ORIGINAL ARTICLE

PROGNOSTIC CATEGORIZATION OF PRIMARY MYELOFIBROSIS PATIENTS OF PESHAWAR

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Background: Primary myelofibrosis (PMF) is a least common type of myeloproliferative neoplasm (MPN) and is clonally derived stem cell disorder classified as Philadelphia chromosome negative MPN. The Dynamic International Prognostic Scoring System (DIPSS) utilizes five variables including age, haemoglobin level, white blood cells count, peripheral blood blasts and other symptoms for characterization of myelofibrosis patients. The objective of this study was to categorize primary myelofibrosis patients of Khyber Pakhtunkhwa. **Methods:** This cross-sectional analysis was carried out from June 2018 till May 2019. Blood samples and other information were collected from 50 PMF patients enrolled at the assigned health care facilities of Peshawar. Non-probability convenience sampling technique was used, and an informed and written consent was obtained from the participants. DIPSS was utilized for the prognostic categorization of PMF patients. **Results:** Majority (26, 52%) of the patients were in the age group II (41–60 years) and most (34, 68%) of them were male. Participants were categorized into four risk groups (low, intermediate-1, intermediate-2, and high) by applying DIPSS scoring system. Among the 50 patients, 3 (6%) were in low-risk group, whereas only one was in the high-risk group. Thirteen (26%) patients fell in intermediate-1 risk category and 33 (66%) were placed in the intermediate-2 risk group. **Conclusion:** Most of the myelofibrosis patients in Peshawar fall in intermediate-risk group while small percentage was included in high-risk group.

Keywords: Myeloproliferative neoplasms, Primary myelofibrosis, DIPSS, Prognosis, Peshawar

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INTRODUCTION

Primary myelofibrosis (PMF) is a clonally derived stem cell disorder, classified as Philadelphia negative myeloproliferative neoplasm (MPN). Polycythaemia Vera (PV) and essential thrombocythaemia (ET) are also included in this category.[1] PMF has the most heterogeneous clinical presentation among the MPNs which may encompass anaemia, hepatosplenomegaly, leukocytosis or leukopenia, thrombocytosis or thrombocytopenia and disease related constitutional symptoms.[2]

PMF is the least common of MPNs with an annual incidence of 0.5–1.5 cases per 100,000 individuals.[3] It usually affects older individuals (median age of 65 years at the time of diagnosis) but young people are not necessarily spared.[4] Reported median length of survival is 3.5–5.5 years with worst prognosis compared to PV and ET.[5] The main causes of death are infections, bleeding, thromboembolism and transformation to acute leukaemia. Allogenic stem cell transplantation is the only chance of cure.[6] Advanced age, anaemia, red blood cells transfusion needs, leukopenia, leukocytosis, thrombocytopenia, peripheral blast count and constitutional symptoms are associated with poor outcome in PMF patients.[8]

Previously, based on recommendations of an International MDS Risk Assessment Workshop (IMRAW) in 1997 a prognostic scoring system called as International Prognostic Scoring System (IPSS) was developed to estimate the survival of PMF patients. This model is applied at the time of diagnosis and utilizes five risk factors for survival (age older than 65 years, haemoglobin level <10 g/dL, WBC count >25×10^9/L, peripheral blood blasts ≥1%, and presence of constitutional symptoms). It identifies 4 risk categories by assigning 1 adverse point to each one of these risk factors. The presence of 0, 1, 2, and ≥3 adverse points defines low, intermediate-1, intermediate-2 and high-risk disease, respectively.[9] However, acquisition of additional risk factors during the disease may substantially modify the patient's survival.

The Dynamic International Prognostic Scoring System (DIPSS) can be applied any time during the disease course and utilizes the same prognostic variables as IPSS.[10] It, however, allocates 2, instead of 1, adverse points for haemoglobin concentration lower than 10 g/dL. The resulting risk categories are low (score=0), intermediate-1 (score=1 or 2), intermediate-2 (score=3 or 4) and high (score=5 or 6) with corresponding survival rates.[11] A refined version, i.e., DIPSS-Plus, has been developed in which platelets count abnormalities, karyotype deformities and blood transfusion needs are addressed.[12] Beside these, two recently developed scoring systems are developed, i.e., MIPSS70 (Mutation-enhanced International Prognostic Score System) and GIPSS (Genetically Inspired International Score System). MIPSS70 is based upon assessment of genetic mutations and other clinical risk factors. MIPSS70-Plus

and MIPSS70-Plus version 2.0 are latest forms which included cytogenetic and haemoglobin assessment in relation to age and sex. GIPSS rely on karyotype deformities and genetic mutations such as presence of *CALR*, *JAK2*, *MPL* and others.[13] Based on DIPSS, the aim of this study was to prognostically categorize the PMF patients in Peshawar.

MATERIAL AND METHODS

This cross-sectional analysis of PMF patients was conducted at the Department of Haematology, Institute of Basic Medical Sciences, Khyber Medical University Peshawar, from June 2018 to May 2019. Blood samples and other information were collected from already diagnosed PMF patients enrolled at different health care settings in Peshawar, i.e., Haematology/Oncology Department of Hayatabad Medical Complex, Institute of Radiotherapy and Nuclear Medicine (IRNUM), and Blood Diseases Clinic, Peshawar. A total of 50 patients were observed and consecutive non-probability sampling technique was used while selecting the patients. Sample size was calculated according to WHO formula for sample size determination.[14]

Patients were enrolled based on pre-set inclusion and exclusion criteria. Diagnosed patients of primary myelofibrosis (PMF) and all patients of PMF, of either gender were included in study. Patients with secondary myelofibrosis due to other conditions like tuberculosis, fungal infections, Hodgkin or Non-Hodgkin lymphoma, other variants of MPNs (PV, ET, Chronic Myeloid Leukaemia) and post-PV and post-ET myelofibrosis and patients suffering from other neoplastic disease were excluded. Study was initiated after endorsement from Ethical Board of Khyber Medical University, Peshawar. Informed written consent was obtained from each patient. Data was collected through a specially designed proforma which included demographic details, clinical history, physical examination and investigations profile of the patient.

Blood samples were collected from the diagnosed patients of PMF at specified centres by trained phlebotomists applying standard techniques. The samples were transported immediately to laboratory, applying standard protocols for blood sample transportation. Blood smear was prepared and examined using light microscopy to look for anaemia, white blood cells, platelets, blasts, total blood cells count, and mean haemoglobin concentration. The data was primarily recorded on Microsoft Excel Spreadsheet. Statistical analysis was performed using SPSS-23. Simple arithmetic analyses (mean, standard deviation and/or percentages) were deduced for each parameter. Age and gender wise stratification was also performed.

RESULTS

A total of 50 diagnosed PMF patients were included in the current study. Mean age of the study population was 50.60±13.01 years. Out of these 50 patients, 34 (68%) were male and 16 (32%) were female. Patients were distributed into three different age groups, i.e., 13 (26%) were in the age group I (20–40 years), 26 (52%) in age group II (41–60 years), and group III (61–80 years) comprised of 11 (22%) patients. The commonest presenting clinical features were pallor, splenomegaly and disease related constitutional symptoms (fatigue, fever, night sweats and weight loss), whereas hepatomegaly was observed in only 3 (6%) patients (Table-1).

Mean total leukocyte count (TLC) was 19.5×10^9 cells/L with a minimum of 1.19×10^9 cells/L, and a maximum of 77.60×10^9 cells/L. The mean haemoglobin concentration was 9.42 g/dL (Range: 5.5 g/dL–18.8 g/dL), whereas mean platelets count was 272.64×10^9 cells/L (Range: 10×10^9 cells/L–656×10^9 cells/L) (Table-2).

Peripheral blood blasts observed in all patients were more than 1%. The participants were categorized into four risk groups (Low, Intermediate-1, Intermediate-2, and High) by applying Dynamic International Prognostic Scoring System (DIPSS). Among the 50 patients, 3 (6%) were in low-risk group, whereas only one was in high-risk group. Thirteen (26%) patients fell in intermediate-1 risk category while 33 (66%) were placed in intermediate-2 risk group (Table-3).

Table-1: Clinical characteristic of study patients (n=50)

Constitutional Symptoms	Patients	Pallor	Splenomegaly	Hepatomegaly
Yes	43	31	48	03
No	7	19	2	47

Table-2: Descriptive statistics of haematological parameters (n=50)

Parameters	Hb (g/dl)	TLC (cells/L)	Platelets (cells/L)
Mean	9.426±3.08	19.5×10^9	272.64×10^9
Minimum	5.5	1.19×10^9	10×10^9
Maximum	18.8	77.60×10^9	656×10^9

Table-3: Categorization of study participants (n=50)

Risk Category	Frequency	Percentage
Low Risk	3	6
Intermediate-1	13	26
Intermediate-2	33	66
High Risk	1	2
Total	50	100

DISCUSSION

The current study was conducted to prognostically categorize PMF patients in Peshawar. A total of 50 patients of primary myelofibrosis were analyzed and majority of the patients were male (68%). These

findings are supported by a study conducted on 1,000 US PMF patients which identified male predominance (male:female=3:2) and a strong correlation with old age (median age 60 years).[15] The higher median age, however, may pertain to the overall higher life expectancy of US population in comparison to Pakistani population.

The median length of survival for PMF patients is 3.5–5.5 years.[16] The disease course is complicated by progressive anaemia, symptomatic splenomegaly and severe constitutional symptoms.[17] International Prognostic Scoring System (IPSS) was developed to estimate the survival of PMF patients.[9] This model is applied at the time of diagnosis and identifies four risk categories. However, acquisition of additional risk factors may substantially alter the disease course. So Dynamic International Prognostic Scoring System (DIPSS) was developed which can be applied any time during the disease course. DIPSS also utilizes the same five prognostic variables (age older than 65 years, haemoglobin level <10 g/dL, WBC >25×10^9/L, peripheral blood blasts ≥1%, and presence of constitutional symptoms) as IPSS, however it allocates 2 instead of 1 adverse points to Hb level <10 g/dL. The current study provides valued data regarding the percentage of PMF patients who present with adverse risk factors including age, haemoglobin concentration, leukocytosis, and presence of disease related constitutional symptoms. More than two third patients (36, 72%) had anaemia whereas, leukocytosis was identified in 32 (64%). Disease related constitutional symptoms were observed in 43 (86%) patients while 7 (14%) were lacking them. Similar observations were made by others[18,19].

By applying DIPSS model for survival, the participants of the current study were categorized into four risk groups (Low, Intermediate-1, Intermediate-2, and High). Among the 50 PMF patients, majority (66%) of them were placed in Intermediate-2 risk category while 26% patients were categorised in Intermediate-1 risk group. A low percentage of patients (6% and 2% respectively) were in low and high risk categories. This may be because as many PMF patients are elderly at diagnosis or present with several co-morbidities, death is the ultimate result due to poor prognosis. Thus, a high degree of prognostic certainty is desired to permit aggressive therapeutic procedures and enable better therapeutic planning, especially for patients who are young and eligible for bone marrow transplantation.[20]

CONCLUSION

The intermediate risk group of myelofibrosis patients was most common in our study population followed by low risk group and then high risk group. The poor survival rate of high-risk patients may be the reason behind our findings.

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SH: Concept, Design, Manuscript writing
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