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Assessment of Clinical Manifestation and Prognostic Risks for Patients with Philadelphia – Negative Myeloproliferative Neosplasms (MPN) by IPSET- Thrombosis, IPSS and DIPPSS Model

[1,2]Shahzad Ali Jiskani
[3]Zareen Irshad,
[4]Rizwan Ali Talpur
[5]Aliena Sohail, [6]Asma Mustafa

[1]Department of Pathology, Chandka Medical College, SMBBMU, Larkana
[2]School of Medicine, Shenzhen University, China
[3]Department of Pathology, Jinnah Sindh Medical University, Karachi
[4]Department of Physiology, Bilawal Medical College for Boys @ LUMHS, Jamshoro
[6]Department of Pathology, Pakistan Institute of Medical Sciences, Islamabad
[7]Employees Social Security Institution, Hattar

Address for Correspondence
Dr Shahzad Ali Jiskani
Department of Pathology, Chandka Medical College, SMBBMU, Larkana
shahzadbaloach289@gmail.com

Abstract

Objective: To evaluate clinical patterns, prognostic risks, as well as thrombotic complications in patients with Philadelphia – negative myeloproliferative neoplasms.
Methodology: This prospective, cross-sectional study was carried out at Department of Pathology, Chandka Medical College, SMBBMU Larkana between March 2021 to October 2022. Demographic variables, clinical patterns, previous history of treatment, current baseline data of laboratory, mutation status, and management history were analyzed. Assessment of prognostic risk model was done as: ET (IPSET-thrombosis), PV (IPSS), and PMF (IPSS and DIPPS).
Results: Total of 73 participants were chosen for the study and were categorized into polycythemia vera (31.5%), essential thrombocythemia (38.35%), and primary myelofibrosis (30.13%) with mean ages of 52.23, 54.04, and 53.51 years, respectively. The most diverse clinical manifestations were observed in primary myelofibrosis. Mutation in JAK2V617F was detected in PV (78.26%), ET (42.85%), and PMF (77.27%). The highest events of thrombosis were seen in PV (26.08%), with predominant arterial thrombosis. The common risk groups were ISPSS intermediate-risk in patients with PV, IPSET-thrombosis low-risk in patients with ET, and IPSS and DIPSS intermediate-2 among patients with primary myelofibrosis.
Conclusion: Among all patients of Philadelphia – negative myeloproliferative neoplasms, essential thrombocythemia (ET) had the most prevalent rate. The highest thrombotic event was arterial thrombosis in polycythemia vera (PV) in spite of common group of low-risk IPSET-thrombosis. In patients with positive JAK2V617 mutation, thrombotic events were also high in polycythemia vera (PV).
Keywords: Philadelphia – negative myeloproliferative neoplasms, prognosis, patterns, essential thrombocythemia, polycythemia vera, primary myelofibrosis.

Introduction

Philadelphia – negative myeloproliferative neoplasms (Ph-MPNs) are important stem cell malignancies which consist of polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMV).[1] All types of Philadelphia – negative myeloproliferative neoplasms shared character of mutations associated with normal physiological hematopoietic pathway, because the problem rises from one hematopoietic stem cell suffering from somatic mutation. [2]

From research of Philadelphia – negative myeloproliferative neoplasms in 17 countries, it was estimated that the prevalence is 64.14/100,000 in 2016, and incidence of 12.05/100,000 cases.[3] Other study showed the incidence between 1-1.5 for polycythemia vera, 2-3 for essential thrombocythemia, and 0.5 for primary myelofibrosis.[4]

Initially, patients having Ph-MPNs have no symptoms and are diagnosed usually incidentally on routine investigations or when complications occur.[5,6] Such complications affect the prognosis and survival of myeloproliferative neoplasms patients. In patients having Ph-MPNs the heath quality is poor because of various symptoms affecting routine work, mood disturbance, anxiety, as well as interruptions in daily plans.[7,8] Additionally, these patients also have high risk of mortality and morbidity as compared to normal population. Relative survival ratio (RSR) of one decade was 0.64 for polycythemia vera (PV), 0.68 for ET, and 0.21 PMF.[9] According to previous data, the median life expectancy in patients having Ph-MPNs were 7.5 years.[10]

Authorship Contribution: [1] Conceived and planned the idea of the study, final approval of the version to be published, [2,3]Collecting the data, [3]Manuscript drafting, analysis, [4,5]drafting the work or revising it critically for important intellectual content,[6,7] Active participation in active methodology.

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Cardiovascular events and thrombosis are essential causes of mortality in patients having Ph-MPNs.[11,12] Furthermore, these patients are also at high risk for transformation into leukemia and fibrosis, contributing to further mortality and morbidity of patients.[13,14] Current data is not sufficient to provide adequate information, therefore this study is aimed to evaluate various clinical patterns, complications, and prognostic risks in patients with Philadelphia – negative myeloproliferative neoplasms.

Methodology

This prospective, cross-sectional study was carried out at Department of Pathology, Chandka Medical College, SMBBMU Larkana, from March 2021 to October 2022. The ethical approval was taken from ERB. Informed consent was taken from all participants prior to study. All patients with myeloproliferative neoplasms were included. Age of patients included between 20-80 years. Patients having borderline diagnosis, or unclassified cases were excluded from this study. Demographic variables, clinical features including present and past symptoms and complications, treatment history and baseline laboratory data was analyzed. Status of JAK2V617F mutation was also observed among patients. For patients with polycythemia vera, International Study of PV was implemented to estimate the survival.[15] For essential thrombocythemia, International Prognostic Sore for ET-thrombosis (ISPET-thrombosis) was assessed for thrombosis risk.[16] For with primary myelofibrosis patients, International Prognosis Scoring System (IPSS) and the Dynamic IPSS (DIPSS) was evaluated to estimate the survival.[17,18]

The data was analyzed using SPSS 24.0. Descriptive statistics were shown in frequency/percentages for categorical parameters. For continuous variables, median/range was measured.

Results

Total of 73 patients having Philadelphia – negative myeloproliferative neoplasms (Ph-MPNs) were involved in the study, consisting of polycythemia vera(23/31.5%), essential thrombocythemia (28/38.35%), and primary myelofibrosis (22/30.13%) (Table I). Mean age of patients in all three groups (e.g., PV, ET, and PMF) were 52.23, 54.04, and 53.51 years respectively. In patients with polycythemia vera (PV), most common symptoms headache and erythromelalgia (43.4%), followed by abdominal symptoms (17.4%), epistaxis, dyspnea (13.04%), and others. Likewise, in patients with essential thrombocythemia (ET), headache was commonest (39.28%) clinical feature followed by erythromelalgia (32.14%), abdominal pain (25%), dyspnea (14.28%) and others. In patients with primary myelofibrosis, splenomegaly was most prominent. (68.18%) Table I

Table I: Baseline Parameters and Characteristics of Patients. (n=73)

Parameters	PV (n=23) (31.5%)	ET(n=28) (38.35%)	PMF(n=22) (30.13%)
Age (in years)	52.23 ± 4.33	54.04 ± 4.94	53.51 ± 5.14
Symptoms			
Fever	2 (8.7%)	2 (7.14%)	4 (18.18%)
Weight loss	1 (4.3%)	2 (7.14%)	4 (18.18%)
Fatigue	1 (4.3%)	6 (21.42%)	9 (40.9%)
Headache	13 (45.5%)	11 (39.28%)	2 (9.1%)
Abdominal symptoms	4 (17.4%)	7 (25%)	11 (50%)
Erythromelalgia	13 (45.5%)	9 (32.14%)	5 (22.7%)
Epistaxis	3 (13.04%)	2 (7.14%)	2 (9.1%)
Dyspnea	3 (13.04%)	4 (14.28%)	-
Hemiparesis	1 (4.3%)	1 (3.5%)	-
Splenomegaly	8 (34.78%)	6 (21.42%)	15 (68.18%)
Schuffner (1-4)	7 (87.5%)	6 (100%)	13 (86.66%)
Schuffner (>4)	1 (12.5%)	-	2 (13.33%)
Baseline laboratory data			
Hemoglobin (g/dL)	19.01 ± 2.01	13.91 ± 1.98	9.1 ± 2.01
Hematocrit (%)	58.2 ± 1.02	41.09 ± 2.31	29.44 ± 2.39
WBC Count ($x10^9$/L)	19.33 ± 2.45	15.58 ± 3.44	16.14 ± 4.19
Platelet Count ($x10^9$/L)	683 ± 124	1244 ± 289	319 ± 95
Status of JAK2V617F Mutation			
Positive	18 (78.26%)	12 (42.85%)	17 (77.27%)
Negative	5 (21.73%)	16 (57.14%)	5 (22.72%)
Co-Morbid Conditions			
Present	19 (82.6%)	22 (78.57%)	13 (59.09%)
Absent	3 (13.04%)	5 (17.85%)	8 (36.36%)
Cardiovascular disease	7 (36.84%)	5 (22.72%)	4 (21.42%)
Hypertension	13 (68.42%)	14 (63.63%)	6 (42.85%)
Diabetes Mellitus	1 (5.2%)	2 (9.09%)	2 (15.38%)
Smoking	3 (15.78%)	5 (18.18%)	2 (15.38%)
Liver failure	2 (10.52%)	1 (4.5%)	2 (15.38%)
Renal failure	3 (15.78%)	4 (18.11%)	1 (7.6%)
Treatment			
Observation	4 (17.4%)	1 (3.5%)	15 (68.18%)
Phlebotomy	2 (8.7%)	-	-
Hydroxyurea	5 (21.73%)	25 (89.28%)	7 (31.81%)
Phlebotomy + Hydroxyurea	12 (57.12%)	2 (7.14%)	-

In patients with polycythemia vera, status of JAK2V617F mutation was positive in majority (78.16%) cases, while it

was positive in only some cases of essential thrombocythemia and primary myelofibrosis patients (Table I). Ischemic stroke was seen in 21.73% cases of PV,10.7% patients with ET and in 4.5% cases of PMF (Table II). Thrombosis was more common (22.2%) in patients with patients with polycythemia as compared to essential thrombocythemia (16.6%) and primary myelofibrosis (5.8%). (Table III)

Table II: History of Bleeding and Thrombotic Events in Patients (n=73)

Event(s)	PV (n=23) (31.5%)	ET (n=28) (38.35%)	PMF (n=22) (30.13%)
History of Bleeding Event(s)	2 (8.7%)	3 (10.71%)	5 (22.72%)
Cerebral hemorrhage	1 (4.3%)	1 (3.5%)	0
Gastrointestinal hemorrhage	1 (4.3%)	-	3 (13.63%)
Skin or mucosal bleeding	-	2 (7.14%)	2 (9.09%)
History of Thrombotic Event(s)	6(26.08%)	6 (21.42%)	1 (4.5%)
Ischemic stroke	5(21.73%)	3 (10.71%)	1 (4.5%)
Acute myocardial infarction	1 (4.3%)	2 (7.14%)	-
Peripheral arterial disease	-	-	-
Acute limb ischemia	-	-	-
Deep vein thrombosis	-	1 (3.5%)	-
Recurrent pregnancy loss	-	-	-
Previous history of antiplatelet therapy	7(30.43%)	10 (35.71%)	2 (9.09%)

In patients with PV, the IPSS stratification shows that most patients were fell into intermediate-risk (47.8%) and high-risk groups (34.7%). In ET patients, IPSET-thrombosis model shows that most patients fell in low-risk (46.4%) and high-risk groups (31.1%). By use of IPSS and DIPSS model in patients of PMF, it was observed that most patients fell into intermediate-2 risk (36.3%) group (Table IV-VI). Bleeding and thrombotic events in patients of PV according to IPSS score is shown in figure 1. The risk of thrombosis seems to have same between high-, intermediate-and low-risk groups. In patients with ET, both the bleeding and thrombosis risks were raised gradually as there was rise in stratification (Figure 2).

Table III: Bleeding and Thrombotic Events in JAK2V617F Mutation Positive Patients (n=37)

Event(s)	PV (n=18)	ET (n=12)	PMF (n=17)
History of Bleeding Event(s)	2 (11.1%)	1 (8.3%)	2 (11.7%)
Cerebral hemorrhage	1 (5.5%)	1 (8.3%)	0
Gastrointestinal hemorrhage	1 (5.5%)	-	1 (5.8%)
Skin or mucosal bleeding	-	-	1 (5.8%)
History of Thrombotic Event(s)	4 (22.2%)	2 (16.6%)	1 (5.8%)
Ischemic stroke	3 (16.6%)	1 (8.3%)	-
Acute myocardial infarction	-	-	1 (5.8%)
Peripheral arterial disease	-	-	-
Acute limb ischemia	-	-	-
Deep vein thrombosis	-	1 (8.3%)	-
Recurrent pregnancy loss	-	-	-
Previous history of antiplatelet therapy	5 (27.7%)	4 (33.3%)	1 (5.8%)

Table IV1: IPSS in Patients of Polycythemia Vera (PV) (n=23)

	Category	Number (%)
Age (in years)	>66	2 (4.3%)
	57-66	7 (30.4%)
WBC Count	≥ 15 x 10^9/L	17 (73.9%)
Previous history of venous thrombosis		-
IPSS Score	Low risk (0)	4 (17.4%)
	Intermediate (1-2)	11 (47.8%)
	High risk (≥3)	8 (34.7%)

Table V: IPSET-Thrombosis Model in Patients with Essential Thrombocythemia, (ET) (n=28)

	Category	N(%)
Age (in years)	≥60	4 (14.28%)
Previous history of thrombotic event		6 (21.42%)
Cardiovascular risk factors	Presence of hypertension/ diabetes mellitus/ tobacco or smoking	16 (57.14%)
JAK2V617F mutation status		10 (35.71%)
IPSET-thrombosis score	Low risk (0-1)	13 (46.42%)
	Intermediate (2)	6 (21.42%)
	High risk (≥3)	9 (31.14%)

Discussion

The current study evaluates the clinical patterns of Philadelphia – negative myeloproliferative neoplasm patients. Essential thrombocythemia (ET) was

Table VI: ISPSS and DIPSS Model in Patients with Primary Myelofibrosis. (PMF) (n=22)		
	Category	N (%)
Age (in years)	>65 years	3 (13.6%)
Constitutional symptoms	Fever/ fatigue/ weight loss	10 (45.4%)
Blood parameters	Hemoglobin <10g/dL	16 (72.7%)
	WBC >25 x 10^9/L	5 (22.7%)
	Circulating blast ≥1%	4 (18.1%)
IPSS Score	Low risk (0)	3 (13.6%)
	Intermediate-1 Risk (1)	7 (31.8%)
	Intermediate-2 Risk (2)	8 (36.3%)
	High Risk (≥3)	5 (22.7%)
DIPSS Score	Low Risk (0)	3 (13.6%)
	Intermedia Risk-1 (1-2)	8 (36.3%)
	Intermediate Risk-2 (3-4)	11 (50%)
	High Risk (5-6)	1 (4.5%)

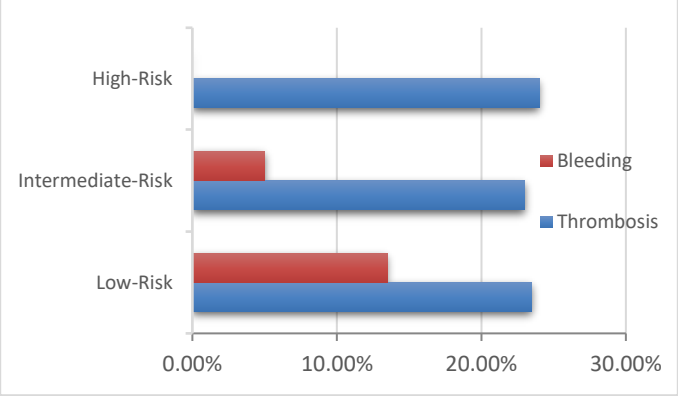

Figure 1. Bleeding and Thrombotic Events in PV Patients according to IPSS Score. (n=23)

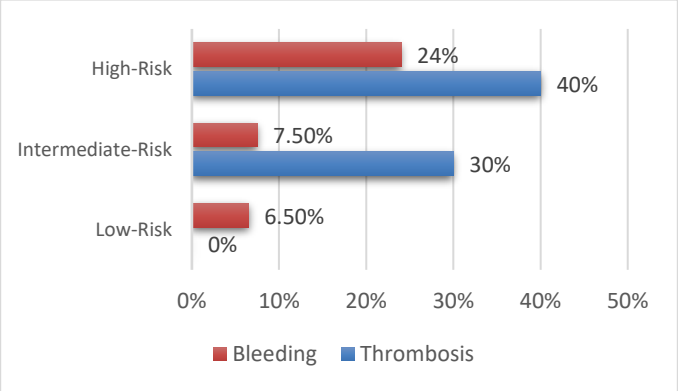

Figure 1. Bleeding and Thrombotic Events in ET Patients according to IPSET-thrombosis Score (n=28)

commonest Philadelphia – negative myeloproliferative neoplasms in current study. Valladares et al. showed same findings, in which 46 participants were having polycythemia vera (PV) with median age of 54 years at diagnosis, which was somehow lower than an international study of PV (e.g, 61 years).[15,19] Additionally, ratio of male to female was almost equal, which was also like another research.[15, 20] In our study, median age of patients with essential thrombocythemia (ET) was also like IPSET-thrombosis study.[16]

In current study, median age in participants with primary myelofibrosis (PMF) was 55 years, which was lower than database of Mayo Clinic and Porto-Soares et al.[21,22] The prominent symptoms in patients were fatigue, splenomegaly, and abdominal pain. In current study. The patients with primary myelofibrosis had much decline in hemoglobin levels and various range of white blood cells and platelet counts. Similar results were also observed by Gangat et al. and Duangnapasatit et al.[21, 23] Presence of cytopenia is always a challenge in patients with primary myelofibrosis (PMF). At diagnosis, about 30% patients present with anemia, and eventually anemia develops in all patients.[24] The underlying mechanism of anemia in primary myelofibrosis (PMF) is still not completely understood, but the participating factors consist of ineffective erythropoiesis because of scarring of bone marrow, significant splenomegaly, and expression of aberrant inflammatory cytokines.[25]

The somatic mutation in JAK2V617F is acquired and is seen in patients of polycythemia vera (PV), as well as in 50% patients of essential thrombocythemia and primary myelofibrosis.[26] In current study, we observed decreased incidence of JAK2 mutation for polycythemia vera and increased for primary myelofibrosis in comparison of various studies having different incidences e.g., 93.5% for polycythemia vera, 48% for essential thrombocythemia, 60.8% for primary myelofibrosis by Porto-Suares et al and 66% for PMF by Gangat et at.[19,21,22]

The JAK2 participates in processes of cellular signaling including proliferation, differentiation, survival as well as renewal of cells. Mutations in JAK2 converse hypersensitivity to various cytokines such as thrombopoietin, erythropoietin, and granulocyte colony-stimulating factor (G-CSF). This can give explanation why individuals having mutations in JAK2 had significant increase in various parameters of blood i.e., hemoglobin, hematocrit, platelets etc., therefore linked with the thrombosis.[27-29] In current study, evaluation of bleeding and thrombotic events was also done among patients positive for JAK2V617F and observed comparable risk of bleeding as well as thrombosis as matched to all

participants irrespective of their mutation position and status.

High level of hematocrit and white blood cell (WBC) count impact viscosity and flow of blood, and additionally persuade activation of platelets and thrombosis.[30, 31] Additionally, clinical manifestations including old age, obesity, hypertension, dyslipidemia, history of thrombotic event, lead to high risk for development of thrombosis.[11] In current study, events of thrombosis were more evident in PV followed by ET as the levels of blood parameters were higher in PV patients. Arterial thrombosis was more evident as compared to venous thrombosis. Such findings are in similarity with other studies e.g., IPSET-thrombosis and Malaysia, although much evidence from Western countries showed greater incidence of venous thrombosis.[32,33] Such finding may be justified by increased arterial risk factors in old age including diabetes, hypertension, or dyslipidemia. In our study, hypertension was dominated as important pre-existing risk factor.

For polycythemia vera (PV), a prognostic model with 3-tiered groupings was prepared by International Study of Polycythemia Vera, and median survivals of 26 years (low-risk group), 15 years (intermediate-risk group), and 8.3 years (high-risk group).[15] In current study, majority of patients came into intermediate category. The score of survival risk was considerably linked along with thrombosis.[23] Although, in current analysis, the risk of thrombosis did not vary substantially among risk groups of IPSS. This may be due to high prevalence of co-morbid conditions in study population, even in low-risk group. Hence, risk of thrombosis was also seen in low-risk patients. Complications related to thrombosis are one the commonest cause of mortality in polycythemia vera patients. International Study of Polycythemia Vera showed that 20% deaths were due to complications related to thrombosis.[15] Consequently, for high – risk polycythemia vera (PV) cytoreductive therapy is recommended.[34]

In patients with age ≥60 years (advanced age), previous event of thrombosis, cardiovascular risk factors and mutations of JAK2V617F are recognized predictors for complications of thrombosis in essential thrombocythemia.[34,35] Study by IPSET-thrombosis integrates such risk factors among IPSS for thrombosis. In current study, when participants of essential thrombocythemia (ET) were categorized with this model, majority of patients fell into low-risk followed by high- and intermediate-risk. Furthermore, risk of bleeding and thrombosis increased along higher risk score. Sevindik et al. showed that patients were categorized by 33%, 26.8%, and 40.2% into low-risk group, intermediate-risk group, and high-risk groups group, respectively. Moreover, thrombotic events occurred among low-risk (5.4%), intermediate-risk (26.7%), and high-risk (66.2%) groups.[36]

Median survival of primary myelofibrosis patients is about 6 years, although it may be few years to months only. Clinically, IPSS is utilized at diagnosis level for the prediction of survival in patients with primary myelofibrosis. Depending upon risk categories, median survivals were low-risk group (135 months), intermediate-1 risk group (95 months), intermediate-2 risk group (48 months), and high-risk group (27 months). While the period of disease, individuals may get further risk factors affecting the prognosis of patients. In current study, proportion of participants in 4-IPSS groups was same as previous study.[17]

Currently, the management of polycythemia vera and essential thrombocythemia is planned to lessen the symptoms and for the prevention of thrombosis. The aspirin, phlebectomy, and cytoreductive drugs show antithrombotic result.[37] In current study, history of antiplatelet treatment was seen in both patients of essential thrombocythemia and polycythemia vera. Whereas there is obvious advantage of antiplatelet treatment in polycythemia vera (PV) patients, studies also showed unpredictable outcomes in terms of antiplatelet treatment in patients of essential thrombocythemia.[38]

Analysis demonstrated that treatment with antiplatelet remedy did not reduce risk of thrombosis although raised risk of bleeding in individual shaving essential thrombocythemia.[39] In current analysis, episodes of bleeding were seen in only small fraction of participants of primary myelofibrosis and essential thrombocythemia, in spite of low use of antiplatelet in these groups as compared to polycythemia vera (PV).

Conclusion

Essential thrombocythemia (ET) was most common Philadelphia-negative myeloproliferative neoplasms.

Arterial thrombosis rate was higher among patients with polycythemia vera (PV) despite of low-risk IPSET-thrombosis common group.

In patients with JAK2V617F mutation, event of thrombosis was also higher in polycythemia vera (PV).

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