

*Original Research Article*

# Myeloproliferative Neoplasms other than Chronic Myeloid Leukemia - A Five Year Single Center Experience

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Abstract

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A retrospective analysis of 5 years data of myeloproliferative neoplasm (MPN) other than chronic myeloid leukaemia (CML) was done. All the cases were diagnosed and classified according to World Health Organization (WHO) Classification 2008 and studied for demographic, clinical, laboratory & molecular characteristics along with treatment. Out of total 89 cases, we found 37% cases of Polycythemia Vera (PV), 31% each of Essential Thrombocythemia (ET) and Primary Myelofibrosis (PMF) respectively. Haemoglobin (Hb) was found raised in PV, Platelets in ET but lesser than normal values were seen in PMF. Jak2 V617F mutation was detected in 54%, 35% and 11% cases of PV, ET and PMF respectively. Splenomegaly was found in 27%, 28% and 78% in PV, ET and PMF respectively. Hydroxyurea was given in 76% of PV and 71% of ET patients along with aspirin. Venesection was done in 51% of PV patients. However, thalidomide, steroids, androgens and azathioprine were given for PMF. We found relatively younger median age at presentation as compared to previous data. On account of considerable overlap in signs & symptoms of these disorders, molecular analysis are essential in diagnosis in addition to bone marrow biopsy. Lower frequency of Jak2 V617F positivity in our cohort might be due to the use of NESTED PCR and financial constraints. The use of newer molecular markers in future like Calreticulin, JAK2 exon12 and MPL mutations will fill the diagnostic gap to considerable extent in cases where JAK2 v671f mutation is not detectable in MPN.

**Keywords:** Essential thrombocythemia, Jak2V617F mutation, Myeloproliferative Neoplasm, Polycythemia vera, Primary Myelofibrosis

## INTRODUCTION

The WHO (World Health Organization) classification system for hematological malignancies includes eight clinic-pathological entities under the category of myeloproliferative neoplasms (MPNs); chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis

(PMF), chronic neutrophilic leukemia, chronic eosinophilic leukemia-not otherwise specified, mastocytosis and MPN-unclassifiable (Vardiman et al., 2009). Among these, the first four were assembled in 1951 by William Dameshek (Tefferi, 2008), as 'myeloproliferative disorders'; they are now referred to as 'classic' MPNs. As CML is specifically

**Table 1.** Age and gender distribution among cases of MPNs other than CML

MPN	NUMBER OF CASES (%)	MEDIAN AGE –YEARS (RANGE)	MALE/FEMALE
Polycythemia Vera	33 (37)	35 (9-80)	24/9
Essential Thrombocythemia	28 (31.5)	33 (10-75)	12/16
Myelofibrosis	28 (31.5)	28 (25-80)	14/14
Total	89	32 (9-80)	50/39

**Table 2.** Haematological parameters at presentation

Haematological Parameters (mean)	Polycythemia Vera	Essential Thrombocythemia	Myelofibrosis
Hb(gm/dl)	18.2±2.3	11.3±0.5	8.46±3.0
TLC (10 <sup>9</sup> /l)	12.5±6.9	12.3±6.16	8.56±6.3
Platelets (10 <sup>9</sup> /l)	435±299	1288±599	168.7±2.7
ANC (10 <sup>9</sup> /l)	9.2±6.7	9.7±3.6	3.74±3.9

Hb: Haemoglobin, TLC: Total Leucocyte count, ANC: Absolute Neutrophil Count

associated with *BCR-ABL1*, the other three (i.e. PV, ET and PMF) are called as '*BCR-ABL1*-negative MPN' (Tefferi and Vardiman, 2008).

JAK2 tyrosine kinase (V617F) mutation is found in most patients with polycythemia vera (PV), as well as one-third to one-half of patients with either essential thrombocythemia (ET) or myelofibrosis with myeloid metaplasia (MMM) (Baxter et al., 2005; Levine et al., 2005; Kralovics et al., 2005; James et al., 2005).

In the US, MF prevalence ranges from 3.6-5.7 per 100,000 patients. Incidence estimates of MF range from 1.7-2.4 per 100,000 patients. PV prevalence estimates range from 45-57 cases and ET prevalence ranges from 39-57 cases per 100,000 patients. PV tends to affect more males while ET affects more female (Mesa et al., 2012).

A 25 years data from a French registry showed E.T to be the most frequent entity with an incidence rate 1.2/100,000 inhabitants/year, followed by CML (0.9/100,000) and P.V (0.6/100,000). E.T was also characterized by a reversed sex ratio (0.9), contrasting with other MPN in which the male predominance was marked. The mean age of occurrence of CML was approximately 10 years lower than that for other MPN. With regard to age, incidence rates of MPN increased from 25-29 years onwards, although a slight decrease was observed after 80 years old (Maynadie et al., 2011). An increase in incidence throughout the period studied was noted in women with an annual rate of 2.3% per year ( $P < 0.001$ ), while there was a slight decrease in men. In this large cohort, the median observed survival was 91.7 months for patients with MPN (Maynadie et al., 2011).

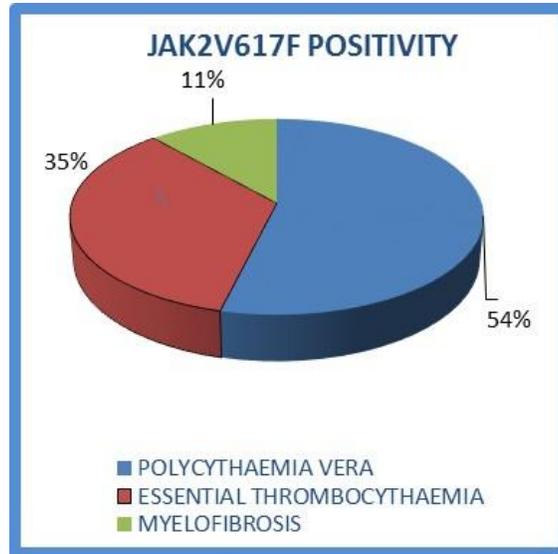
There are very few local studies available on these disorders except CML. The objective of the present study was to see the spectrum of MPN other than CML in southern region of Pakistan.

## MATERIAL AND METHODS

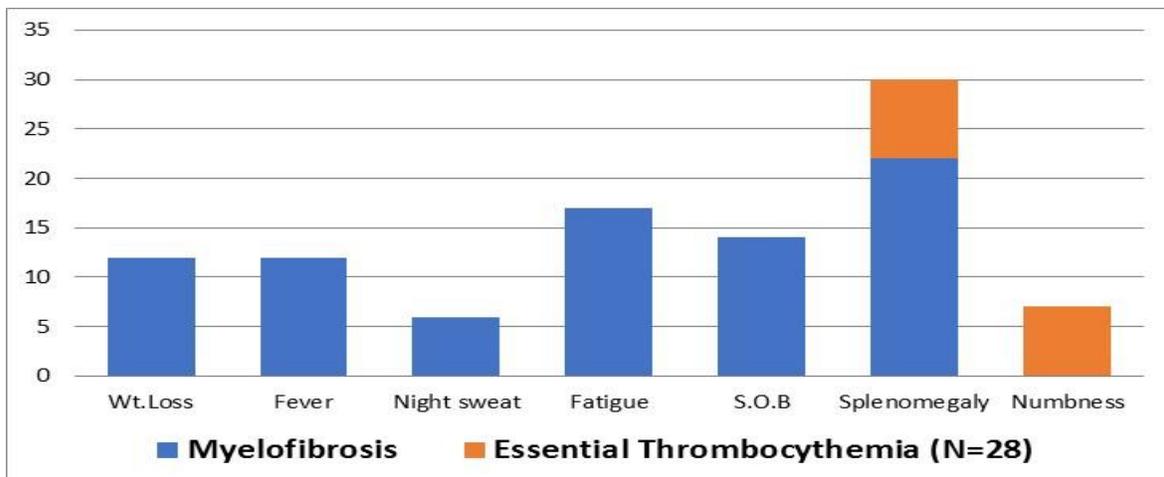
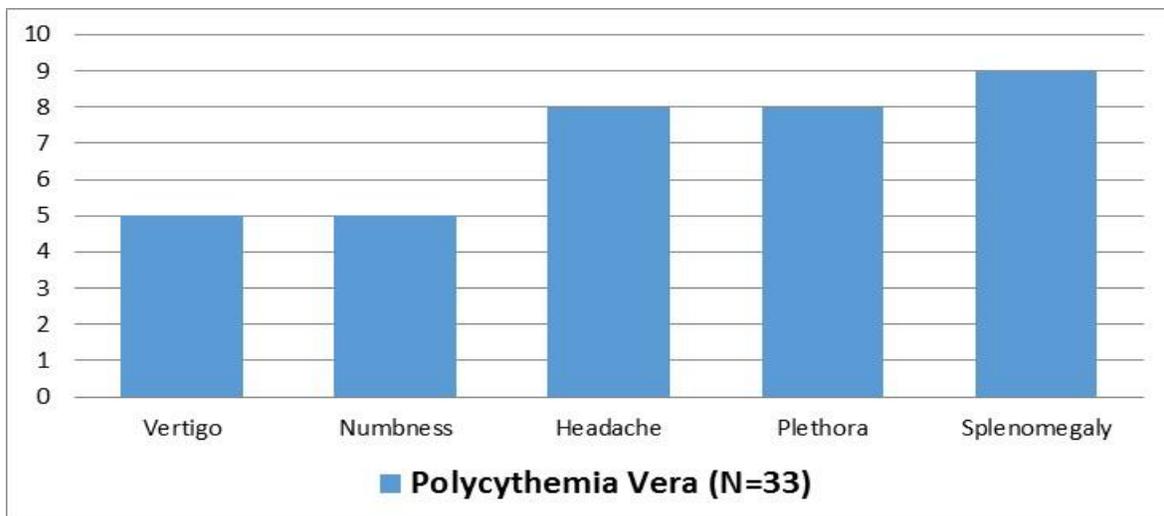
We conducted a retrospective study and analyzed the 5 years data of myeloproliferative neoplasm other than CML presenting in the clinics of NIBD from year 2008 -2013. All the cases were diagnosed and classified according to WHO Classification of 2008. Demographic details, clinical presentation, laboratory and molecular data and treatment options were the main focus of our study. Approval was taken from institute's ethics committee. Statistical analysis was performed by using SPSS version 17.

## RESULTS

A total of 89 cases were found to have MPNs other than CML including 33(37%) cases of PV, 28(31%) and 28(31%) of ET and PMF respectively. PV was found mostly in males (72.7%) while ET was found in majority of the female patients (57%) (Table1). No male or female distinction was found among cases of PMF. A characteristic pattern was seen in the laboratory parameters. Haemoglobin was found raised in PV, Platelets in ET but lesser than normal values were seen in PMF particularly in Hb and TLC (Table 2). Jak2 v617f mutation was detected in 54%, 35% and 11% cases of PV, ET and PMF respectively (Figure 1). The signs and symptoms found in majority of patients with all the three entities involved splenomegaly (PV 27%, ET 28% and PMF 78%) followed by headache and plethora (24%) in PV and fatigue (61%), weight loss and fever (43%) in PMF and numbness (25%) in ET (Figure 2A and B). Hydroxyurea was used as the treatment option for PV (76%) and ET (71%). Aspirin was also used simultaneously among these patients. Allopurinol and Venesection (51%) each was only required in PV. Similarly, thalidomide, steroids, androgens



**Figure 1.** Frequency of JAK2V617F among MPNs



**Figure2 (A and B).** Frequency of common presenting symptoms among cases of MPNs

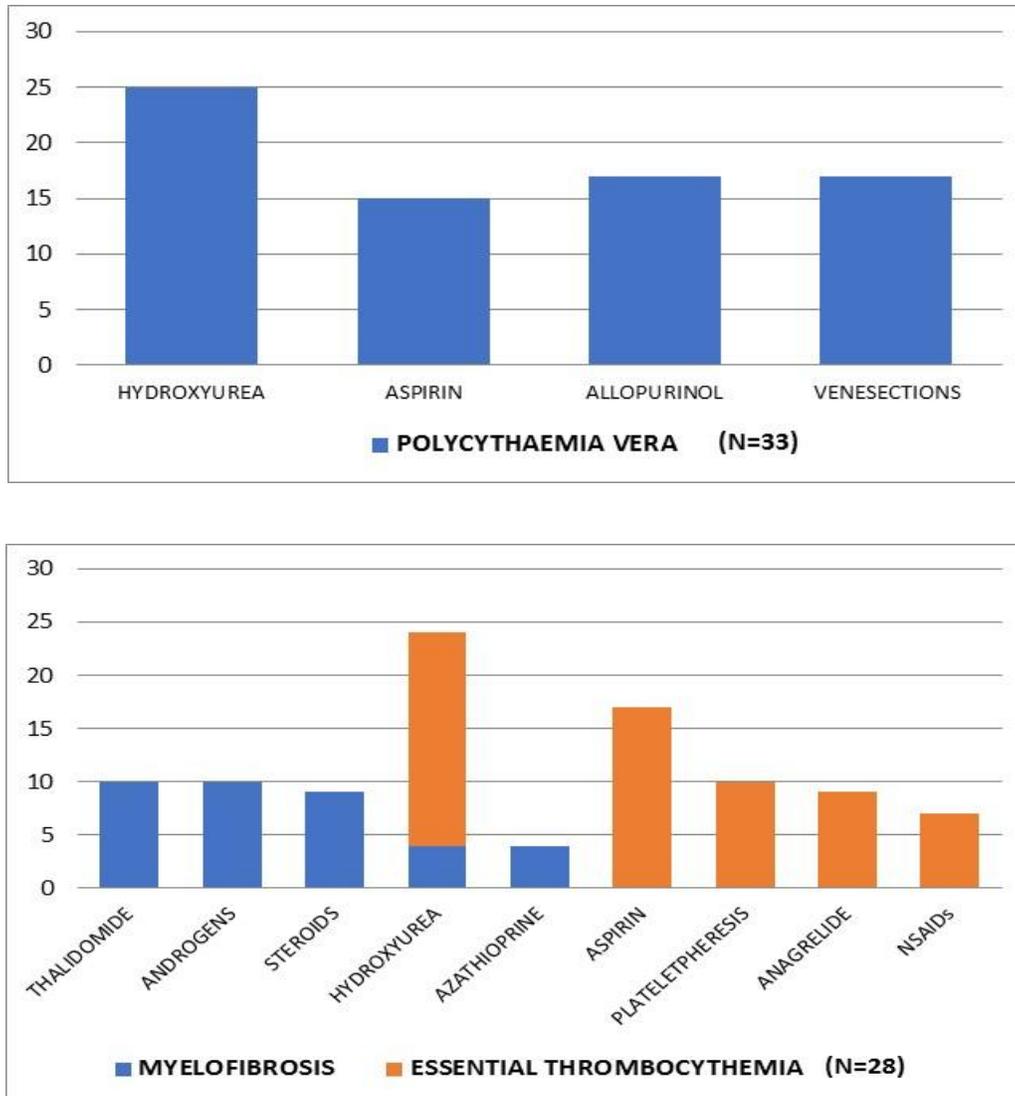


Figure3 (A and B). Various treatment modalities employed in cases of MPNs

and azathioprine were used only for PMF (Figure 3A and B).

Four cases of myelofibrosis initially presented as ITP and one as SLE, one case in our cohort of PMF transformed from P.V and one patient expired.

## DISCUSSION

PV, ET, and PMF are stem cell derived clonal disorders. However, clonal architecture and hierarchy in these diseases is complex and not always predictable (Tefferi, 2010).

Limited data are available on this group of disorders in our country and region. The data we report upon here is the first of its kind in our country. It allows us to provide information about epidemiology, clinical presentation and

haematological parameters for one of the longest registration periods reported so far in our country i.e. from 2008 to 2013.

In this study a total of 89 cases were included, of which 33(37%) were PV and 28(31%) each were ET and PMF (Table 1) which is comparable to US data on MPNs (Mesa et al., 2012), but differs from French and UK data in which ET was found to be more prevalent (Maynadie et al., 2011; Phekoo et al., 2006). PV was found mostly in males (72.7%) while E.T was found in majority of the female patients (57%) which is in concordance with the US and French data, no male or female distinction was found among cases of PMF in our cohort, which is different than 25 years experience of a French registry (Maynadie et al., 2011), however no statistically significant difference was found amongst the two genders in a study done in UK (Phekoo et al., 2006).

Our results show that 54% of the cases of PV, 35% of ET and 11% of PMF were positive for JAK2V617F mutation (Figure 1) which is significantly lower as compared to the international data. Reason behind this was the initial use of NESTED PCR which was later replaced by ARMS PCR technique a more reliable technique and secondly in 17% patients JAK2 mutation analysis was not performed due to financial constraints. JAK2 has lent itself to be a sensitive diagnostic marker for PV (Tefferi et al., 2007; Verstovsek et al., 2006). It is not only specific for PV but is also found in approximately 50% of patients with ET and PMF (Tefferi et al., 2005; Antonioli et al., 2005; Campbell et al., 2006). JAK2 mutation has also been reported at a lesser frequency in cases of RARS-T and in other myeloid neoplasm (Remacha et al., 2006; Steensma et al., 2005).

Among the haematological parameters at the time of presentation Hb and TLC were higher in PV patients, thrombocytosis was observed in ET patients whereas significant cytopenias was the feature in PMF patients (Table 2). The distinction among the three BCR-ABL-negative classic MPNs (i.e. PV, ET and PMF) is not always apparent from the hemoglobin or hematocrit readings. In the past, the PVSG advocated the use of red cell mass (RCM) measurement to address the aforementioned shortcomings in the diagnosis of PV (Berlin, 1975). However, such practice was based mostly on a conceptual argument rather than systematic evidence and the 2001 WHO criteria instead emphasized the value of histology in this regard (Sirhan et al., 2005; Thiele et al., 2006).

Splenomegaly was the commonest presenting feature in our patients (Figure 2A, 2B) followed by numbness in PV & ET only. Hydroxyurea (HU) was given as the first line therapy for PV (76%) and ET (71%) along with Aspirin (Figure 3A, 3B). HU has been found to be effective in reducing the thromboembolic events when compared to phlebotomy alone in a phase II PVSG trial (Mascarenhas et al., 2014). Results of the 2 trials done in ET patients found HU to be effective in reducing life threatening thromboembolic events and superior to anagrelide, while in the third study results were comparable to anagrelide (Mascarenhas et al., 2014). Controlled studies have confirmed the antithrombotic value of low-dose aspirin in PV (all risk categories) and hydroxyurea in ET (high-risk disease) (Landolfi et al., 2004; Harrison et al., 2005; Finazzi and Barbui, 2008). In our patients, venesection (51%) was only offered in cases of PV. There is uncontrolled evidence to support the need to phlebotomize all patients with PV and a recent study suggested a hematocrit target of lower than 55% as being acceptable in patients receiving aspirin therapy (Di Nisio et al., 2007). On the other hand, thalidomide, steroids, androgens and azathioprine were used only in PMF patients. Anemia and symptomatic splenomegaly are the main indications for treatment in PMF and is treated with androgens, prednisone, danazol, thalidomide or lenalidomide (Cervantes et al., 2007). Hydroxyurea is the

drug of choice for symptomatic splenomegaly in PMF. Hydroxyurea-refractory patients are often managed by splenectomy since the value of other conventional drugs in this regard is limited. Tyrosine kinase inhibitors such as imatinib have also been used, but their efficacy is limited. Tipifarnib, a farnesyl transferase inhibitor, has shown benefit in the anemia (Cervantes et al., 2007). Only curative option for PMF is Allogeneic stem cell transplantation (Cervantes et al., 2007).

Clinical trials are being conducted for several JAK2 kinase inhibitors for patients with MPNs. In one of these trials for PMF, JAK2 inhibitors produced rapid spleen size reductions and significant improvements in constitutional symptoms and quality of life (Quintás-Cardama and Verstovsek, 2011). However, in ET and/or PV, JAK2 inhibitors normalize hematocrit levels, platelets and WBC, and splenic size in a large number of patients that are resistant/ intolerant to cytoreductive therapy such as hydroxyurea. Inhibitors are not specific for the JAK2V617F mutant protein. They inhibit the JAK2- signal transducer and activator of transcription (STAT) pathway and therefore any patient with MPN may benefit from therapy regardless of JAK2 mutational status (Quintás-Cardama and Verstovsek, 2011).

## CONCLUSION

In our study patients suffering from MPN are relatively younger than reported internationally. Considerable overlap in sign & symptoms is seen among the three disorders. Therefore, the role of molecular markers has become essential in diagnosis of these disorders along with standard procedures like peripheral blood morphology, bone marrow aspirate and trephine biopsy. Lower frequency of JAK2 v617f positivity in our cohort might be due to the use of NESTED PCR technique at initial stage but later replaced by ARMS PCR, secondly it could be due to the fact that in many cases JAK2 mutation analysis could not be performed due to financial constraints. New molecular markers like somatic mutation in Calreticulin gene, JAK2 exon12 and MPL mutations will fill the diagnostic gap to considerable extent in cases where JAK2 v617f mutation is not detectable in myeloproliferative neoplasms.

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