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The Proportion, Clinical characteristics, complications, treatment pattern & outcomes of Ph-negative Classic Myeloproliferative Neoplasms at TASH: A Hospital based retrospective Cross-Sectional study.

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A RESEARCH THESIS SUBMITTED TO HEMATOLOGY UNIT, DEPARTMENT OF INTERNAL MEDICINE, COLLEGE OF HEALTH SCIENCES, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE SUB SPECIALITY CERTIFICATE IN ADULT CLINICAL HEMATOLOGY.

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List of Abbreviations and Acronyms

CALR- Calreticulin gene

DIPSS - Dynamic International Prognosis Scoring System

ET- Essential thrombocythemia

HSCT- hematopoietic stem cell transplantation

IPSETT- International Prognostic Score for ET-thrombosis

IPSS- International Prognosis Scoring System

JAK2 - Janus Kinase 2

LDH- Lactate dehydrogenase.

MPN- Myeloproliferative neoplasms

NAACCR- North American Association of Central Cancer Registries

SEER- Surveillance, Epidemiology, and End Results

PF-PMF- Pre-fibrotic primary myelofibrosis

PMF- Primary myelofibrosis

PV- Polycythemia vera

Ph - Philadelphia chromosome

MPL- Thrombopoietin receptor gene

OS- Overall survival

WBC- White blood cell count

WHO- World Health Organization

LIST OF TABLES AND FIGURES

Table 1……Demographics distribution pattern of Ph –ve MPNs Patients.

Table 2……..Age - group distribution of Ph –ve MPNs.

Table 3………Circumstance of disease detection at time of diagnosis.

Table 4………Clinical & laboratory data distribution pattern of MPNs Patients.

Figure 1…….Symptoms by PH –ve MPN subtypes

Figure 2…….Thrombotic complication by Ph –ve MPNs subtypes

Figure 3……. Probability of 5 year survival rate of Ph –ve MPNs

Figure 4……. Probability of five year survival rate of ET

Figure 5……. Probability of five year survival rate of PMF

ABSTRACT

Background

Haematological malignancies are among non-communicable diseases that are becoming increasingly more common both globally and in our country, Ethiopia. Out of these Philadelphia-negative classic myeloproliferative neoplasms, affecting the elderly population group of the society is seen in increased frequency in outpatient department. This is due to progressively rising global population age and life expectancy, so it is becoming an important public health problem worldwide. Investigations done with a small number of African countries indicated a gradually increasing frequency of philadelphia-negative MPNs in the continent. In growing country, there are few studies that truly define the clinical feature of these patients. Especially in Ethiopia there is no data regarding Ph negative classic MPNs. This will aid to estimate the characteristics, treatment pattern & outcomes based on a local data of patients with diagnosed Philadelphia-negative classic MPNs.

Objective: The main objective of the study is to measure the clinical characteristics, complications, treatment pattern & outcomes of Ph negative classic MPN patients.

Methods: A single cantered hospital based retrospective cross sectional study was conducted at haematology follow up clinic from January 1, 2019 to December 31, 2023; data was collected and analyzed with IBM SPSS version 27.

Result: A total of 151 study participants with the age of 18 & above were included in this study. 57 %(86/151) of study participants are male & 43% are females, with a male to female ratio of **1.3:1. 58.3**% of PV patients were male, 56.7% of ET patients were females. Similarly 72.2% of PMF cases were male. PV was the most common (68%) with a median age at diagnosis of 56 years, followed by ET (20%, median age 55.5 years) and Primary Myelofibrosis (12%, median age 60 years). Female patients had mostly a history of ET; a higher number of male patients had a history of PV and PMF. Among PV cases, the main presenting symptoms were headache/vertigo (37%) followed by fatigue (31.4%), early satiety/ LUQ pain (31%) & splenomegaly was found in 28%. In ET, the main presenting symptoms were fatigue (36.8%), headache, joint pain, and splenomegaly being the other common presenting symptoms Among the PMF patients', the main presenting symptoms were symptoms of anaemia (40%), fatigue (38%), constitutional symptoms (35%), early satiety/ LUQ pain (35%) & Splenomegaly (72%). JAK2V617 mutation was positive in 92%, 54%, and 44.4% of PV, ET and PMF patients, respectively. The frequency of thrombotic events were high in PV patients compared to other subtypes (PV=33%, ET=26% and PMF=5.6%) and venous thrombosis being higher than arterial. In contrast to other subtypes, bleeding was prevalent in PMF patients (PMF=11%). Thrombotic complication was high in high risk PV & ET patients, while Jak 2 mutation status didn't affect thrombosis risk. Phlebotomy, ASA and hydroxyurea, Thalidomide/prednisolone and transfusion support were the treatment options used. The five year survival rate of Ph –ve MPNs with median diagnosis of 27months were 81%, which was higher for ET (95%), PV=84% and low for PMF (median survival rate is 4 years).

Conclusion: This study showed that, PV is a more prevalent ph negative MPN than ET and PMF. Thrombosis is an important complication in these patients, especially in PV patients occurring in ~1/3rd of the cases. Based on our findings we emphasize that that Ph negative MPNs should be considered & proper evaluation should follow in patient with unexplained abnormalities in hematologic parameters.

Table of Contents

1. Introduction……1

1.1 Background……1

1.2 Statement of the problem……..3

1.3 Significance of the study……4

2. Objective 5

3.1 General objective.....5

3.2 Specific objective 5

4. Methods and materials.....…6

4.1 Study design.....6

4.2 Study period……6

4.3 Study area 6

4.4 Study Population 6

- 4.4.1 Inclusion Criteria ……6

- 4.4.2 Exclusion Criteria……6

4.5 Study Variables……..7

4.5.1 Dependent variable……7

4.5.2 Independent variable…….....7

4.6 Data collection procedure 7

4.6.1 Data quality assurance……..7

4.7 Data Management and Analysis Methods.....……8

4.8 Ethical consideration.....8

4.9 Dissemination of the study.....8

4.10 Definition of key terms/concepts……9

5. Result..…..10

6. Discussion.....16

7.Conclusion……20

8. Strength & limitations……21

9. References. 22

10.Annexes.…… .24

1. INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Myeloproliferative neoplasms are clonal hematopoietic stem cell disorders defined by the proliferation of one or more myeloid lineage cells [1]. Philadelphia chromosome-negative MPNs are a heterogeneous group of hematopoietic clonal disease, with the main subtypes being polycythaemia vera, essential thrombocythemia, and primary myelofibrosis. Despite differences among the disease type, MPNs are characterized by shared clinical, pathological, and molecular features [2].

Worldwide few articles reported the prevalence, based on these the prevalence of PV ranging from 0.49 to 46.88 per 100,000 [3]. The prevalence of ET was ranging between 11.00 and 42.51 per 100,000. Prevalence rates for PMF were ranging from 1.76 and 4.05 per 100,000. PV is slightly more prevalent in males, ET is more prevalent in female and the overall frequency of PMF is roughly equal in males and females worldwide [3]. Most patients are diagnosed with Ph negative MPNs after age 60 years, the median age at diagnosis of PV is 64 years, 55 years for ET and 65 years for PMF [1]. The most prominent mutations in Ph negative MPNs are in the genes that encode for JAK2, MPL, and CALR [4]. With increased life expectancy and aging of the population, the prevalence and incidence of Philadelphia-negative classic MPNs is increasing and becoming an important public health problem worldwide. However local data regarding the clinical feature of the disease is lacking, few studies done in sub-Saharan population reported a progressively increasing prevalence of Philadelphia-negative MPNs in the continent.

The 2016 revision of the WHO diagnostic criteria for PV, ET, and PMF were updated by adding the molecular data with bone marrow morphology and blood counts. These remain the current recommended diagnostic markers [5]. The new ICC 2022 & WHO 5th edition classification is largely unchanged, but aimed to increase diagnosis certainty in early-stage disease [5]. Although it is considered relatively indolent diseases, even among patients with the same MPN subtype, the symptom profiles vary. Symptoms include excessive sweating, fatigue, bruising, headaches, joint pain, difficulty concentrating, bleeding, and abdominal discomfort and pain. PV and ET are both associated with long clinical courses, frequent thrombosis and bleeding events, and the development of myelofibrosis and acute leukaemia [6]. A history of thrombosis or age older than 60 years is associated with a high risk of thrombosis in PV and ET [6]. The published incidence reports of thrombosis and bleeding among patients who were newly diagnosed with Ph negative MPNs varied throughout the studies [7]. Adverse risk factors in PMF include advanced age, low platelet and hemoglobilin levels, red cell transfusion dependency, a high WBC count, constitutional symptoms, a circulating blast count, or unfavourable karyotype or molecular features [1].

They are classes of incurable diseases except with allogenic SCT, so the treatments are based on risk stratification; however it is heterogeneous and not standardized among the different

countries. Currently, the therapeutic landscape of Ph negative MPNs has been revolutionized by JAK 2 inhibitors, which have proven effective in controlling disease-related symptoms and splenomegaly [8].

Patients with any Ph negative classic MPN subtype to have significantly reduced life expectancy compared with the general population. The median overall survivals of PV and ET are 10-16 years and 10-22 years, respectively. However, PMF patients have a much lower median survival of 4-5 years [9]. Increasing survival over time was seen for PV and PMF in all age categories.

In growing countries, there are few reports that truly describe the clinical feature of these patients. Especially in Ethiopia there is no data regarding Ph negative classic MPNs. As a result, the purpose of this study is to provide a single center's experience of the clinical manifestation, complications, treatment patterns, and outcomes of patients managed at TASH. This will aid to estimate the proportion, common clinical presentation based on a local data and clinical parameters determining patients' disease related complications and survival of patients with a diagnosed Philadelphia-negative classic MPNs.

1.2 STATEMENT OF THE PROBLEM

Myeloproliferative neoplasms are hematologic disorders that have progressive rising prevalence worldwide and in our country. Out of these, Ph negative classic MPNs, which is a clonal malignant neoplasm of single hematopoietic stem cell that causes excessive production of mature blood cells. Affecting the elderly population group of the society and it is seen in increased frequency in outpatient department of governmental hospitals of the country. The disease burden is more frequently seen in Tikur Anbessa Specialized Hospital (TASH) located in Addis Ababa, Ethiopia, as it has been the only tertiary referral governmental treatment canter for hemato oncologic disorders in the country.

Nevertheless, local data regarding the magnitude or proportion, clinical characteristics, treatment pattern and outcome of patients with these disorders are not available. Therefore, this study aims to provide the clinical manifestations, complications, treatment pattern and survival of patients managed at Tikur Anbessa Specialized Hospital over a five-year period.

I hope that the results of this study will highlight the possible clinical features, disease burden, complications and outcomes based on the local data of patients related to Ph negative classic MPNs.

1.3 SIGNIFICANCE OF THE STUDY

Though the prevalence of Ph negative classic MPNs are extremely varied across the globe, but over the past few decades, it has consistently increased. The largest increase in reported prevalence rate is seen in westerns, while Japan and Israel have reported the lowest rates. These wide variations could be the result of variations in study design, diagnostic standards, reporting procedures, and racial/geographic disparities, among other factors. However, Using standard diagnostic criteria & real data reporting is very limited in many countries of low socioeconomic status, particularly in sub-Saharan Africa.

Although it is considered relatively rare & indolent diseases, knowing the prevalence and clinical characteristics are the core of health system responses to the lifelong increased risk of thrombosis, hemorrhage, myelofibrosis or leukemic transformation which contribute to significant impact on morbidity and mortality.

In order to create awareness and address the impact of hematologic malignancy among the public, physicians and minster of health should be equipped with the necessary knowledge regarding the prevalence, disease characteristics & survival of Ph negative classic MPNs. This will plays an important role in planning health education to the public concerning hematologic malignancy & fulfilling the Ministry of health sector transformation plan, which aimed to increase awareness of non-communicable disease.

Therefore, in this continuously evolving field of study it is always important to study the clinical features and treatment outcome of patients. Especially in our country where most therapy including standard targeted therapy for resistant disease or bone marrow transplant for refractory and high risk patients were no visible. The extent of treatment response to prevent complications or progression of disease with the existing treatment regimens needs to be studied. Though, few studies have been conducted in Ethiopia involving different hematologic malignancy, but no study was conducted to explore the prevalence, disease characteristics & treatment outcome of Ph negative classic MPNs.

Thus, the aim of this study is to assess the clinical characteristics,complications,treatment pattern and survival of patients with Ph negative classic MPNs in TASH, Ethiopia for the period 2019-2023.

3. OBJECTIVES

3.1 General objective

- To evaluate the proportion, clinical characteristics, complication, treatment pattern and outcomes of Philadelphia-negative Classic Myeloproliferative Neoplasms:

3.2 Specific objectives

- To determine the proportion.
- To identify disease characteristics and complications
- To assess treatment pattern
- To assess the outcomes.

4: METHODS & MATERIALS

4.1: Study design

A single centred Hospital based retrospective Cross-sectional study was conducted to determine the proportion, disease manifestation and outcomes of Philadelphia-negative classic MPNs patients who had follow up at TASH, hematologic clinic, Addis Ababa University. We looked over the laboratory results and clinical feature records for each patient who visited the clinic between January 1, 2019 and December 30, 2023 with Ph negative classic MPNs and treatment in the outpatient unit.

4.2 Study period

The study period for this retrospective study was from January 1, 2019 and December 31, 2023.

4.3 Study area

The study was conducted at TASH which is located in Addis Ababa, the capital city of Ethiopia. It is the biggest referral hospital in the country with 700 inpatient beds and providing service to an estimated 500,000 patients annually. It also serves as a teaching hospital for undergraduate & post graduate medical & other health science students under the administration of adiss ababa University College of health sciences.

4.4 Study population

All patients with suspected or confirmed Ph negative classic MPNs, according to the 2016 WHO diagnostic criteria, and on follow up at the outpatient hematology clinic of TASH in the specified study period were included in the study.

4.4.1 Inclusion criteria

- ✓ All patients Age >=18 years with a suspected or confirmed Ph negative classic MPNs according to the 2016 WHO diagnostic criteria

4.4.2: Exclusion criteria

- Patients with incomplete laboratory work up for diagnosis and follow up
- Those patients with absent or incomplete clinical data record were excluded from the study

4.5: Study variables

4.5.1 Dependent variables

- Development of thrombosis, bleeding,
- Progression of the disease to secondary MF or acute leukaemia.
- Outcomes

4.5.2 Independent variables

- Age and Sex, Comorbidity, smoking
- B symptoms, splenomegaly, Hepatomegaly
- BMB, EPO level, JAK 2, CARL, MPL mutational status.
- PV, ET, PMF
- Specific complication of PV, ET, PMF at diagnosis.
- Type of treatment

4.6: Data collection process

Retrospective data was obtained from medical records for all Ph-negative MPN patients who visited the Haematology Clinic between January 1, 2019, and December 31, 2023. This included information on demographics, clinical characteristics (signs and symptoms, including splenomegaly), CBC at diagnosis, JAK2V617F mutation analysis, types of MPNs, treatment, and complications (thrombosis, haemorrhage, secondary myelofibrosis, and leukemic transformation). Number of cases of each diagnosis registered to HIMS & electronic I care during the same period was also obtained. At the end, 151 diagnosed cases were reviewed after excluding 129 patients.

The international prognostic score for PV and ET was used to evaluate the prognostic score, while the conventional score was utilized in PV and ET to predict thrombotic complications. The Dynamic International prognosis scoring system (DIPSS) was assessed to determine the estimated survival for patients with PMF. To analyze survival rate, passive follow up using phone numbers was conducted until December 31, 2023. The survival analysis was calculated based on the Kaplan Meier plot.

4.7: Data Management and Analysis Methods

Excel 2010 and SPSS version 27, the statistical package for social sciences, were used to analyse the data that had been gathered. Descriptive analysis was used to examine the laboratory data, clinical features, and demographic information. The independent t-test was utilized to analyze continuous variables, while the Chi-square test was employed to analyze categorical variables. These variables were examined to ascertain their association with complications. These variables included signs, symptoms, laboratory data, and results of the JAK2V617F mutation. If the P value was less than 0.05, the differences were considered significant. The independent risk factors of bleeding and thrombosis were identified through multivariate analysis using backward selection on the variables with a P value of less than 0.05 from the univariate analysis.

4.8: Ethical consideration

The research proposal was submitted to the Ethical Review Committee of College of Health Sciences of Addis Ababa University. Data collection started after the proposal was approved and cleared by the Ethical Review Committees. In this retrospective study, obtaining informed consent was not feasible. Confidentiality of patient's data was maintained throughout the study.

4.9: Dissemination of the study results

The final report of this study submitted and presented to the department of internal Medicine Haematology unit, college of health science, Addis Ababa University. Efforts will also be made to distribute research findings to national and international medical journals for publication.

4.10: Definition of key terms/concepts

Fatigue (recorded on the patients history) = is a feeling of constant exhaustion, burnout or lack of energy.

Early satiety (recorded on the patients history part) = is the inability to eat a full meal or feeling full after only a small amount of food.

Aquagenic pruritus (recorded on the patients history part) = is development of severe itching on contact with hot water without observable skin lesions.

Erythromelagia (recorded on the patients' history part) or episodes of pain, redness, and swelling in various parts of the body, particularly the hands.

Headache (recorded on the patients' history part) or pain or discomfort in the head or face area.

Dizziness (recorded on the patients' history part) or the feeling of being lightheaded, woozy, or unbalanced

Night sweats (recorded on the patients' history part) or repeated episodes of very heavy sweating during sleep, heavy enough to soak your nightclothes or bedding.

Anorexia (recorded on the patients' history part) or eating problem leading to low weight, body image disturbance.

Weight loss (recorded on the patients' history part) or decrease in body weight resulting from involuntary circumstances not related other cause.

Thromboembolic events (events recorded on the patients' history or diagnosis) = blood clot that blocks a vein or arteries like stroke, TIA, AMI, peripheral arterial or venous thrombosis.

5. RESULT

5.1 Socio demographic characteristics of the study participants

A total of 280 patients suspected Ph –ve MPNs were found in the study period of January 1st, 2019 to December 31st, 2023. Of these, 151 patients with confirmed diagnosis of PV, ET and PMF were included in this study. Total of 129 patients were excluded from this study due to misdiagnosis and incomplete record of clinical and laboratory data.

The medical records of the 151 patients were retrospectively evaluated. Male accounting for 57% (86) and Female accounting for 43% (65), the male to female ratio was 1.3:1. Majority (58.3 %(88/151)) of patients were from Addis Ababa, the rest from other regions. 45% of the patients had comorbidity at time of diagnosis.

PV was the most frequent Ph –ve MPN (68.2%) in this study followed by ET (20%) and MF (12%) as shown on table 1. The clinical & laboratory data distribution pattern of MPNs Patients are summarized in Table 3 and 4.

Table 1: Demographics distribution pattern of MPNs Patients

Characteristics	PV	ET	PMF
Case no. (%)	103 (68%)	30 (20%)	18 (12%)
Median age in years (range)	56 (21-82)	55.5 (25-78)	60 (42-80)
Gender			
Male n (%)	60 (58.3%)	13 (43.3%)	13 (72.2%)
Female n (%)	43 (41.7%)	17 (56.7%)	5 (27.8%)

Table 2: Age-group distribution of MPNs

Age categories (years)	PV no. (%)	ET no. (%)	PMF no. (%)
< 18	0 (0.0 %)	0 (0.0%)	0 (0%)
18-40	20 (19.4%)	9 (30%)	0 (0%)
40-59	39 (37.9)	9 (30%)	10 (55.6%)
>=60	44 (42.7%)	12 (40%)	8 (44.4%)

5.2 Polycythemia Vera

The median age for PV patients was 56 years (range: 21-82 years), and majority (58.3%) were males (58.3 %(60) males versus 41.7 %(43) females) (table 1). Based on the age distribution, the majority of adults affected by PV were those between the ages of 20 and 59 years (57.3%), (table 2). More than half (68 % (70/103)) of PV patients were symptomatic at presentation, (Table 3).

Table 3: Circumstance of disease detection

Characteristics of MPNs patients			
Circumstance of detection	**PV no. (%)**	**ET no. (%)**	**PMF no. (%)**
Incidental	23 (22.2%)	8 (26.7%)	0 (0%)
Symptomatic	70 (68%)	19 (63.3%)	18 (100%)
Not mentioned	10 (9.7%)	3 (10%)	0

The common presenting symptoms were headache (37%), fatigue (31.4%) of cases, early satiety/ LUQ pain (31.4%), joint pain & aquagenic pruritus (5.7%), (figures 1). splenomegaly (26.2 % (27/103)), hepatomegaly (10%). In 13.6% (14/103) of the cases, thrombotic event was the presenting symptom and 19.4 %(20/103) of patients had prior history of thrombosis before diagnosis or it was not the major symptom at presentation, While 8.7% (9/103) of patients developed thrombotic complication after the diagnosis. Overall about 33% (34/103) of the PV cases had thrombotic complications, (figures 2); of which 80% of cases were venous thrombosis & 20 % were arterial thrombosis.

Figure 1: Symptoms by MPNs Subtypes

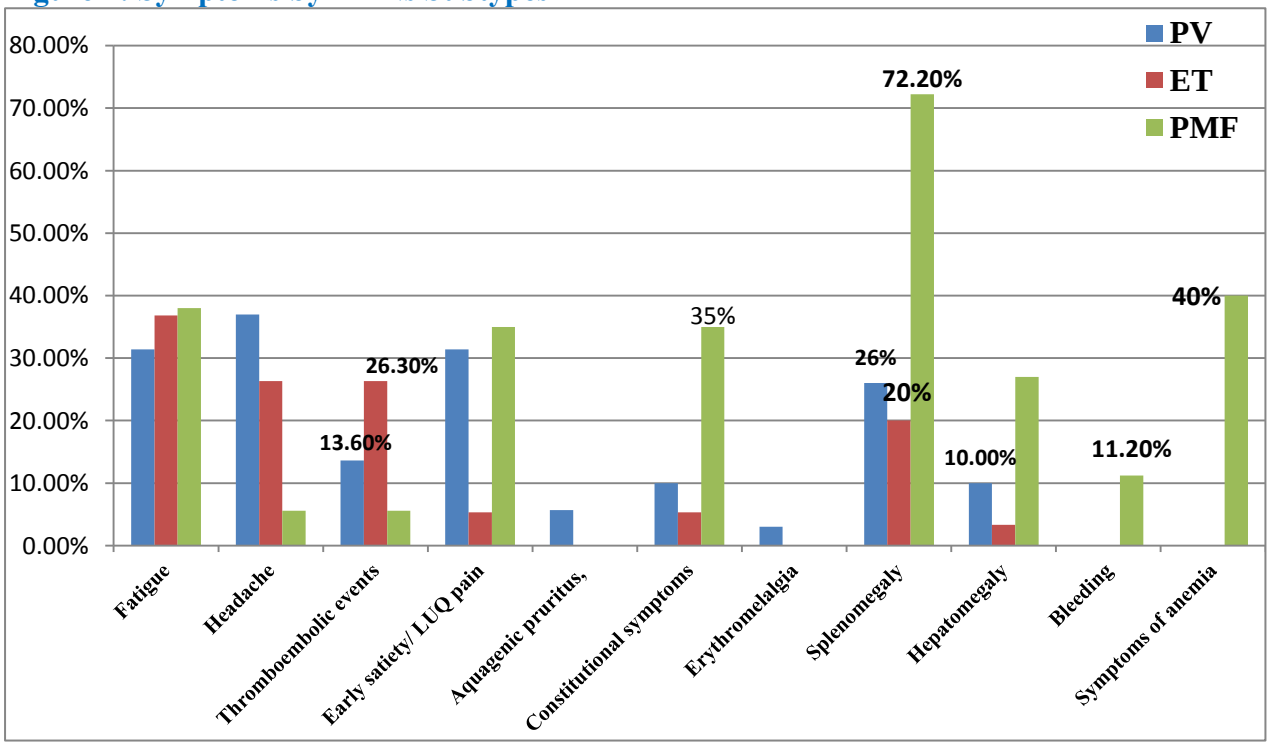


Table 4 revealed that, the median haemoglobin= 18.6g/dl, range from 15.1 to 24.3g/dl, Haematocrit= median 53.2%, range from 36 to 76%, WBC= median 10.2k/microl, ranges from 3-17.2k/microl, platelet= median 282,000/microl, ranges from 70,000-1, 100,000/microl. Among the 103 PV patients 40.8 %(42/103) had BMB at time of diagnosis and it was suggestive of PV in 95.2%.

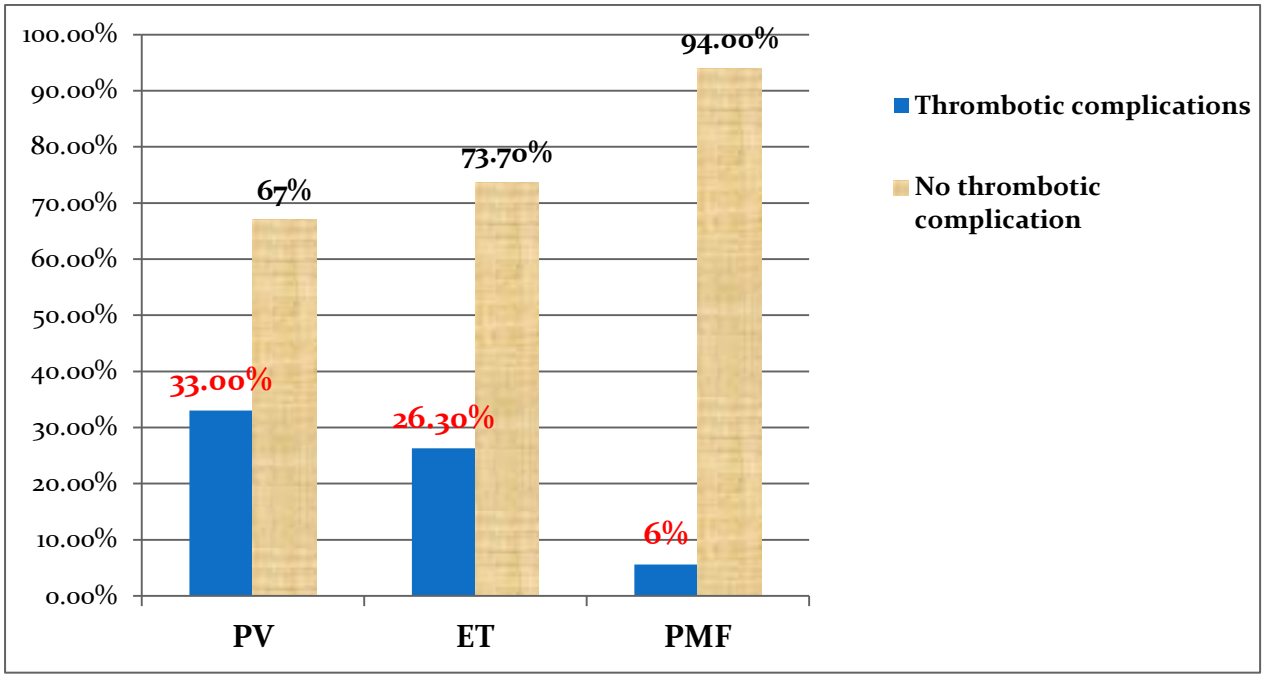
Driver gene mutation was done for 95.1 %(98/103) of patients, and not done in the rest (5%) because of financial reason. The JAK2 V617F mutation was found in 91.8 %(90/98), Exone 12 mutation was detected in 1 %(1/98) of cases of PV and the rest 7.1% (7/98) were negative for Jak 2 mutation. Epo level were determined for 88 patients (85.4%) and it is suboptimal in 68 %(60/88), Normal range (32 %(28/88)) of PV cases.

According to the conventional Scoring System, 58.3 %(60/103) PV patients were in the high risk group, 41.7 %(43) in the low risk group. Thrombotic complications were higher in high risk groups (56.7%) compared with low risk group (P value < 0.001, 95% CI = 0.358 – 0.592). There is significant association between prior history of thrombosis & the development of thrombotic complication after diagnosis with two sided significance P value < 0.031, 95% CI = 0.016 – 0.311 by Pearson chi-square.

Table 4: Clinical & laboratory data distribution pattern of MPNs Patients

Characteristics		**PV=103**	**ET= 30**	**PMF=18**
Driven gene (yes vs. no %)		95.1%(98) vs. 5%	93.3(28/30)% vs.6.7%	50%(9/18) vs. 50%
Driven gene subtypes	V617F +ve: %	91.8%(90/98)	54%(15/28)	44.4%(4/9)
	Exon 12:%	1%(1)		
	CARL/TN: %		3.6%(1)/ 14.3%(4)	11.1% /11.1%(1)
	V617F –ve: %	7.1% (7)	28.6%(8)	22.2%(2)
Epo level done: suboptimal		85.4% : 68%(60/88)		
Prognostic score	**Low Risk**	41.7% (43)	33.7%(10)	16.7% (3)
	Int 1 Risk			38.9% (7)
	Int 2 Risk	58.3%(60)	66.3% (20)	33.3% (6)
	High risk			11.1% (2)
Current Response status	PR	64.1%(66)	83.3%(25)	44.4%(8)
	No response	18.4% (19)	6.7% (2)	33.3% (6)
	Death/NA	11.65% (12)	3.3%(1)	22.2% (4)
	Progressed	5.8% (6)	6.7%(2)	0%

Figure 2: Frequency of thrombotic complication by MPNs subtypes



According to the conventional Scoring System, 58.3 %(60/103) PV patients were in the high risk group, 41.7 %(43) in the low risk group. Thrombotic complications were higher in high risk groups (56.7%) compared with low risk group (P value < 0.001, 95% CI = 0.358 – 0.592). There is significant association between prior history of thrombosis & the development of thrombotic complication after diagnosis with two sided significance P value < 0.031, 95% CI = 0.016 – 0.311 by Pearson chi-square.

Majority (90.3% (93)) of the cases required phlebotomy at the time of diagnosis. At the time data analysis 74 %(76/103) of PV patients were requiring phlebotomy and most (40%) need it every one or two months. 59.2% (61/103) of the patients received ASA & HU as the first line of therapy, ASA was prescribed in 23.3% (24/103) patients & 14.6%(15) receiving HU and oral anticoagulants. In others, HU alone, & thalidomide with prednisolone were used. Around two third (64.1% (66/103)) of the patients were in PR at time of analysis and alive, 22.3 %(23/103) were alive with no response for the current treatment & 13.6 %(14/103) disappeared from follow up, from these 10.7 %(11/103) were died. 5.8 %(6/103) of cases were transformed in to post PV MF, mostly after 2 years of diagnosis.

The median time of diagnosis was 33 months. The five year survival rate of PV patients who were diagnosed from 2019 to 2023 was 84%. The median overall survival is not reached. Overall, five-year survival rates of the patients who were diagnosed with the three MPNs from 2019 to 2023 were 81% (Figure 3). The factors that significantly associated with lower survival was development of thrombotic complication after the diagnosis (p=0.045), there is also a trend towards lower survival in patients with high risk group, but it is not clinically significant (p=0.0.105).

5.3: Essential thrombocythemia

Table 1 illustrates that the median age of ET diagnosis was 55.5 year, range: 25-78 year, with a preponderance of females accounting for 56.7%. Table 2's age distribution showed that young adults b/n the ages of 18 and 59 year made up 60% of those who experienced ET.

Table 3 showed that, 63.3 %(19/30) of ET cases were symptomatic at presentation. 36.8% of cases presented with fatigue, followed by headache (26.3%), and joint pain (4.5%). Splenomegaly was detected in 20% of patients with ET, hepatomegaly (3.3%) (Figure 1). Thrombotic complications were noted in 26.3% (8/30) of patients, (figure 2). In 16.7% (5/30) cases, thrombotic events were the presenting symptom.

Table 4 revealed that, the median haemoglobin was 12.2g/dl, ranges from 8.1-17.8g/dl, the median WBC was 8k/microl, ranges from 2-24k/microl, the median platelet was 648k/microl, ranges from 90k-2,200k/microl. From the 39 patients, 64 %(25/39) had–BMB at time of diagnosis and 92% suggestive of ET. Driver gene done for 93.3 %(28/30) of patients, the remaining cannot afford the test. The JAK2 mutation was positive in 54 %(15/28) of ET patients. According to the convectional Scoring System, sixty seven percent of ET patients were high risk and the remaining (33%) were low risk. Moreover, more (26.7 %(8/30)) thrombotic complication occurred with the higher risk groups (23.1% vs. 0% (9/27), p=0.020, 95% CI= 0.051- 0.607) compared to low risk group, but JAK2 mutational status is not associated with thrombotic complications, P value= 0.057, 95% CI = -0.649 – 0.011). 83.3% (25/30) of the patients were in PR at time of analysis and alive, 6.7 %(2) were progressed to secondary myelofibrosis. 3.3% disappear from follow up or died. HU & ASA were used as the first line of therapy by 56.7 %(17). ASA was prescribed in 30 %(9) patients with ET. In other cases, anticoagulants & HMA are used.

The median time of diagnosis was 28 months. The five year survival rate of ET patients who were diagnosed from 2019 to 2023 was 94%. The median overall survival is not reached as seen on Figure 4. Clinical, laboratory and molecular factors didn’t significantly affect the overall survival in ET patients.

Figure 3: Probability of 5 year survival rate of Ph –ve MPNs

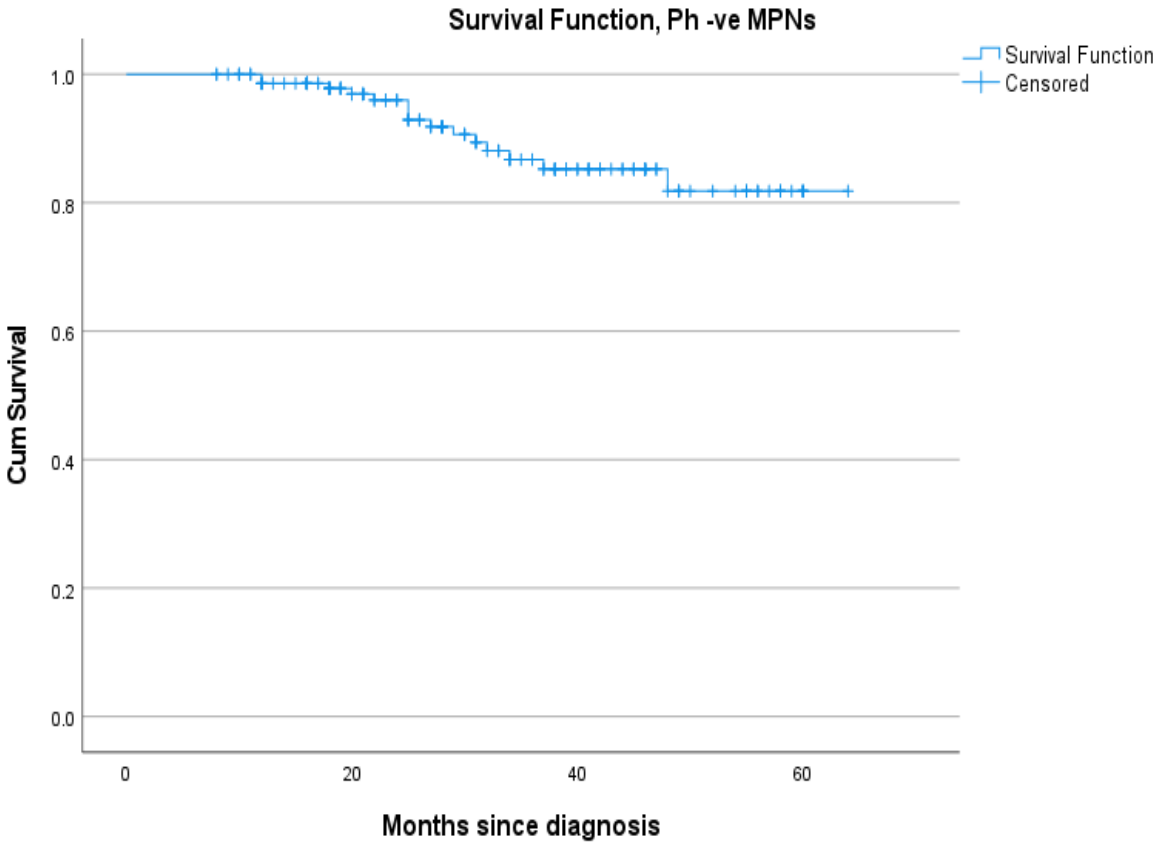
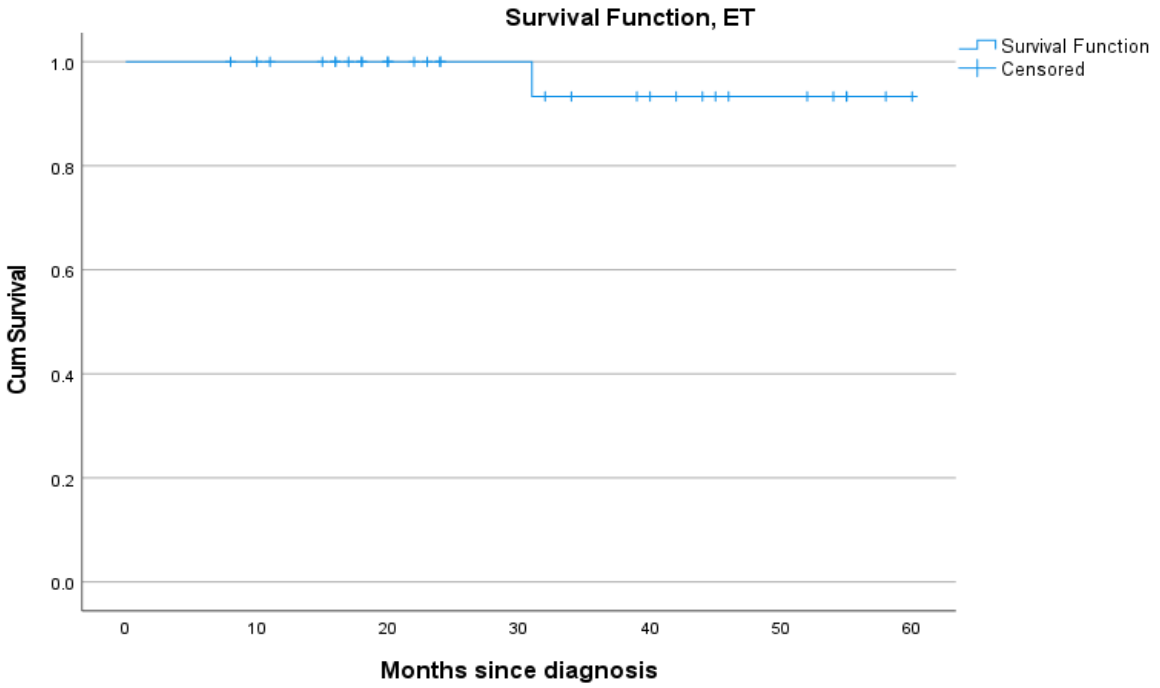


Figure 4: Probability of five year survival rate of ET



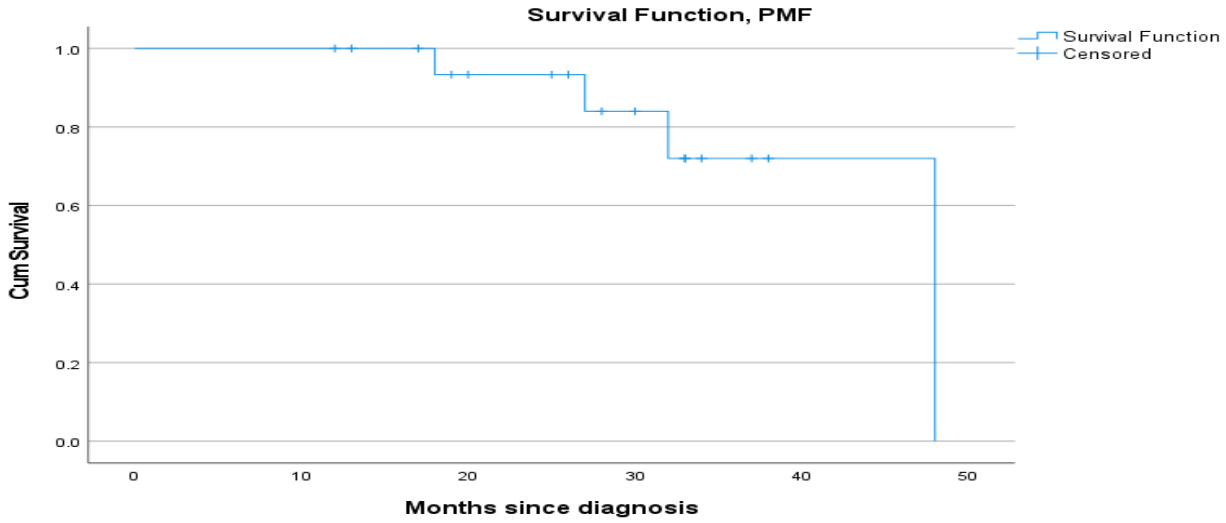
5.4: Primary Myelofibrosis

In this study, the median age at diagnosis of PMF was 60 year, ranges from 42-80 year. Majority (72 %(13/18)) were males versus 28% females. According to Tables 1 and 2, adult PMF patient's b/n the ages of 40-59 (55.6%) were the most affected age categories. All of PMF patients were symptomatic at presentation (tables 3). The most frequent symptoms (figure 1) were fatigue (38%), constitutional symptoms (35%) and early satiety/ LUQ pain (35%). Splenomegaly present in 72.2% of PMF patients and hepatomegaly in 27%. Figure1 & 2 showed that anaemia (44%) was the most common complication followed by bleeding (11.2%) and thrombotic events (5.6%).

Driver gene done for 44.4 %(8/18) of patients, the remaining 50 %(9/18) cannot afford the test and the rest is not mentioned (1) (table 4). The JAK2 mutation was positive in 50 %(4/8) of PMF cases (Triple Negative (1) =12.5%, CARL +ve=12.5 %(1), only JAK2 V617F Negative=25 %(2). According to the Dynamic International Prognostic Scoring System (DIPSS), 11.1 %(2) of PMF patients were high risk, 38.9 %(7) were intermediate 1 risk patients, 33.3 %(6) were intermediate 2 risk and 16.7 %(3) were low risk patients. 44.4% (8/18) were in PR at time of analysis and alive, 33.3 %(6) alive and no response, 22.2 %(4/18) of patients died.

The most used therapy was thalidomide & prednisolone, received by 44.4% (8/18) of the PMF cases. HU was prescribed in 39% (7/18) patients with PMF. In other cases, EPO, antiplatelet, anticoagulants & HMA are used. 39% (7/18) of patients with PMF were transfusion dependent. The median time of diagnosis was 27 months. The median overall survival is 48 months (4 years) for PMF patients (Figure 5).

Figure 5: Probability survival rate of PMF



6. Discussion

According to our study, PV was the most common Ph –ve MPNs, followed by ET and PMF. The proportional data and epidemiological reports of Ph –ve MPNs from other nations were largely with in the same ranges. Based on our finding a higher percentage of PV patients affect younger adults aged b/n 20-59 year. Although PV had been reported in elders, approximately 20-25% of these patients were younger than 40 years in the report by Tibes and Mesa, 2013.

6.1 Polycythemia vera

A t the time of diagnosis of PV, the median age was 56 years, which was slightly higher than the median age reported from Sudanese study [10] but less than the median age from the international study of PV [10] [9]. In addition, mostly male sex more affected than females compared to the 1:1 ratio in the international study [9]. The most frequent presenting symptoms of PV were Fatigue, headache and early satiety or LUQ pain, which is similar to the reports from different studies (scherber et al., 2011, Hensely et al., 2013, Mesa et al., 2016).

Based on this study, thrombotic events were more frequently occurred in PV, which was similar to Asian studies [11], but higher than few African studies [10]. Compared to arterial thrombosis, venous thrombosis happened more frequently. These results were consistent with western country report [12], despite the majority studies done in Malaysia and IPSET thrombosis study showed a higher incidence of arterial thrombosis [13].

In this study, we found a slightly lower percentage of JAK 2 mutation positive PV (91.8%) and PMF (44.4%) patients, this mostly due to small sample size or the diagnosis of PV made by BM exam. might be wrong in some of our patients. Almost similar percentage in ET (54%) compared to many previous studies done by porto-suares et al. Based on the prospective ECLAP study, age more than 60 years & prior hx. of thrombosis were risk factors for recurrent thrombosis (Marchioli et al.,2005). We also evaluated thrombotic events among 92 JAK 2 mutation-positive subjects in this study, and found that their risk of thrombosis was similar to that of all patients, regardless of their mutational status.

The survival risk score and prior history of thrombosis were highly related with recurrent thrombosis [9]. Based on our study, the thrombotic events were significantly high in high risk patients, which was consistent with available research.

6.2 Essential Thrombocythemia

Based this study, ET was more commonly occurred in females when compared to males; this is consistent with results reported from different studies (Passamonti F, 2004, Srour SA, 2016). The mean age in this study was 55.5 year, which is similar to the mean age reported from IPSET thrombosis study.

In our study, the common presenting complaints were fatigue and headache. The common complication was thrombosis which occurred in 26.3% of ET cases. Based on the international studies the frequency of thromboembolic event ranges b/n 7-26% (Barbui T, 2012). The frequency of thromboembolic event in this study was higher than the results reported from IPSET thrombosis study which is 12% (Barbui et al, 2012). At time of diagnosis splenomegaly is the presenting complaints of 5-20% in ET patients (Andrian et al, 2016). Twenty percent of ET cases had splenomegaly at time of diagnosis in our study, which was consistent with the literatures.

The percentage of JAK 2 V617 positive ET patients were 54%, which was lower than the results from western country published studies (Klampfl et al., 2013: Tefferi et al., 2014) and including those results from Thailand (Kunnim and Auewarakul, 2010). In patients with ET, thromboembolic events are associated with advanced age (>60 year), prior hx. of thrombosis, underlying cardiovascular risk factors and JAK 2 mutational status [14]. In this study, the risk of thromboembolic events increased significantly in the higher risk group. But, JAK2V617F mutation status, higher haemoglobin level or high Platelet count had no association with thrombosis risk in our study patients.

Despite receiving antiplatelet and cytoreductive treatment, one ET patient and nine PV patients developed thrombotic complications during follow-up. This supports a higher risk of recurrent thrombosis.

6.3 Primary Myelofibrosis

According to our research, male's patients were more likely to have PMF, but it is reported to be similar sex distribution (Tefferi A, 2012). Our study's median age for PMF patient was 60 years, it is lower than the result from the large international cohort study [7]. According to Tefferi et al. (2012) and Srour et al. (2016), the median age was 65–70 years old, but there are reports from Egyptian studies of younger median age around 55 year.

In our study, the predominant symptoms were fatigue, symptoms of anemia, constitutional symptoms, abdominal symptoms that differed from ET and PV. The symptom burden among patients with PMF has not been extensively studied in published studies: the most commonly reported symptoms were joint pain, constitutional symptoms, fever, fatigues and symptoms of anemia (Michiels, 2015: Hensley B, 2013). 10- 56% of PMF patients have splenomegaly at diagnosis (Mesa et al., 2007), which was slightly lower than our study. Symptoms of anemia were present in 40% of the patients with PMF at diagnosis. The frequency of thromboembolic events was reported to be comparable to that of ET (Barbui T., 2010), although it received less attention. In our study, thrombotic events were uncommon (5.6%) in PMF patients; this might be due to small sample size of PMF cases. We also assessed the liked hood of thromboembolic events in four JAK 2 positive PMF patients, and we discovered that their risk of thrombosis was similar to that of all patients, regardless of their mutational status.

When a patient is diagnosed with PMF, IPSS score is used in clinical practice to predict the patient's survival. Although it can vary from a few months to years, the estimated median survival of PMF is six years [9]. In the present study, the estimated median survival rate of PMF patients were 4 years with currently available treatment options, which is lower than available survival reports. The five year survival rate of all Ph –ve MPNs were 81%,with PMF having the lowest survival rate, which was lower than previous reported population based studies of, the five-year relative survival rates of Ph –ve MPNs is 89%, 85% for PV and 95% for ET and 55-60% for PMF patients. (Srdan Verstovsek, 2022).

7. **CONCLUSION**

According to the results of the current study, PV is a more prevalent ph negative MPN than ET and PMF. The most common presenting symptoms and signs of PV and ET patients were fatigue, headache, Early satiety/LUQ pain, splenomegaly and thromboembolic events, patients with PMF mostly presented with constitutional symptoms, Fatigue, abdominal symptoms, symptoms of anemia & splenomegaly.

Thrombosis is an important complication in these patients, especially in PV & ET patients occurring in one third of the cases, mostly venous thrombosis than arterial. Anaemia & bleeding are an important complication in PMF patients. The available treatments for Ph -ve MPNs includes: phlebotomy, ASA and hydroxyurea, thalidomide/prednisolone, and blood transfusions. The five year survival rate that were diagnosed with PH –ve MPNs were 81%, with lowest probability of survival rate in patients with PMF with median OS of 4 years and highest in patients with ET (95%) & PV (84%).

It is recommended from this study that, understanding of the clinical features of Ph-ve MPNs is very important to prevent complications and disease progression as well as to enhanced patients quality of life. We also emphasize that that Ph negative MPNs should be considered & proper evaluation should follow in patient with unexplained abnormalities in hematologic parameters.

8. STRENGTHS AND LIMITATIONS OF THE STUDY

This study is one of the studies performed on Ph –ve MPNs & the 1st of its kind reporting the prevalence, clinical characteristics, complication and outcomes in the country so far.

Limitations:

We had to deal with the issue of incomplete and missing data because we lack a suitable system for maintaining hospital records. So, Fellows, medical residents, interns & hematology unit outpatient nurses need orientations about proper documentation on HMIS & Electronic I care system.

A single centred hospital based retrospective Cross-sectional study is the limitations of the study which will make the generalization of the results to the wider Ph –ve MPN population difficult;

Therefore it is recommended to study wider population over a longer period in the future so that the incidence, prevalence and outcomes of Ph –ve MPNs including those that are not identified in our study will be determined.

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