

or haematoligic change. The identification of JAK2 mutations as the underlying genetic foundation for PV has considerably aided our understanding of the disease's etiology and enabled the development of targeted therapeutics. Majority of the patients have severe financial constraints as they were unable to carry out the required investigations. This is due to the fact that treatment is out-of-pocket payment system.

Physicians should be enlightened on the referral of the PV patients to a haematologist for diagnosis and treatment rather than advising the patients to undergo blood donation which could be injurious or harmful to the patient and put them at high risk of developing cancer in the future.

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Conflicts of interest

There are no conflicts of interest.

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