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ORIGINAL ARTICLE

Frequency of clinico-hematological features and JAK 2 status of young adults presenting with polycythemia in RMI hospital, Peshawar.

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ABSTRACT… Objective: To determine the frequency of clinico-hematological features and JAK 2 status of young adults presenting with Polycythemia Vera at the department of hematology. **Study Design:** Cross-sectional study. **Setting:** Department of Hematology, RMI Hospital, Peshawar. **Period:** 25th November 2023 to 25th May 2024. **Methods:** A total of 190 patients aging between 18-45 years and presented as suffering from Polycythemia Vera as per diagnosis of consultant hematopathologists, were included in this study. Samples with clear evidence of hemolysis, coagulation, or clots were excluded. Patient's demographics, details of physical appearance, clinical findings and history of adverse events were recorded. Hematological and pathological investigations were done and analysis of JAK2 V617F mutation was conducted using polymerase chain reaction from the diagnostic lab of the institute. The primary outcome of the study was to determine the frequency of clinico-hematological features and JAK 2 status. **Results:** The Mean±SD of age in our study was 36.81±6.11 years with an age range of 21-45 years. Out of total patients, 49 (25.79%) patients were asymptomatic. The major symptoms affecting the daily life activities were headache 65 (34.21), abdominal discomfort 41 (21.58%), blurred vision 27 (14.21%) and fatigue 27 (14.21%). These patients had plethoric face 61 (32.11%), splenomegaly 64 (33.68%) and budd-chiari syndrome 8 (4.21%). The results of hematopathological findings showed abnormal hemoglobin (17±3.92 gm/dL), hematocrit (52.94±4.8 g %), platelet (579.63±227.68 10^3/µL) and leukocyte (10.32±2.6, 10^3/µL) levels while 177 (93.16 %) patients had mutated JAK2 levels. **Conclusion:** Plethoric face and splenomegaly are the commonly found clinical findings in patients with Polycythemia Vera while these patients also have abnormal levels of hemoglobin, hematocrit, platelet and leukocyte. JAK 2 status serves conclusive role in the diagnosis of Polycythemia Vera.

Key words: Clinico-hematological Features, JAK 2 Status, Polycythemia Vera, Young Adults.

INTRODUCTION

Clonal myeloid disorders are characterized by myeloproliferative neoplasms (MPN) and are linked to Philadelphia Chromosome (Ph)-negative abnormalities. These excessive proliferations are linked to the serious risks including hemorrhages and thrombosis. MPN progresses to complications like myelofibrosis (MF), acute and chronic myeloid leukemia, myelodysplastic syndrome and other accelerated phases. Among these complications polycythemia vera (PV) and essential thrombocythemia (ET) are more common and these patients are especially vulnerable to the thromboembolic incidences.[1,2] The worldwide estimated prevalence of MPN in young adults and children is 0.82/100,000 patients/year. For PV this incidence is 0.18, while for ET its nearly 0.6/100,000 patients/year.[3]

In PV, there is abnormal multiplication of red blood cell beyond the regulatory mechanisms and age is considered as an important factor as PV mostly reported after the age of 60 years.[1,2] In their review, Palandri F also emphasized the importance of gender-based discussions in young PV patients and mentioned that gender, especially the female gender in their reproductive years, may potentially act as a modifying factor in PV and may influences various aspects of the disease process.[4]

PV and ET are both slowly progressing disorders

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that can lead to bleeding episodes, thrombotic events, an increased risk of MF, and the conversion to the stage called acute myeloid leukemia, which shortens the patient's survival period.[5]

As with other hematological disorders, a number of genetic mutations have been identified that are closely related to MPN, and their role in its pathogenesis has been elucidated. Recent developments in the field of molecular pathogenesis have also made the identification of genetic mutations, the primary determinant of diagnosis and prognosis in hematological malignancies. Hence identification and description of the relevant genetic mutations has become necessary in order to diagnose MPN. The clinical guidelines on polycythemia and thrombocythemia diagnosis focus on recommending biopsy and finding driver mutations. Janus kinase 2 (JAK2), a protein tyrosine gene, is involved in the growth and proliferation of cells. For the PV patients, the mutations of JAK 2 are reported to be present in as high as 90% of the cases.[5,6,7]

The World Health Organization (WHO) has listed JAK 2, KALR, and MPL mutations as the primary diagnostic criteria for MPN since 2008. The treatment is usually focused on the age and is decided on the basis of history to address the risks of hemorrhages and thrombosis (cytoreductive drugs/aspirin).[8] The initial characteristics of patients at the time of diagnosis are very important which includes the cause of initial consultancy, clinico-hematological features and results of biopsies taken from bone marrow. This data regarding MPNs is mainly available for the patients of age ranging from 40 to 60 years old but the data comprising of patients diagnosed at younger years is scanty.[9] These details are especially absent in shape of a comprehensive data for young adults. The young adults suffering from MPN are said to be at very lower risk level and for PV patients under 60 years of age, cytoreductive therapy is often not prescribed due to concerns about potential treatment-related toxicity. However, the chances of complications can't be ignored and this approach may result in under treatment, as there is a lack of conclusive evidence suggesting that the benefits of treatment outweigh the associated risks.[10,11]

As the data of the JAK 2 allele burden establish a link between the incidences of venous thromboembolism and progression of the disease to leukemia or MF, the clinico-hematological features and JAK 2 status is very important in the process of diagnosis of polycythemia and assessment of associated complication.[12] This study was therefore planned to determine the frequency of clinico-hematological features and JAK 2 status of young adults presenting with PV at the department of hematology, RMI hospital, Peshawar.

The findings of this study will help in diagnosis of polycythemia and assessment of associated complications thereby setting the therapeutic strategies.

METHODS

This cross-sectional study was conducted at the department of hematology, RMI hospital, Peshawar from 25th of November 2023 to 25th of May 2024 over a period of 6 months.
Sample size was calculated using WHO sample size software.
Confidence interval=95%.
Prevalence (Clinical symptoms influencing daily activities) = 14.3%.[13]
Precision= 5%, Estimated sample size=189.

A total of 190 patients aging between 18-45 years and presented at the department as suffering from PV, (Diagnosed by consultant hematopathologists in accordance with the WHO criteria at the time of first presentation) were included in this study.

Samples with clear evidence of hemolysis, coagulation, or clots were excluded.
(WHO criteria: The presence of either all 3 major criteria or the first 2 major criteria accompanied by the minor criterion where major criteria include hemoglobin levels exceeding 16.5 g/dL in males and 16 g/dL in females, or a hematocrit value higher than 49% in males and 48% in females, or a red blood cell mass that is more than 25% above the predicted mean normal value. The minor criteria includes a serum erythropoietin

level that falls below the normal range).[8]

Patient's demographics were noted including age and gender. Details of physical appearance, clinical findings and history of adverse events were recorded for these young adults presented with PV. Hematological and pathological investigations were done by taking blood samples and using biopsy. Analysis of JAK2 V617F mutation was conducted using polymerase chain reaction. All these investigations were conducted at the diagnostic lab of the RMI.

Approval of conducting the study was taken from the ethical committee of the hospital (Ref: RMI/RMI-REC/Approval/193, November 23, 2023).

A written consent was obtained by each participant for inclusion in this study.

Data was analyzed using SPSS version 25. Quantitative variables of clinico-hematological features were calculated in shape of Mean±SD while qualitative variables were presented in shape of frequency and percentages.

RESULTS

The Mean±SD of age in this study was 36.81±6.11 years with an age range of 21-45 years. The number of male patients were higher (56.56%) as compared to female patients. The details of demography and the symptoms affecting daily life activities of patients are shown in Table-I.

Age (Mean±SD) years		36.81±6.11
Gender	Male n (%)	106 (55.79)
	Female n (%)	84 (44.21)
Patients with symptoms n (%)		141 (74.21)
Patients without symptoms n (%)		49 (25.79)
Symptoms affecting daily life activities		
Headache n (%)		65 (34.21)
Abdominal discomfort n (%)		41 (21.58)
Blurred vision n (%)		27 (14.21)
Fatigue n (%)		27 (14.21)
Pruritus n (%)		18 (9.47)
Inactivity n (%)		20 (10.53)
Insomnia n (%)		18 (9.47)
Pain in bones n (%)		16 (8.42)
Fever n (%)		13 (6.84)

Table-I. Demographics n=190

The results of physical appearance, clinical findings and history of adverse events were recorded for these young adults presented with PV as shown in Table-II.

Physical appearance and clinical findings	
Plethoric face n (%)	61 (32.11)
Splenomegaly n (%)	64 (33.68)
Spleen length (Mean±SD) cm	18.54±3.34
Budd-chiari syndrome n (%)	8 (4.21)
History of adverse events	
Cerebrovascular events n (%)	14 (7.37)
Gangrene n (%)	11 (5.79)

Table-II. Clinical findings and history of incidences. n= 190

The results of hematopathological findings showed abnormal hemoglobin, hematocrit, platelets and leukocyte levels while 93.16% patients had mutated JAK2 levels as shown in Table-III.

Hematological findings	
Hemoglobin (Mean±SD) g/dL	17±3.92
Hematocrit (Mean±SD) g%	52.94±4.8
Platelets (Mean±SD) $10^3/\mu L$	579.63±227.68
Leukocytes (Mean±SD) $10^3/\mu L$	10.32±2.6
PCR findings	
Number of patients with mutated JAK2617F n (%)	177 (93.16)

Table-III. Hematopathological findings n=190

DISCUSSION

As mentioned earlier, very few work has been conducted in young adults diagnosed with PV especially in Pakistan for finding the clinico-hematological features and JAK status.

The Mean±SD of age in our study was 36.81±6.11 years with an age range of 21-45 years. The number of male patients were higher 106 (55.79%) as compared to female 84 (42.21%) patients. In the studies conducted by Nathany S, there was also a predominant male patients compared to females patients (76.19% and 23.81% respectively). Shaikh MS in a study with Pakistani patients also mentioned a predominant male population compared to female population (1.1:1 respectively) however this ratio was similar in a study by Barzilai conducted in young adults.[7,13,14]

It is important to mention that out of total patients in our study, 49 (25.79%) patients were asymptomatic. Sultan S[15] in a study conducted in Pakistan also mentioned that that 30.7% of the patients remained asymptomatic till the time of diagnosis.[15]

The major symptoms affecting the daily life activities in our study patients were headache 65 (34.21%), abdominal discomfort 41 (21.58 %), blurred vision 27 (14.21%), fatigue 27 (14.21%), inactivity 20 (10.53 %), pruritus 18 (9.47), insomnia 18 (9.47%), pain in the bones 16 (8.42) and fever 13 (6.84). Sheikh MS found that common symptoms affecting the daily life activities in PV were fatigue, inactivity and insomnia presented in 14.3% of the cases of PV while symptoms like fever, weight loss and night sweats were reported in 10.7% of the cases. Complaints of itching and bone pains typical to MF were present in 10.7% of cases.[13] In the study conducted by Sultan S, the major symptoms reported in patients with PV were headache (30.8%) and abdominal discomforts (23.15%). Blurredness of vision, vascular incidences and pruritus were the other complaints reported by these patients.[15] Sobas M presented the data of children and young patients aging below 25 years. In this study the median age of patients was 19.7 years. Fatigue (34.5%) and aquagenic pruritus (19.7%) were the most common symptoms in these young patients.[16]

In our study, the results of physical appearance and clinical investigations showed that plethoric face was present in 61 (32.11 %), splenomegaly in 64 (33.68%) and budd-chiari syndrome in 8 (4.21%) of the patients. The spleen length was recorded as 18.54±3.34 cm. Sobas in his study with PV patients of younger age also found that hyperviscosity (42.22%), splenomegaly (39.1%) and plethoric face (21.3%) were the most prominent characteristics among these patients.[16] Barzilai reported that in the young PV patients the median of spleen length was 15 cm.[7] Nathani S found hepatomegaly (61.90%) and splenomegaly (80.95%) as the most frequent clinical findings in these patients.[14] As far as the data of our local population is concerned Sultan S mentioned that on physical assessment plethoric face (34.6%) and splenomegaly (30.7%) were the major findings and the length of spleen measured was 15.9±2.04 cm.[15] Sheikh MS also found splenomegaly as an important clinical feature reported in 28.6% of the patients with PV.[13]

History of adverse events in our study showed cerebrovascular events in14 (7.37%) and gangrene in 11 (5.79 %) of patients. These events were 7.1% and gangrene 3.6% respectively in study by Sheikh MS.[13] Barzilai also reported that the young patients are at same mortality risk as older patients with MPN and thrombotic events are a commonly presented sign in young adults.[7] The results of hematopathological findings in our study showed abnormal hemoglobin (17±3.92 gm/dL), hematocrit (52.94±4.8 g%), platelets (579.63±227.68 10^3/µL) and leukocytes (10.32±2.6 10^3/µL) levels. The hematopathological findings of retrospectively extracted 8 years data, by Barzilai shared abnormal levels of hemoglobin, hematocrit, platelet and leukocyte with median values of 17 g/dl, 51 g %, 486 10^3/µL and 710^3/µL respectively.[7] In the results of laboratory investigation shared by Nathani[14], median levels were shared as hemoglobin 17.5 g/dL, hematocrit 56.7%, leukocyte count 17.6$10^9$/l and platelet count 493 10^9/l.[14] The hematological reports shared by Sultan S showed disturbed levels of hemoglobin (18.1±1.9 g/dl), hematocrit (55.6±8.3 g%), leukocyte (12.8±7.1x10^9/l) and platelet (511±341.9x10^9/l).[15] This study also concluded that most of the symptoms appearing in these patients were associated with hyperviscosity.

The PV patients having mutated JAK2 levels in our study were 177 (93.16 %). Previous studies done over this subject both in young and old age patients suffering from PV have also reported high percentage of patients with mutated JAK2 status including Barzilai (91%), Shaikh MS (89.3%), Nathany S (80.95%), and Sobas M 86.4%.[7,13,14,16] Studies conducted by Najam MB and Al Dayyeni AM in Iraq and Zulkeflee RH in Malaysia have also confirmed these hematological abnormalities and mutated JAK 2 status as important diagnostic criteria for PV in different age groups.[16,17,19]
A recently published update on PV recommend

that males with Hb and Hct levels higher than 16.5 gm/dL and 49% and females with Hb and Hct levels higher than 16 g/dL and 48% respectively are suspect of PV. All these patients must be screened for mutated JAK2V617F. This update mentioned that results of laboratory detection are important for diagnosing PV as they have 97% sensitivity and 100% specificity.[20]

Hence the results of our study are in line with the studies discussed above and describe important clinical, hematological features and JAK 2 status in young adult PV patients. These findings add up in the data available for diagnosing PV in young adults and will help our local clinicians in early diagnosing and setting up early treatment plans.

The major limitation of our study is that we have worked on the patients within a specific geographical area which include a certain type of class and ethnicity. Future studies with large sample size and involving different institutes will provide more useful data of young adults diagnosed with PV in our local population.

CONCLUSION

This study provided useful details of the clinico-hematological features of the patients presented with PV. While a certain percentage of patients remains asymptomatic, the common symptoms affecting their daily life activities are headache, abdominal discomfort, blurred vision, fatigue and pruritus. Plethoric face and splenomegaly are the commonly found clinical findings while these patients also have abnormal levels of hemoglobin, hematocrits, platelets and leukocytes. As these clinico-hematological abnormalities can also be shared in other Ph-negative MPNs, JAK 2 status is important in the diagnosis of PV.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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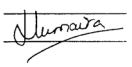
2	Humaira Taj Niazi	Study concept, Data interpretation, Manuscript writing, Critical review.	
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