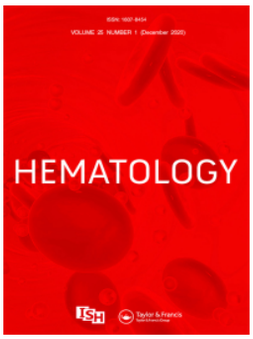

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A comparative retrospective study of pre-fibrotic primary myelofibrosis *versus* overtly fibrotic stage in Qatar: clinicopathological, genetic landscape, risk stratification and survival data (2008–2021) – a single center experience

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ABSTRACT

Background: In MENA region, there is a lack of evidence on Primary Myelofibrosis (PMF), leading to its underrepresentation in medical literature. This study marks the first comprehensive report on PMF data in Qatar, presenting findings from a single-center study spanning 13 years (2008-2021).

Methods: Clinicopathological data, genetic features, and disease progression parameters of pre-PMF and overt PMF subgroups were collected. Overall survival (OS), progression-free survival (PFS), DIPSS plus four categories and merged low and high-risk DIPSS scoring groups were assessed.

Results: Pre-PMF patients showed higher hemoglobin ($P < 0.001$), and platelet counts ($P < 0.05$) but lower blast counts, LDH levels, constitutional symptoms ($P < 0.0001$), and splenomegaly ($P < 0.010$) than overt PMF patients. *JAK2* V617F mutation was more common in pre-PMF ($P = 0.059$), while unfavorable karyotypes were exclusive to overt PMF ($P = 0.028$). Median overall survival was significantly longer at 276.9 months (IQR: 315.9, 276.9 months) to what was previously reported. Overt PMF patients predominantly fell into the higher DIPSS risk category ($P < 0.001$) and showed greater disease progression than pre-PMF ($P < 0.0001$). Complications including refractory anaemia ($P < 0.001$) and leukemic transformation ($P = 0.043$), increased notably in the high-risk group. Furthermore, 86.2% of high-risk patients required treatment versus 59.4% of the lower-risk group ($P = 0.020$).

Conclusions: To the best of our knowledge our research represents the first and largest published dataset on PMF in MENA region to be published. Merged DIPSS plus scoring came to be a pragmatic tool for defining high-risk patients who significantly differ in mortality, progression, need for treatment and leukemic transformation.

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KEYWORDS
Primary myelofibrosis; pre-PMF; overt PMF; DIPSS; survival; cytogenetics

Introduction

Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm (MPN) characterized by the proliferation of predominantly abnormal megakaryocytes and granulocytes, which in fully developed disease is associated with reactive deposition of fibrous connective tissue and with extramedullary hematopoiesis. The estimated annual incidence of overt primary myelofibrosis (overt PMF) is 0.5–1.5 cases per 100,000 population [1,2]. Valid data on the incidence of pre-fibrotic primary myelofibrosis (pre-PMF) are not available, but data from reference centers suggest that early-stage PMF accounts for 30-50% of all PMF cases [2]. The prevalence of PMF is likely to increase due to earlier diagnosis, i.e. diagnosis of pre-PMF, and prolonged survival [3]. The literature is still lacking data on PMF in the Middle East and North Africa (MENA) and gulf region, hence, this region is not well represented in the international statistics concerning its incidence, prevalence, clinicopathologic features or genetic make-up.

PMF arises from somatic mutation of a pluripotent hematopoietic progenitor cell. This clonal myelo-proliferation is followed by nonclonal fibroblastic proliferation ending with bone marrow fibrosis [4,5]. The most common presenting complaints range from severe fatigue to other constitutional symptoms, such as weight loss, low-grade fever, bone pain, and night sweats. PMF patients also suffer from marked splenomegaly, hepatomegaly due to extramedullary hematopoiesis, and thrombotic events [5–7].

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The main somatic driving mutations that have been identified in PMF are Janus kinase 2 exon 14 (*JAK2* V617F), myeloproliferative leukemia virus oncogene exon 10 (*MPL*), and calreticulin exon 9 (*CALR*) mutations. Approximately 60-65% of patients have *JAK2* V617F mutations. Another 20-25% of patients have *CALR* mutations, and approximately 6-7% have *MPL* mutations. No *JAK2* V617F, *CALR*, or *MPL* mutation 'triple-negative PMF' constituted 8 to10 percent of PMF cases. These mutations have various impacts on prognosis [8–12].

PMF has the least favorable prognosis among the MPNs. Patients are at risk of premature death due to disease progression, leukemic transformation, thrombo-hemorrhagic complications, and infections [13,14]. Several scoring systems have been adopted clinically, and the most widely used is the Dynamic International Prognostic Scoring System Plus (DIPSS-plus) score, which includes various clinical and pathological parameters [15].

There is a stepwise evolution from an initial pre-fibrotic/early stage, characterized by hypercellular bone marrow (BM) with absent or minimal reticulin fibrosis, to an overt-fibrotic stage with a polyclonal increase in fibroblasts that drive secondary reticulin and/or collagen marrow fibrosis, osteosclerosis, and extramedullary hematopoiesis. According to the World Health Organization (WHO) classification of myeloid neoplasms (4th and 5th edition in 2022), there are distinct diagnostic criteria for diagnosing pre-PMF and overt PMF. The criteria mainly depend on BM morphologic features with megakaryocytic proliferation and atypia, accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis and fibrosis grade (grade 0–1 indicating pre-PMF and grade 2–3 indicating overt PMF). Ultimately, peripheral blood leucoerythroblastic picture (with teardrop-shaped red blood cells) is considered a minor diagnostic criterion for overt PMF, whereas anemia, leukocytosis, increased lactate dehydrogenase (LDH) and palpable splenomegaly may be present in both diseases [16,17].

This is a retrospective single-center study aiming to analyze the clinicopathologic and genetic features of PMF and conduct a comparative analysis between pre-PMF and overt PMF patient characteristics. The patients were risk stratified according to the DIPSS Plus to categorize patients into low, intermediate-1, intermediate-2 and high-risk groups [18]. Additionally, overall survival (OS) and progression-free survival (PFS) of both PMF subgroups (pre-fibrotic and overt PMF) were compared to determine the prognostic relevance of this distinction. To the best of our knowledge, this single-center experience of a unique tertiary cancer hospital in the country represents the largest dataset and provides insights on PMF in the region over a period of 13 years.

Methods

Patients and data collection

The current retrospective study was carried out in our cancer hospital for patients older than 18 years and diagnosed with MPN with features of PMF between 01/01/2008 and 31/12/2021. The study was approved by Hamad Medical Corporation Medical Research Center under the protocol number MRC-01-23-066/ MRC-01-19-4666 and was exempted from the Institutional Review Board. PMF diagnosis was established based on the WHO diagnostic criteria (2016), pre-PMF requires the fulfillment of three major criteria: (i) Megakaryocytic proliferation and atypia, without reticulin fibrosis grade >1, accompanied by BM hypercellularity, granulocytic proliferation, and (often) decreased erythropoiesis, (ii) Exclusion of any WHO-specific entity of myeloid neoplasms, and (iii) *JAK2, CALR,* or *MPL* mutation or presence of another clonal marker or absence of reactive BM reticulin fibrosis. Supporting this, the diagnosis should include one or more of the following secondary criteria: anemia, leukocytosis $\geq 11 \times 10^9$/L, palpable splenomegaly and High LDH. The diagnosis of overt PMF requires meeting all three major criteria plus at least one minor criterion. The major criteria include: (i) Megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis of grade 2, with criteria (ii) and (iii) being identical to those required for pre-PMF. The minor diagnostic criteria for overt PMF are also the same as pre-PMF stage with the addition of leukoerythroblastosis. Furthermore, all cases in the study population are negative for *BCR:ABL-1* rearrangement which is the hallmark of chronic myeloid leukemia.

Patients' demographic data, clinical features (constitutional symptoms, splenomegaly, LDH), full hematologic counts, peripheral blood blasts (PB blasts), BM pathologic features (including cellularity, blast count, megakaryocyte morphology, CD34 positivity and grading of fibrosis (MF0-3)), molecular and cytogenetic findings, treatment data, complications of the disease (thromboembolic manifestation and transfusion dependency) and features of disease progression were collected from medical records.

The DIPSS Plus scoring was calculated for all cases. The DIPSS Plus score assigns points for the following variables: age >65 years: 1 point, leukocyte count >25,000/microL ($>25 \times 10^9$/L): 1 point, hemoglobin level (Hb) <10 g/dL (<100 g/L): 1 point, circulating blast cells ≥1%: 1 point, constitutional symptoms (weight loss >10% of the baseline value in the year preceding PMF diagnosis, and/or unexplained fever or excessive sweats persisting for more than one month): 1 point, unfavorable karyotype (KT) (complex KT or one or two abnormalities that include +8, – 7/7q –, i(17q), – 5/5q –, 12p –, inv(3), or 11q23): 1 point, platelet count (PLT) <100,000/microL

(<100 × 109/L): 1 point, anemia requiring transfusion. The resulting score is interpreted as follows: 0 points – low risk, 1 point – intermediate-1 risk, 2–3 points – intermediate-2 risk, and 4–6 points – high risk [18].

Study design:

PMF cases were subclassified into two groups, pre-PMF and overt PMF. The need for treatment was also correlated between the two groups and against DIPSS Plus parameters (age, PB blasts, Hb, PLT, white blood cells (WBCs), symptoms, cytogenetics findings and transfusion dependency).

Data collection was designed to include the following parameters for each patient: age, sex, blood counts including WBCs, Hb, PLT, PB blasts, LDH, constitutional symptoms, splenomegaly, molecular and cytogenetic findings, DIPSS Plus score, pathological subgroups (pre-PMF and overt PMF), treatment, complications, transfusion dependency and features of progression.

The aim was to investigate clinical, pathological and genetic characteristics in PMF subgroups and to analyze the relationship between these parameters and DIPSS plus risk subgroups, disease progression, treatment requirement and overall patient survival.

Time to progression was considered as the time to acquisition of ≥1 of the DIPSS Plus laboratory adverse variables (WBCs > 25×10^9/L, PLT <100×10^9/L, PB blasts ≥ 1%, Hb < 10 g/dL, transfusion dependency). OS and PFS were assessed using time-dependent, Cox regression and Kaplan–Meier analyses.

Table 1. Demographic, clinical, hematologic, and molecular characteristics of the study population.

Characteristics	Pre-PMF n = 32 (52.5%)	Overt PMF n = 29 (47.5%)	P-value*
Age (years)			
Median (range), years	43.5 (24, 78)	50 (25, 75)	0.971
<65, n (%)	30 (93.8)	28 (96.6)	0.613
≥ 65, n (%)	2 (6.2)	1 (3.4)	
Gender			
Male, n (%)	20 (62.5)	18 (62.1)	0.972
Female, n (%)	12 (37.5)	11 (37.9)	
Hb level			
Median (range), g/dl	13.8 (7, 16.5)	10.5 (6.9, 15.3)	<0.001
<10 g/dl, n (%)	1 (3.1)	10 (34.5)	0.001
WBCs count			
Median (range), x10^9/L	11.1 (5.1, 24.9)	9.2 (2.3, 43.1)	0.309
>25 x 10^9 /L, n (%)	0 (0)	5 (17.2)	0.020
Platelet count			
Median (range), x10^9 /L	946 (341, 1920)	306 (34, 1145)	<0.0001
<100 x10^9 /L, n (%)	0 (0)	4 (13.8)	0.049
PB blasts			
Median (range), n (%)	0 (0, 1)	2 (0, 14)	<0.0001
≥1%, n (%)	4 (12.5)	25 (86.2)	<0.0001
LDH, n=49	23	26	
Median (range), U/L	301 (154, 642)	574 (178, 4282)	<0.0001
>Normal range, n (%) [>225]	18 (78.3)	25 (96.2)	0.057
Constitutional symptoms, n (%)			
Constitutional symptoms present	7 (21.9)	24 (82.8)	<0.0001
Splenomegaly, n=57	28	29	
Palpable splenomegaly or ≥ 10 cm in any imaging, n (%)	13 (46.4)	23 (79.3)	0.010
Karyotype, n=57	30	27	
Normal karyotype	28 (93.3)	17 (63.3)	0.028
Abnormal karyotype	2 (6.7)	3 (11.1)	
Unfavorable karyotype	0 (0)	7 (25.9)	
DIPSS score, n (%)			
Low	22 (68.8)	1 (3.4)	<0.0001
Intermediate-1	7 (21.9)	9 (31)	
Intermediate-2	3 (9.4)	12 (41.4)	
High	0 (0)	7 (24.1)	
DIPSS re-stratified groups, n (%)			
Low + intermediate 1	29 (90.6)	10 (34.4)	0.0001
Intermediate 2 + High	3 (9.3)	19 (65.5)	
Reticulin staining grades, n=59	30	29	
MF 0	16 (53.3)	0 (0)	<0.0001
MF 1	14 (46.7)	0 (0)	
MF 2	0 (0)	7 (24.1)	
MF 3	0 (0)	22 (75.9)	
Transfusion			
Transfusion dependency, n (%)	3 (9.4)	12 (41.4)	0.004
Driver Mutation			
JAK2 V617F	22/32 (68.8)	13/29 (44.8)	0.059
CALR Exon 9	9/28 (32.1)	10/18 (55.6)	0.116
MPL Exon 10	0/10 (0)	1/5 (20)	0.333

Categorical data were compared using Pearson Chi-Square or Fisher Exact/Yates corrected Chi-square tests (applied in case of small cell frequencies i.e. 50% or more cells have expected frequencies <5), whereas quantitative outcome measures between two groups were compared using unpaired t test or Mann Whitney U test (for skewed data distribution) as appropriate to compute respective statistical *P*-value.

Statistical analysis

Descriptive statistics were used to summarize the demographic, hematological, and clinicopathological characteristics, molecular findings and DIPSS Plus scores of the patients. Normally distributed data and results are reported as mean and standard deviation (SD), whereas the median and interquartile range (IQR) were used for skewed or non-normally distributed data. Categorical data were summarized as frequencies and percentages. A preliminary statistical analysis was conducted to examine the distribution of the data variables using the Shapiro–Wilk test. Associations between two or more qualitative variables were assessed using Chi-square ($\chi 2$) test, Fisher's exact or Yates-corrected Chi-square test as appropriate. Quantitative data and outcome measures between the two independent groups (pre-PMF and overt PMF) were analyzed using unpaired t test (or Mann–Whitney U test for skewed data). OS was calculated from the date of diagnosis to the date of death (uncensored) or last contact (censored). PFS was calculated from the date of diagnosis to the date of progression. The cumulative probabilities of OS and PFS were estimated using the Kaplan–Meier method, and the differences between the groups (pre-PMF and overt PMF) were compared using a Log rank test statistic.

In addition, exploratory statistical analysis using univariate Cox regression method and Chi-Square tests were performed to explore and assess the risk/association between demographic, hematological, and clinicopathological characteristics, molecular findings and DIPSS Plus scores with both mortality and disease progression. Box plots were constructed to depict the distribution of hematological-related parameters. All *P*-values reported were two-tailed, and *P*-values <0.05 were considered statistically significant. All statistical analyses were performed using the statistical packages SPSS version 29.0 (Armonk, NY: IBM Corp) and Epi-info (Centers for Disease Control and Prevention, Atlanta, GA) software.

Results

Patient characteristics

A total of 61 patients (38 male and 23 female) with PMF were enrolled in this study. Patients were classified into 2 groups according to the 2016 WHO criteria: pre-PMF patients n = 32 (52.5%) and overt PMF patients n = 29 (47.5%) with a female: male ratio of 1:1.7 for the former and 1:1.6 for the latter ($P = 0.972$). pre-PMF patients were younger than overt PMF patients, and the median ages were 43.5 and 50 years, respectively ($P = 0.971$). Hematological, clinico-pathological and molecular findings are presented in Table 1. The data showed that pre-PMF patients had significantly higher Hb levels (median, 13.8 g/dL vs 10.5 g/dL; $P < 0.001$). Similarly, the median PLT was significantly higher in the pre-PMF group than in the overt PMF group ($P < 0.001$). However, median PB blasts (median, 0% vs 2%) and LDH (median, 301 U/L vs 574 U/L) were significantly lower in pre-PMF patients than in overt PMF patients ($P < 0.0001$). Box plots (Figure 1) depict the distribution of Hb, WBC, PLT, PB blasts, LDH, Absolute neutrophil count (ANC) and red blood cells (RBC) at diagnosis across both pre-PMF and overt PMF groups.

Furthermore, we categorized complete blood count (CBC) values using standard and clinical cutoff values, and the results indicated that compared with patients with overt PMF, patients with pre-PMF who had Hb levels < 10 g/dL (3.1% vs 34.5%, $P = 0.001$), PLT < 100×10^9/L (0.0% vs 13.8%, $P = 0.049$), leukocyte counts > 25×10^9/L (0.0% vs 17.2%, $P = 0.020$), marked splenomegaly (46.4% vs 79.3%, $P = 0.010$), high LDH >225 U/L (78.3% vs 96.2%, $P = 0.057$), constitutional symptoms (21.9% vs 82.8%, $P < 0.0001$) and need for red cell transfusion (9.4% vs 41.4%, $P = 0.004$). PB blasts ≥1% were significantly lower in pre-PMF patients than in patients with overt PMF (12.5% vs 86.2%, $P < 0.0001$).

Cytogenetics and molecular genetics stratification

Cytogenetic profiles were categorized as either favorable or unfavorable. The favorable group included normal and abnormal KT (other than those mentioned as unfavorable). Unfavorable KT included complex KT or one or two abnormalities including +8, – 7/7q –, i (17q), – 5/5q –, 12p –, inv(3), or 11q23. In this study, five patients with abnormal KT had trisomy 9, 20q-, Y chromosome abnormalities and multiple near tetraploidy. Abnormal KT was more frequently detected in overt PMF (11.1%) than in pre-PMF (6.7%), however, the unfavorable KT category was only found in overt PMF (25.9%) ($P = 0.028$).

The mutational status and mutational frequencies were as follows*: JAK2* V617F in 57.4% (68.8% pre-PMF vs 44.8% overt PMF, ($P = 0.059$)), *CALR* mutation in 41.3% (32.1% pre-PMF vs 55.6% overt PMF,($P = 0.116$)), and *MPL* exon 10 was only detected in overt PMF ($P = 0.333$). No cases with *JAK2* exon 12 mutations were detected in our cohort. Triple-negative mutations were detected in only 2 patients (one from each group). The high mutation risk category (mutations in *ASXL1, SRSF2, IDH1/2 and EZH2*) was not performed (as it was not yet introduced in our institutional molecular laboratory). We observed that *JAK2* positive patients experienced more thrombotic events (11 out of 14 patients).

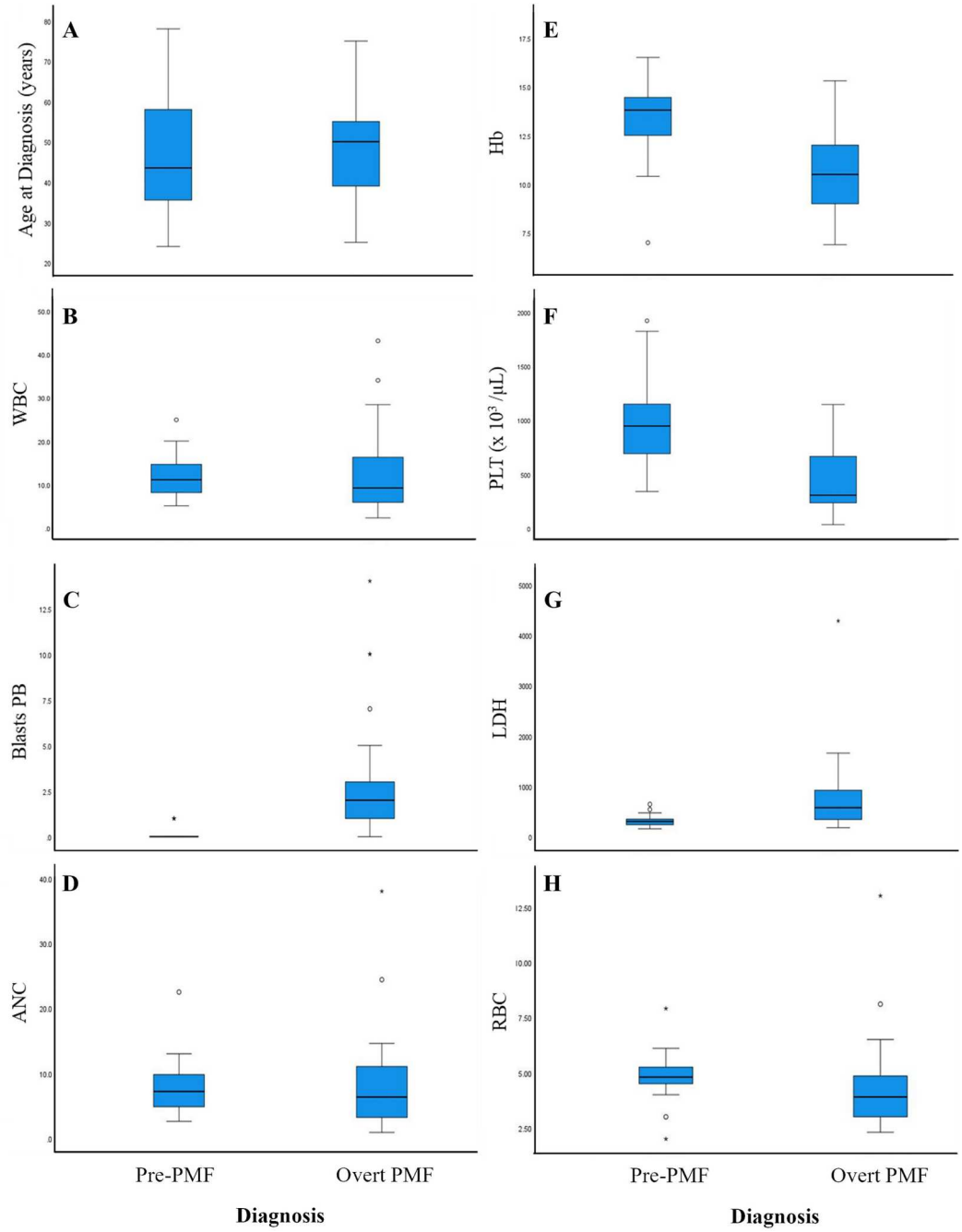

Figure 1. Box-plots of different parameters in pre-PMF and overt PMF patients: (A) age at diagnosis, (B) WBC (white blood cells), (C) PB blasts (peripheral blood blasts), (D) ANC (Absolute neutrophil count), (E) Hb (Hemoglobin), (F) PLT (platelets), (G) LDH (Lactate dehydrogenase), and (H) RBC (Red Blood cells).

DIPSS Prognostication and re-stratification using a merged DIPSS score:

The DIPSS-plus risk stratification for all PMF patients at the time of referral was 37.7% (23/61) low risk, 26.2% (16/61) intermediate-1, 24.6% (15/61) intermediate-2, and 11.5% (7/61) In the high risk category.

The majority of pre-PMF patients were stratified as low risk (22, 68.8%), whilst no patients were detected within the high risk category. This is in contrast to patients with overt PMF, who were predominantly categorized as intermediate 1 to high, with only one patient within the low-risk category ($P = 0.0001$)

The four risk categories of the DIPSS scoring were re-stratified into 2 groups by combining low and intermediate-1 risk groups (low-risk group) versus intermediate-2 and high-risk groups (high-risk group), creating a novel method due to the relatively small patient population size in our cohort.

According to the DIPSS re-stratification performed for our cohort, we found that patients with pre-PMF patients were largely included in the lower-risk group

(low and Intermediate-1) (29, 90.6%), whereas most patients with overt PMF were in the intermediate-2 to higher-risk group (19, 65.5%; $P < 0.0001$).

When we compared the DIPSS re-stratification between the high risk and low risk groups, we found that both disease progression and mortality were significantly higher in the high-risk group (100% vs 23.1%, $P < 0.0001$) and (18.2% vs 0%, $P = 0.014$), respectively. Similarly, unfavorable KT (33.3% vs 0%, $P < 0.001$), refractory anemia (86.4% vs 7.7%, $P < 0.001$), leukemic transformation (13.6% vs 0%, $P = 0.043$) and patients who required treatment (90.9% vs 61.5%, $P = 0.014$), were all significantly higher in the high-risk group (intermediate-2/high DIPSS) than in the low-risk group. In addition, the percentage of thrombotic events and *JAK2* V617F mutation were higher in high-risk group than in the low-risk group; however, their differences were statistically insignificant ($P > 0.05$).

Treatment and modalities

Seventeen of the 61 of our cohort (27.9%) did not require treatment; however, 72.1% (44/61) needed to be managed effectively. In fact, 25 patients (41%) were placed on aspirin (either alone or adjunct therapy). Regarding treatment modalities, 84.1% of patients (37/44) were placed on Cytoreduction (Hydroxyurea or Interferon), 38.6% (17/44) were placed on Ruxolitinib, and 4.5% (2/44) underwent allogenic BM transplantation. This is in addition to supportive measures, such as growth factors (22.7%, 10/44), splenic radiation or splenectomy (6.8%, 3/44) and blood transfusion (36.4%, 16/44). With further comparative analysis between pre-PMF and overt PMF, 25/29 (86.2%) of overt PMF required treatment, compared to 19/32 (59.4%) of pre-PMF with statistically significant difference ($P = 0.020$). Statistical comparative analysis of the treatment details is presented in Table 2.

Disease complications

The main complications of PMF included thrombotic events (14/61, 23.1%) and refractory anemia (22/61, 36.1%). The incidence of disease complications were significantly lower in patients with pre-PMF (43.8%, 14/32) than in those with overt PMF (79.3%, 23/29), $P = 0.005$. Refractory anemia was predominant in Overt PMF compared to pre-PMF (62.1% vs 12.5%, $P < 0.001$), consequently, the need for blood transfusion and growth factors was significantly higher in the overt PMF group (41.4% vs 9.4%, $P = 0.004$) and (36% vs 5.3%, $P = 0.016$) respectively compared to pre-PMF (Tables 2 and 3). Although thrombotic events were noted to be lower in the pre-PMF group (21.9%) than in the overt PMF group (24.1%), this difference was statistically insignificant ($P = 0.834$).

Overall survival (OS) and progression free survival (PFS)

Mortality in the overt PMF group was significantly higher compared to pre-PMF group (0% vs 13.8%, $P = 0.046$) as shown in Table 3B. The median follow-up time (diagnosis to last follow-up time) in the current study was 27.9 months (range, 0.03–316 months). It was observed that 86.8% of patients had an OS of at least 108.7 months, and the overall median survival was 276.9 months (IQR: 315.9, 276.9 months), as shown in Figure 2A. No statistically significant difference was observed in the overall median survival time between the pre-fibrotic and fibrotic groups (Log rank test, $P = 0.440$) (Figure 2B). In patients with DIPSS scores of intermediate-2 and high risk, the 5 year and 10-year OS rates were 94.1% and 84.7%, respectively, whereas no mortality was recorded in the DIPSS plus score low and intermediate-1 group, as shown in Figure 2C (Log rank test, $P = 0.531$).

Disease progression (acquisition of any of the DIPSS plus criteria) in the pre-fibrotic group was significantly lower than in the overt PMF group (12.5% vs 93.1%, $P < 0.0001$) (Table 3B). The overall median PFS was 79.4 months (IQR: 105.3, 17.0 months), as shown in Figure 3A. Patients with pre-PMF had significantly higher PFS (median PFS 107 months, IQR 107.2, 56.4 months) compared to those with overt PMF (median PFS 30.5 months, IQR 86.7, 0.3 months) (Log rank test, $P = 0.003$), as shown in Figure 3B. Patients with DIPSS plus scores of the low and intermediate-1 group had higher PFS (53.1% of patients had PFS of at least 60 months) compared to those with DIPSS scores of intermediate-2 and high risk (median PFS 38.4 months, IQR 93, 0.3 months) (Log rank test, $P = 0.252$), as shown in Figure 3C. The cumulative incidence of disease progression was significantly lower in the pre-PMF group than in the overt PMF group (Log rank test, $P = 0.003$). Moreover, the cumulative incidence of progression of disease were 32.3% and 63.4% at 5 years and 32.3% and 67.4% at 7 years in patients with pre-PMF and overt PMF, respectively (Figure 4).

Patients with unfavorable KT had significantly higher mortality (42.9%, 3/7) than patients with favorable KT (2%, 1/50), $P = 0.005$. Same goes for disease progression which was significantly higher in patients who presented with unfavorable KT than in those who presented with favorable KT (100%, 7/7 vs 44%, 22/50, $P = 0.006$). Similarly, within the favorable group, patients who were presented with abnormal KT had a higher percentage of disease progression (80%, 4/5) than those in the normal KT (40%, 18/45); however, this difference was not statistically significant ($P = 0.087$). Leukemic transformation was significantly higher in patients with unfavorable KT (28.6%, 2/7) than in those with favorable KT (2%, 1/50), $P = 0.037$.

Table 2. Treatment and supportive modalities in our cohort across Pre-PMF and overt PMF groups.

Treatment	Total	Pre-PMF	Overt PMF	*P*-value
Need for treatment	44/61 (72.1%)	19 (59.4%)	25 (86.2%)	0.020
Aspirin	25/61 (41.0%)	15 (46.9%)	10 (34.5%)	0.326
Ruxolitinib	17/44 (38.6%)	2 (10.5%)	15 (60.0%)	0.001
Cytoreduction	37/44 (84.1%)	19 (100%)	18 (72.0%)	0.012
BMT	2/44 (4.5%)	0 (0%)	2 (8.0%)	0.498
Splenic removal/radiation	3/44 (6.8%)	0 (0%)	3 (12.0%)	0.247
Growth factors	10/44 (22.7%)	1 (5.3%)	9 (36.0%)	0.016

One patient died in the favorable KT-normal group compared to none (0%) in the favorable KT-abnormal group ($P = 0.998$).

Four of the 61 PMF patients died during the observed study, all were overt fibrotic, three patients developed leukemic transformation and carried

Table 3. Association between various demographics, clinical, laboratory and other related characteristics with mortality and progression of the disease (Exploratory statistical analysis), (A) Univariate Cox regression analysis, (B) Chi-Square test.

Table 3A: Univariate Cox regression analysis

	Progression of disease (acquisition of DIPSS plus risk factors) 31/61 (50.8%)	
Characteristics	Unadjusted hazard ratio (HR) (95% CI)	P-value
PMF		
Pre-PMF	1.0 (reference)	
Overt PMF	4.48 (1.52, 13.23)	0.007
Age (years)		
<65 years	1.0 (reference)	
≥ 65 years	0.55 (0.13, 2.39)	0.425
Gender		
Male	1.0 (reference)	
Female	0.90 (0.41, 1.96)	0.785
Hb level		
<10 g/dl	1.0 (reference)	0.632
≥ 10 g/dl	1.25 (0.51, 3.08)	
WBCs count		
25x 10^9 /L	1.0 (reference)	
>25 x 10^9 /L	0.54 (0.16, 1.83)	0.321
Platelet count		
<100 x10^9 /L	1.0 (reference)	0.574
≥100 x10^9 /L	0.73 (0.24, 2.22)	
PB blasts (%)		
< 1%,	1.0 (reference)	
≥1%	3.31 (1.21, 9.08)	0.020
LDH		
≤ 225	1.0 (reference)	
> 225	4.44 (0.58, 33.87)	0.150
Constitutional symptoms		
No	1.0 (reference)	0.027
Yes	3.03 (1.14, 8.12)	
Splenomegaly		
Non-splenomegaly	1.0 (reference)	0.436
Palpable splenomegaly or ≥ 10 cm in any imaging	1.45 (0.57, 3.68)	
Karyotype		
Normal karyotype	1.0 (reference)	
Abnormal karyotype	1.38 (0.45, 4.19)	0.571
Unfavorable karyotype	0.78 (0.29, 2.07)	0.613
DIPSS score		
Low to Intermediate-1	1.0 (reference)	
Intermediate-2 to High	1.67 (0.69, 4.08)	0.258
Reticulin staining grades		
MF 0	1.0 (reference)	
MF 1	1.08 (0.21, 5.43)	0.927
MF 2	2.19 (0.49, 9.77)	0.303
MF 3	2.94 (0.83, 10.48)	0.096
Transfusion dependency		
No	1.0 (reference)	0.996
Yes	0.99 (0.43, 2.33)	
Driver Mutation *JAK2* V617F		
No	1.0 (reference)	0.034
Yes	0.45 (0.22, 0.94)	
***CALR* Exon 9**		
No	1.0 (reference)	0.487
Yes	1.42 (0.53, 3.85)	
***MPL* Exon 10**		
No	1.0 (reference)	0.062
Yes	14.0 (0.88, 223.87)	

Table 3B: Chi-Square test

Characteristics	Mortality n=4/61 (6.6%)	P-value*	Progression (Yes) n=31/61 (50.8%)	P-value*
PMF				
Pre-PMF	0 (0)	0.046	4 (12.5)	<0.0001
Overt PMF	4 (13.8)		27 (93.1)	
Age (years)				
<65 years	3 (5.2)	0.187	29 (50)	0.988
≥ 65 years	1 (33.3)		2 (66.7)	
Gender				
Male	4 (10.5)	0.287	21 (55.3)	0.372
Female	0 (0)		10 (43.5)	
Hb level				
≥ 10 g/dl	2 (4)	0.146	20 (40)	<0.0001
<10 g/dl	2 (18.2)		11 (100)	
WBCs count				
25x 10^9 /L	3 (5.4)	0.296	27 (48.2)	0.354
>25 x 10^9 /L	1 (20)		4 (80)	
Platelet count				
≥100 x10^9 /L	4 (7.1)	0.988	27 (48.2)	0.113
<100 x10^9 /L	0 (0)		4 (100)	
PB blasts (%)				
< 1%,	0 (0)	0.046	5 (15.6)	<0.0001
≥1%	4 (13.8)		26 (89.7)	
LDH				
≤ 225	0 (0)	0.998	1 (16.7)	0.024
> 225	4 (9.3)		28 (65.1)	
Constitutional symptoms				
Yes	4 (12.9)	0.113	26 (83.9)	<0.0001
No	0 (0)		5 (16.7)	
Splenomegaly				
Palpable splenomegaly or ≥ 10 cm in any imaging	3 (8.3)	0.998	25 (69.4)	0.003
Non-splenomegaly	1 (4.8)		6 (28.6)	
Karyotype				
Normal karyotype	1 (2.2)	0.007	18 (40	0.025
Abnormal karyotype	0 (0)		4 (80)	
Unfavorable karyotype	3 (42.9)		7 (100)	
DIPSS score				
Low to Intermediate-1	0 (0)	0.028	9 (23.1)	<0.0001
Intermediate-2 to High	4 (18.2)		22 (100)	
Reticulin staining grades				
MF 0	0 (0)	0.273	3 (15.8)	
MF 1	0 (0)		3 (25)	0.0001
MF 2	0 (0)		5 (71.4)	
MF 3	4 (19)		19 (90.5)	
Transfusion dependency				
Yes	3 (20)	0.043	15 (100)	<0.0001
No	1 (2.2)		16 (34.8)	
Driver Mutation				
***JAK2* V617F**				
Yes	3 (8.6)	0.629	15 (42.9)	0.149
No	1 (3.8)		16 (61.5)	
***CALR* Exon 9**				
Yes	1 (5.3)	0.998	10 (52.6)	0.116
No	1 (3.7)		8 (29.6)	
***MPL* Exon 10**				
Yes	0 (0)	0.998	1 (100)	0.467
No	1 (7.1)		6 (42.9)	

*Fisher Exact/ Yates corrected Chi-square tests were applied in case where ≥50% of the cells had expected frequencies <5 to compute the respective statistical *P*-value.

unfavorable KT: del (7) (2 patients), i(17)q (1 patient), and del(11)(q21) (1 patient), during progression and died after repeated infections.

Higher but statistically insignificant mortality was recorded in the group of patients who required treatment (9.1%, 4/44) compared to the patients who did not require treatment (0%, 0/17). Disease progression was found to be significantly higher in patients who required treatment than in the group who did not require treatment (63.6%, 28/44 vs 17.6%, 3/17, $P = 0.001$). Disease progression was also significantly associated with patients who received Ruxolitinib compared to those who did not ($P < 0.001$), and patients who needed cytoreduction therapy ($P = 0.029$).

Given the small sample size of this study, we conducted exploratory statistical analysis (using univariate Cox regression and Chi-Square tests) to explore and assess the risk and associations between various demographic, hematological, and clinico-pathological characteristics, molecular findings and DIPSS scores with mortality and progression of the disease. Univariate Cox regression indicated that in patients who presented with overt PMF (HR 4.48, 95% CI 1.52, 13.23, $P = 0.007$), PB blasts ≥1% (HR

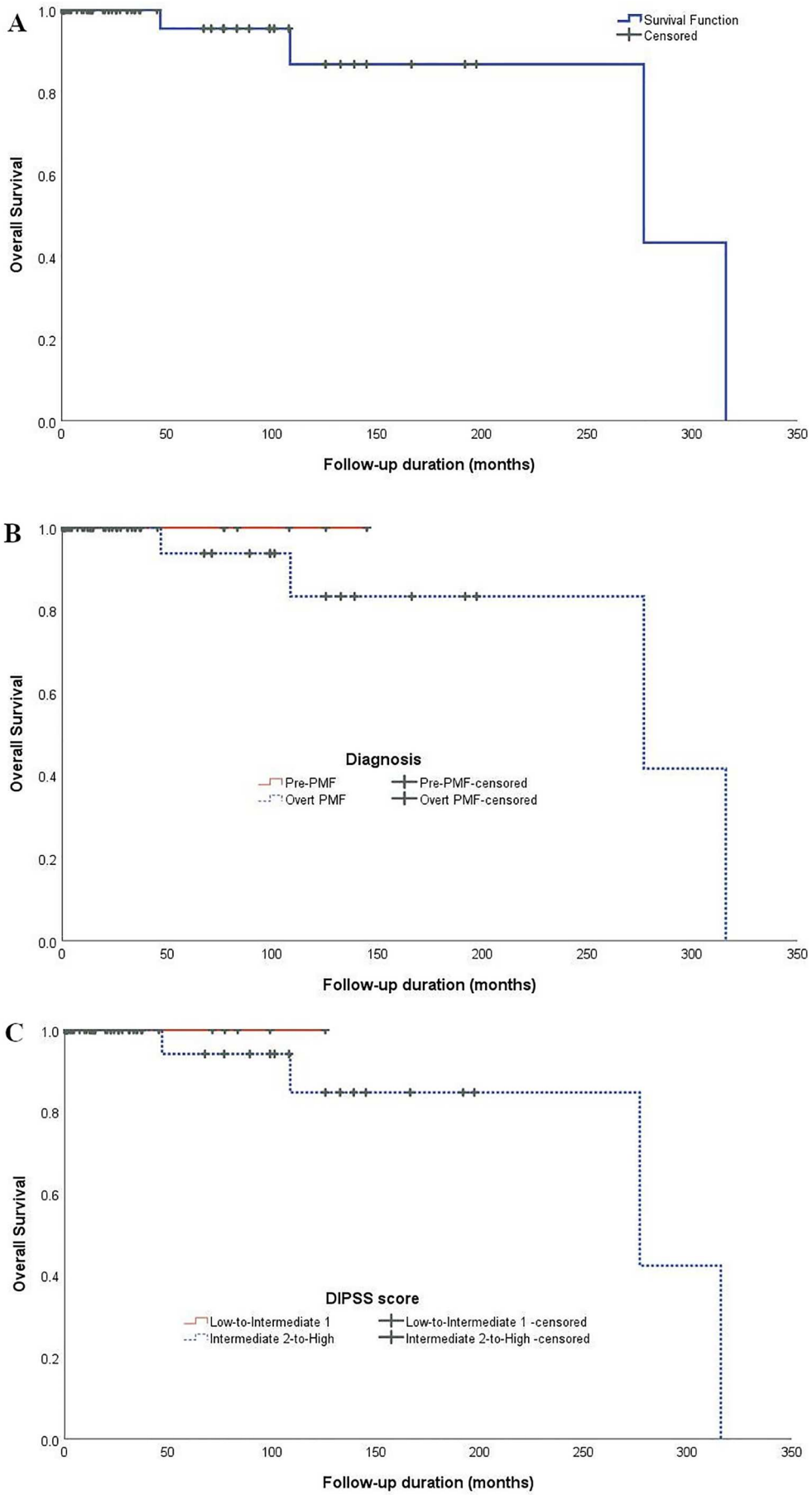

Figure 2. Kaplan-Meier survival curves for patients with primary myelofibrosis (PMF), (A) overall survival, (B) by different stages of disease diagnosis (Pre-PMF and overt PMF), (C) by different risk subgroups based of the DIPSS plus scoring system.

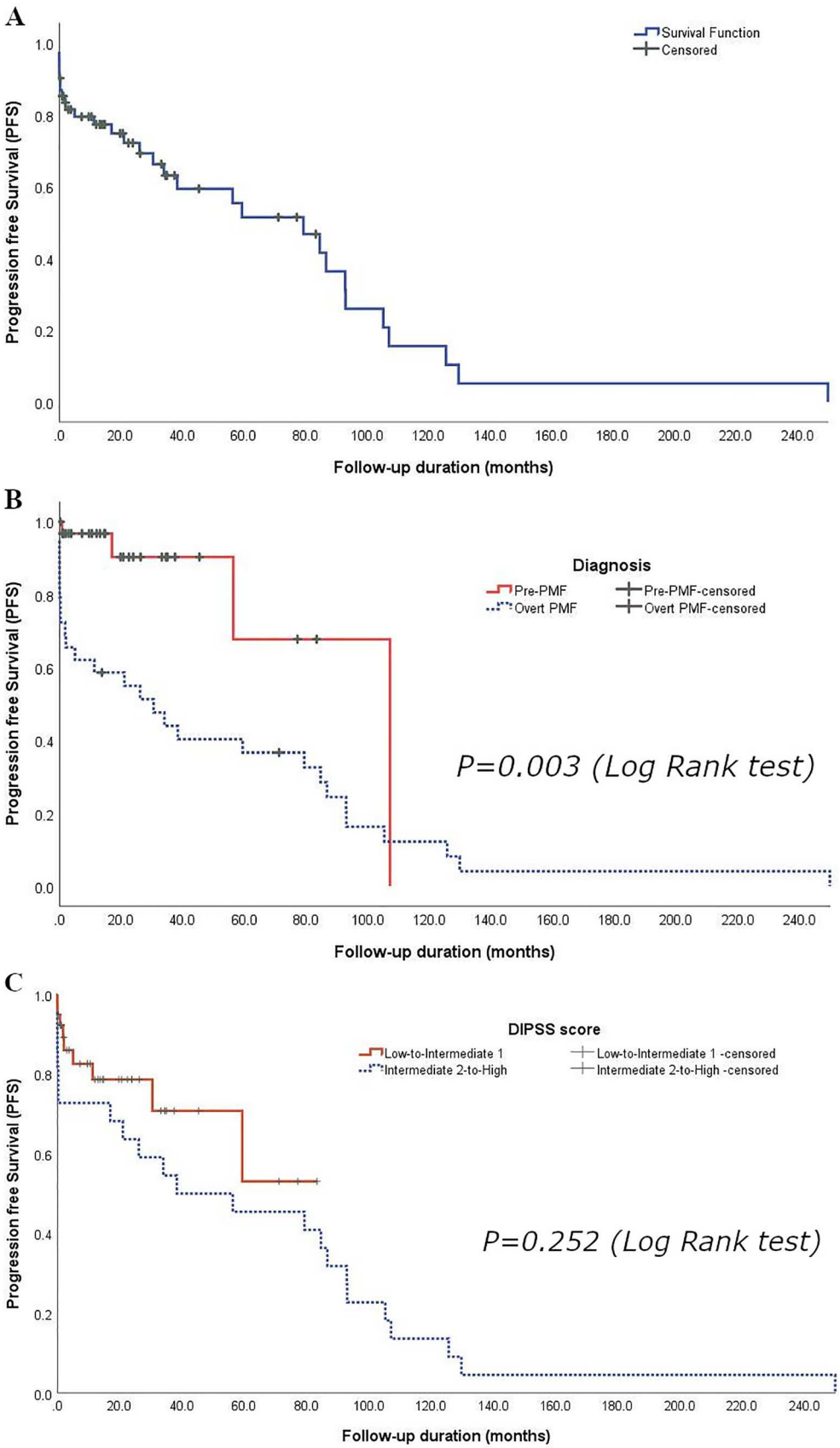

Figure 3. Progression free survival (PFS) for patients with primary myelofibrosis (PMF) (A) Overall PFS (B) by different stages of disease diagnosis (Pre-PMF and overt PMF), (C) by different risk subgroups based of the DIPSS plus scoring system.

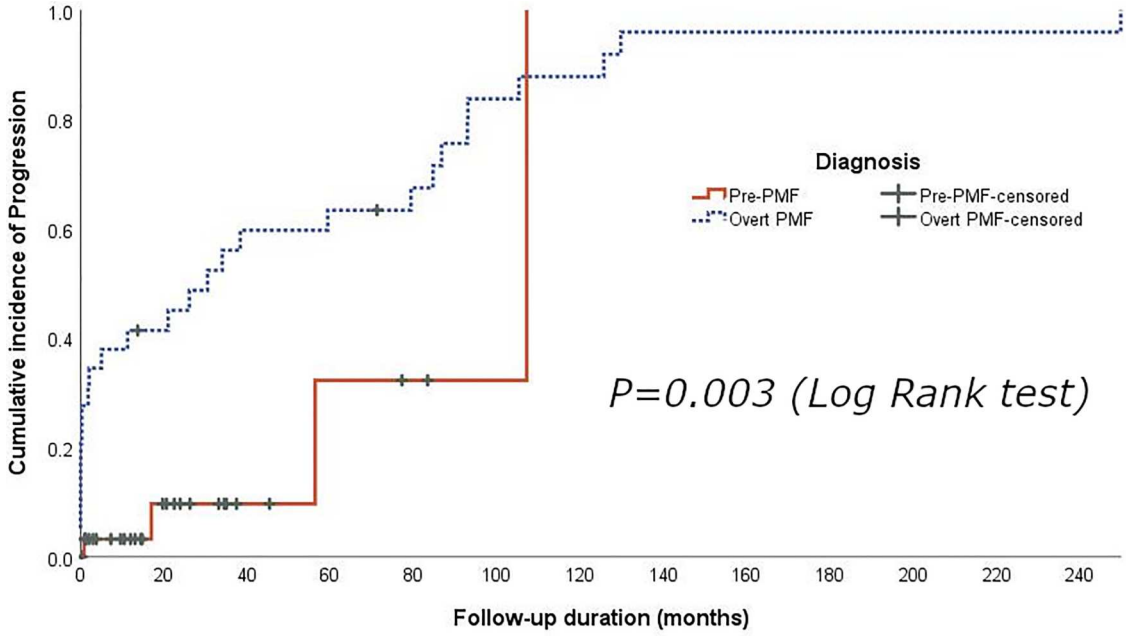

Figure 4. Cumulative incidence of progression of disease by both stages, Pre-PMF and overt PMF.

3.31, 95% CI 1.21, 9.08, $P = 0.020$), constitutional symptoms (HR 3.03, 95% CI 1.14, 8.12, $P = 0.027$) were significantly associated with higher risk of progression of the disease. Similarly, LDH >225, palpable splenomegaly or ≥ 10 cm in any imaging, abnormal KT, intermediate-2 to high DIPSS score, reticulin staining grades (MF2 and MF3), *CALR* EXON 9, *MPL* Exon 10 were associated with higher risk of progression of the disease, however these differences were statistically insignificant ($P > 0.05$) as depicted in Table 3A. Table 3B, compared the absolute percentage values of various such potential factors and their association with mortality and progression of the disease and observed similar trend in the results as in Table 3A.

Discussion

PMF follows a bi-phasic clinical course, once the overt-fibrotic phase of the disease is reached, the prognosis is usually dismal, and BM transplantation becomes the only curative therapy [19,20]**.** Hence, there is a crucial need for early diagnosis at the pre-fibrotic stage, defining the risk of progression in individual cases and accurately distinguishing pre-PMF from overt PMF, which exerts meaningful differences in the clinicopathologic and molecular phenotype and importantly in the disease outcome. Therefore, reinforcing the importance of applying the most updated WHO diagnostic criteria in clinical practice [17,21].

In this real-life study, 61 PMF patients were included, a comparative study of clinicopathological features, treatment modalities, complications, and survival analysis between pre-PMF and overt PMF was conducted.

The median age of PMF at diagnosis was reported in the literature to be 67 years [22], while the median ages in our cohort were 43.5 and 50 years for both pre-PMF and overt PMF groups, respectively. In this study, PMF was diagnosed at a younger age, 95% of patients in our cohort were younger than 65 years of age, and more than half of them were under the age of 50 years. This is in contrast to a study performed in the UK, which showed that less than 20% of PMF patients are diagnosed before the age of 50 years [23]. The younger age with male predominance observed in our cohort can be partially explained by Qatar demographic profile which is characterized by an immigrant working force (15-64 years) representing 84% of the total population with a female/male ratio of 1:3 [24]**.** However, this could also truly reflect the actual prevalence in our region, which is less represented in the literature.

Similar to what was previously reported by Guglielmelli P et al. and Mudireddy M et al. [25,26]**,** we found that patients with pre-PMF were predominantly of younger age who exhibited a prominent myeloproliferative phenotype with higher median leukocyte count ($P = 0.3$) and significantly higher Hb, and PLT levels (when compared to overt PMF) ($P < 0.05$). On the other hand, pre-PMF less frequently had circulating blasts, constitutional symptoms, transfusion requirements, splenomegaly, and lower LDH levels, with statistically significant difference when compared to overt PMF ($P < 0.05$). Additionally, pre-PMF patients predominantly showed normal KT, whereas unfavorable KTwas exclusively detected in patients with overt PMF, similar to what has been reported by Guglielmelli P et al. and Kim TY et al. [25,27]**.** In agreement with previous literature [25], we found that *JAK2* V617F was

more frequently detected in pre-PMF patients whereas patients with overt PMF in our cohort were more enriched with *CALR* mutation. However, with no statistically significant difference ($P = 0.059$ & $P = 0.116$, respectively). In our cohort, *MPL* exon 10 was only detected in overt PMF ($P = 0.33$), which contrasts with results published by Guglielmelli P et al. [25] who reported that *MPL* was almost equally detected in both groups.

Our median OS was 276.9 months (IQR: 315.9, 276.9 months) (23 years) (Figure 2A), which is significantly higher than the published data [28] who reported median OS of 5–7 years.

No statistically significant difference was found in OS between the pre-fibrotic and fibrotic groups (Log rank test, $P = 0.440$) (Figure 2B).

Similar to published data, we found that patients with pre-PMF had significantly higher PFS compared to those with overt PMF (Log rank test, $P = 0.003$) (Figure 3B) [25,27,29].

Regarding DIPSS plus scoring (into 4 groups), most pre-PMF patients were stratified as low risk while no patients detected within the high-risk category. This is in contrast to patients with overt PMF, who were primarily categorized as intermediate 1 to high, with only one patient in the low-risk category. In view of our relatively small cohort, we re-stratified the four risk categories of the DIPSS scoring system into 2 groups: low-risk group (combining of low and intermediate-1 risk groups) and high-risk group (combining intermediate-2 and high-risk groups). Applying DIPSS plus re-stratification, we found that patients with pre-PMF were included largely in the lower-risk (low and Intermediate-1) group, whereas most patients with overt PMF were in the intermediate-2 to higher-risk group ($P < 0.001$). This modified stratification allows for more precise determination of prognosis and survival.

Disease progression (based on acquisition of DIPSS-plus criteria) was estimated to be 100% among higher-risk group patients, in contrast to only 23.1% in the low-risk group ($P < 0.001$) and same for mortality rate (18.2% in high-risk group vs 0%, in low-risk group $P = 0.014$). Likewise, unfavorable KT, refractory anemia, leukemic transformation and need for treatment were all significantly higher in the high-risk group (intermediate-2/high DIPSS) ($P < 0.05$). PMF Patients who presented with thrombosis and refractory anemia, had significantly higher mortality ($P < 0.05$) and features of disease progression than uncomplicated patients [30,31].

Our results concluded that 90.9% of high-risk group patients required treatment vs 61.5% of lower-risk group patients ($P = 0.014$). This is also supported by the results of Tefferi A., et al. [32] who concluded that there is no evidence that supports the importance of a particular therapy in asymptomatic patients with DIPSS-plus low or intermediate-1 risk in PMF.

Within the overt PMF group, the most remarkable parameters that adversely affected mortality (among DIPSS plus criteria) were circulating blasts ≥1%, unfavorable KT and transfusion dependency ($P < 0.05$). These parameters, in addition to anemia, high LDH, presence of constitutional symptoms, extensive splenomegaly, higher DIPSS scores (intermediate 2, high), and increased fibrosis (MF2 and MF3), were significantly associated with a higher risk of disease progression ($P < 0.05$). This was also detected by Passamonti F et al. Shah S et al. [33,34].

Additionally, we found that the encountered disease complications, including refractory anemia and leukemic transformation were all significantly more prevalent in patients with high-risk group (intermediate-2/high DIPSS plus) than in the low-risk group ($P < 0.001$), $P = 0.043$ respectively. In concordance to recently published data by Barbui T et al. [35], we found that the incidence of *JAK2* V617F mutation and thrombotic events was evident in the higher risk group compared to the lower risk group; however, the differences were not statistically significant ($P > 0.05$).

In this study population, we found that a significantly higher proportion of patients within overt PMF group required treatment as compared to pre-PMF group ($P = 0.020$). Similarly, the need for Ruxolitinib and Growth factors was noted to be significantly higher in overt PMF compared to pre-PMF group ($P < 0.05$), whereas patients treated with Cytoreduction was significantly higher in pre-PMF than overt PMF group ($P < 0.05$). Patients on aspirin, BMT, splenic removal/radiation didn't differ significantly between pre-PMF and overt PMF groups ($P > 0.05$).

Despite its limitations, including the retrospective nature of the data review, the single-center approach, the small patient population size, and the absence of high-risk mutation profiling, which are issues we plan to address in future research, this study stands as a significant contribution. To the best of our knowledge, the current study provides the first and most detailed dataset on PMF in the MENA region, establishing a foundation for subsequent investigations. Our commitment to overcoming these methodological challenges underscores the value of our findings, providing essential baseline data to enhance the understanding and management of PMF in the region. Our research is especially valuable because it originates from the only major cancer hospital in a country with a small population, characterized by high migratory flow and a predominantly young demographic. It offers new insights into patients with PMF in the MENA region, which is crucial for developing better healthcare plans and treatments in the future.

Conclusion

Our results emphasize the importance of early recognition of pre-PMF as a distinct entity that should be diagnosed and identified separately, given the critical differences in terms of clinical presentation, survival, and disease progression. These criteria help identify a special population of patients who can benefit from early diagnosis, monitoring and exclusive management that would hopefully result in better disease outcomes.

Based on our results, using the combined DIPSS-plus as a novel scoring tool for risk stratification of PMF into two risk groups, we concluded that merged DIPSS plus scoring was effective as well as practical tool for segregating high risk patients who significantly differ in mortality, progression, need for treatment and leukemic transformation.

To the best of our knowledge, this study is the first and largest published data on PMF in the MENA region. Despite the limitations, the study highlights the importance of PMF in representing our data in the literature, leading to greater inclusivity and aiding in understanding and treating PMF more effectively.

Abbreviations

Primary Myelofibrosis (PMF)
Myelofibrosis (MF)
Myeloproliferative Neoplasm (MPN)
Pre-Fibrotic Primary Myelofibrosis (Pre-PMF/Pre-fibrotic)
Overt-Fibrotic Primary Myelofibrosis (Overt PMF/Fibrotic)
Bone marrow (BM)
Dynamic International Prognostic Scoring System (DIPSS)
Janus Kinase 2 Exon 14 (*JAK2* V617F)
Myeloproliferative Leukemia virus oncogene exon 10 (MPL)
Calreticulin Exon 9 (CALR)
Lactate Dehydrogenase (LDH)
Overall Survival (OS)
Progression-Free Survival (PFS)
White Blood Cells (WBCs)
Hemoglobin (Hb)
Platelet Counts (PLT)
Peripheral Blood Blasts (PB Blasts)
Karyotype (KT)

Author Contributions

SAK, DS, AEO, HEO: Study design. SAK, DS, RYT, HS, HEO: Data collection and Data verification. PC, SAK, AEO: Analysis and interpretation of results. SAK, and AEO: Performed research. SAK, AEO, PC, DS, HA: Draft manuscript preparation. SAK, DS, AEO, RYT, HS, HA, PC, AEO: Manuscript Revision. SAK, DS, AEO, RYT, HS, HA, PC, AEO: Final manuscript review.

Ethical and IRB approvals

Research protocol references MRC-01-19-4666/MRC-01-23-066 and IRB was exempted since the current research protocol is based on a retrospective study.

Consent for publication

No individual person's data included.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets used and/or analyzed during the current study are available from the first author, the senior author, and the corresponding author based on reasonable request.

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