

# Clinical features and therapeutic outcome of 30 patients diagnosed with primary myelofibrosis at the national center of hematology

Alaa F. Alwan \*

FICMS (int.med), FICMS (clin. Hem)

**Abstract:**

**Background:** Primary myelofibrosis is characterized by clonal expansion of hematopoietic stem cell with a non-reactive clonal proliferation of fibroblasts and bone marrow fibrosis, which occurs at an extramedullary hematopoiesis. The clinical features of Primary myelofibrosis include anemia, marked splenomegaly and constitutional symptoms. Ineffective erythropoiesis and extra-medullary hematopoiesis are the main causes of anemia and organomegaly, respectively

**Objectives :** the aim of this study was to evaluate the clinical features, diagnostic tools and the treatment outcome of patients with primary myelofibrosis.

**Patients and methods:** this is a prospective study conducted at the national center of hematology in Baghdad during the period between October 2009 and October 2013. It includes 30 adult patients diagnosed with primary myelofibrosis. Diagnosis was based primarily on bone marrow aspirate and biopsy. The patients were followed up and assessed monthly with complete blood picture and liver function test and renal function test with serum lactate dehydrogenase level.

**Results:** thirty patients were included in this study. There were 16 male and 14 female, the median age was 58 year with range (26-75) years. The most frequent presentation was in the group older than 60 years. Twenty four (80 %) patients had symptoms at diagnosis. The most frequent presentation were the fatigue, left upper quadrant swelling, night sweats, weight loss and fever. The main clinical features were huge splenomegaly which is found in 29 (97%) of patients, while the main finding in blood count at presentation were anemia followed by leukocytosis with leukoerythroblastic blood picture in 22 (73 %) of cases. The level of LDH was high in about 23 (77 %). The bone marrow biopsy showed fibrosis stage 2 in 24 (80 %). Patients who died were in the highest risk groups. The median survival was approximately 28 months.

**Conclusion:** Primary myelofibrosis is part of myeloproliferative neoplasia; it usually runs chronic course. Till now none of the therapeutic modalities approved for treatment of primary myelofibrosis proved to be superior to others, yet the 5 year survival of this disease considered good.

**Keywords:** anemia, outcome, primary myelofibrosis.

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**Introduction:**

Since its description in 1879.(1) primary myelofibrosis (PMF) has received in the medical literature over 20 different names The most common are: idiopathic myelofibrosis, myelofibrosis with myeloid metaplasia, myeloid metaplasia , Agnogenic, myelosclerosis with myeloid metaplasia, chronic non-leukemic myelosis, chronic granulocytic-megakaryocytic myelosis .(2 )PMF is a clonal expansion of hematopoietic stem cell which is accompanied by a non-reactive clonal proliferation of fibroblasts and fibrosis of bone marrow. As the bone marrow becomes fibrotic no hematopoiesis can be maintained, and an extramedullary hematopoiesis (myeloid metaplasia) occurs, usually in liver and spleen. Its etiology is still not fully established. (3) Several studies point to the origin of biomarker in hematopoietic stem cell with clonal involvement of myeloid progenitors, megakaryocytic and

erythroid, monocytes and Band T lymphocytes. In contrast to other chronic myeloproliferative disorders, PMF exhibited a significant marrow stromal reaction including fibrosis, osteosclerosis and angiogenesis. The principal pathogenetic criteria are an abnormal megakaryocyte resulting from an abnormal neoplastic stem cell. The death of these abnormal megakaryocytes results in the production of mitogens that result in bone marrow fibrosis (3, 4)Two studies done by Teffari found a clonal myeloproliferation with increased levels of stromal cells and proteins extracellular matrix. These changes in the microenvironment of the bone marrow coexist with alterations in the balance of intracellular and extracellular cytokines with angiogenic and fibrogenic potential osteogenesis. (5, 6) Myelofibrosis can occur in two clinical forms: either PMF or secondary MF. in PMF there is no disease that proceed or may attribute to be causative agent for the hallmark and clinical, biological or histopathological features .(7,8) Research over the past 30 years showed that

\*Dept of clinical hematology/the national center of hematology/  
Almustansiriya University.  
E-mail: ala\_sh73@yahoo.com

the PMF has a heterogeneous phenotype, which has motivated the researchers to find other criteria that contribute to the diagnosis of this disease. Like angiogenesis was an integral component of the bone marrow stromal reaction in PMF and it was closely related to many prognostic parameters; thus bone marrow angiogenesis can be used as a tool to assess the disease activity. (9) PMF is one of the low incidence of myeloproliferative disorders in which its prevalence of about 0.3 to 2/100000 population. It is seen mainly in older people with average age of 60 years, although 10% of patients have age less than 46 years; nevertheless it can occur from birth to age 90 years, with a similar frequency in both sex. (10, 11) Given that PMF is rare hematological disorder, (11, 12) with very good 5 year survival after diagnosis, and up to my knowledge no clinical study has been conducted in Iraq concerning this disease therefore this study was designed to evaluate clinical features, diagnostic tools and treatment outcome of patients with primary myelofibrosis.

#### Patients and Methods:

A prospective study designed to include 30 patients with diagnosis of PMF who were treated at the National Center of Hematology /Almustansiriya University in Baghdad, Iraq. The period of study lasted from October 2009 to October 2013. This study was approved by the institutional ethical committee. All patients gave their informed consent. The following measures were done for all patients to establish the diagnosis of PMF.

1. Complete history and physical examination.
2. Complete blood count and blood film, liver function tests, renal function tests, lactate dehydrogenase
3. Imaging techniques including abdominal ultrasound. CT of abdomen was done in few cases to confirm presences of organomegaly
4. Bone marrow aspirate and biopsy to determine the degree of fibrosis with using the reticulin stain
5. Fluorescent in situ hybridizations (FISH) technique for Philadelphia chromosome to exclude chronic myeloid leukemia
6. JAK II V617F mutation analysis done for patients presented from 2012 onwards (included 16 patients only). The following criteria has been adopted for stratifying patients with PMF:

Anemia: hemoglobin figures below:

- Women: 12 g /dL.

- Men: 13 g /dL.

Leukocytosis: - Low:  $10-20 \times 10^9 / L$ .

- Moderate:  $20- 50 \times 10^9 / L$ .

- high: more than  $50 \times 10^9 / L$ .

Thrombocytopenia: platelet count less than  $150 \times 10^9 / L$ .

Thrombocytosis: platelet count greater than  $450 \times 10^9 / L$ .

Treatment selection for patients with PMF was classified into

3 categories based on symptoms, physical examination and the results of the investigations.

1- Asymptomatic.

2- Patients in whom anemia is the main problem.

3- Patients with proliferative disease.

The patients were stratified according to international prognostic scoring system by calculating 1 point for each risk factors which include( age > 65, presence of constitutional symptoms, hemoglobin < 10 g/dL, WBC >  $25 \times 10^9$  and blood blast > 1). (13). The median overall survival of the patient was determined by the Kaplan Meier.

#### Results:

Patient characteristics' at diagnosis

This study enrolled 30 patients with PMF; among them there were 16 male and 14 female. The median age was 58 year with range of (26-75) years. The most frequent presentation was in the group older than 60 years. Twenty four (80 %) patients had symptoms at diagnosis. The most frequent presentation were the fatigue, left upper quadrant swelling, night sweats, weight loss and fever. The main clinical features were huge splenomegaly which is found in 29 (97%) of patients as shown in table 1, while the main finding in complete blood count and blood film at presentation were anemia followed by leukocyte counts of  $10-20 \times 10^9 / L$ , not surprisingly leucoerythroblastic blood picture found in 22 (73 %) of cases as shown in table 2. The level of LDH was high in about 23 patients (77 %). The bone marrow biopsy resulted in stage 2 fibrosis in 24 (80 %). JAK 2 V617F mutation was positive in 9 (56%) of 16 patients.

Risk stratification and clinical endpoints

According to IPSS (table 3) patients classified in the high risk groups (high and int-2 scores) showed a significantly lower overall survival than patients in the low-risk groups (int-1 and low) because all patients who died were in the highest risk groups (intermediate-2 and high risk). The median overall survival was approximately 28 months. (Fig. 1)

Treatment For patients who were asymptomatic, just observation and tonics were given. Those patient who had anemia, prednisone was used with Androgen (Danazole®) supported by growth factors (recombinant human erythropoietin) as stimulator of hematopoiesis. Despite this, 5 patient required high blood transfusion requirements. In other cases, transfusions were used as supportive treatment during course of treatment. Therecombinantalphainterferon(IFN-aR)wasusedin 14patients and in 3 of them, pegylated interferon (peginterferon alfa2a) and hydroxyurea in 16 patients. Just 2 patients required conventional chemotherapy (doxorubicin and cytosine arabinoside) because of transformation to acute myeloid leukemia. Splenic irradiation was not done to any patients. Antiangiogenic drugs like thalidomide tablet 100 mg was used only in 3 patients.

All patients used combinations of the therapies described above, either from time of diagnosis or during the course of the disease. The most common combinations used are either hydroxyurea with danazole and steroid in addition to tonics or Alfa Interferon with prednisolone and tonics.

Six of the 30 patients with a diagnosis of PMF, died in the course of study, 3 of sepsis complicating respiratory disease, 2 patients due to leukemic transformation and one by renal failure.

Table 1: clinical features of 30 patients with PMF

Clinical features	Patients	
	number	Percent
Fatigue	25	83.3
left upper quadrant swelling	20	66.6
night sweats	18	60
Weight loss	10	33.3
Splenomegaly	29	96.6
Hepatomegaly	13	43.3
Lymphadenopathy	5	16.6

Table 2: hematological parameter in 30 patients with PMF

Hematological parameter	Patients	
	number	Percent
Anemia Hb < 12 gm/dl	21	70
Leukocytosis: - Low: 10-20 × 10 <sup>9</sup> / L. Moderate: 20- 50 × 10 <sup>9</sup> / L. high: more than 50 × 10 <sup>9</sup> / L	18	60
	8	26.6
	4	13.4
Thrombocytopenia: platelet < 150 × 10 <sup>9</sup> / L. Thrombocytosis: platelet >450 × 10 <sup>9</sup> / L.	8	26.6
	11	36.6
Leucoerythroblastic blood picture	22	73.3
Lactate dehydrogenase increased	23	77

Table 3 - Risk stratification according to the IPSS scores.

IPSS	N
Low	8 (26.6%)
Intermediate-1	6 (20%)
Intermediate-2	9 (30%)
High	7 (23.4%)

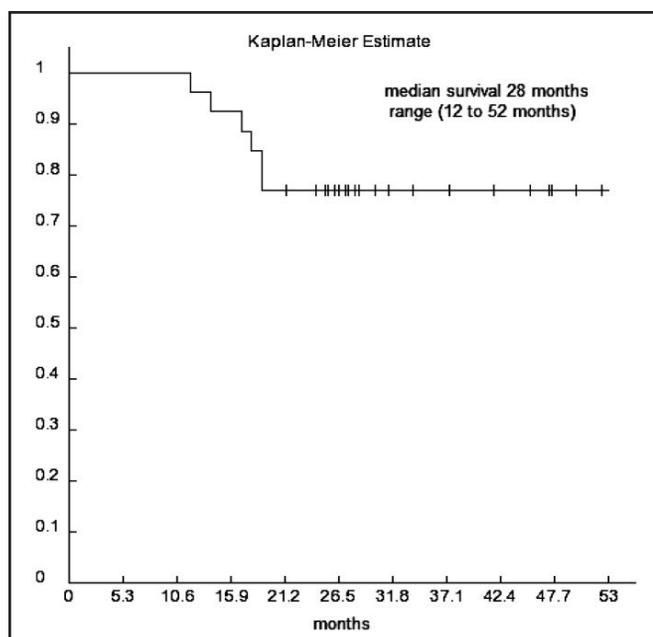


Fig 1: Kaplan-Meier estimate of overall survival rate for PMF patients

Discussion:

Most patients were diagnosed at age of 50 years in this study, which agrees with studies reported in the literature that the diagnosis is established in aged between 50 and 80 years, mostly during 6<sup>th</sup> decade.(1,2,8,14). However, in this study, young patients less than 40 years old were diagnosed with PMF, which agreed with study by Ruben et al which showed that it may arise from the birth through 90 years. (1) Despite the small number of cases studied because of the low incidence of this disease, there was a slight male predominance, as it reported by other authors, on the other hand some studies said that there is no sex predisposition .(1, 8,14). five (17% ) of the patients were asymptomatic at time of diagnosis, This is explained by the insidious onset of PMF in which the diagnosis is made by physical examination or routine laboratory study in which disturbances in blood film appeared or splenomegaly is found.(15) On physical examination splenomegaly was the characteristic finding, similar to what reported by other investigators. (1,8,16) The second most common finding was the presence of hepatomegaly, which was typical in this disease.(1,7,8) the presence of hepatosplenomegaly is explained by extramedullary hematopoiesis, as compensatory mechanism in response to bone marrow fibrosis that prevent normal hematopoiesis (13,17) The lymphadenopathy are rare or of little significance, which was also confirmed by other studies. (1, 8) In this study, anemia was the most common finding among hematologic parameters, while other authors reported that up to 50% of the patients had anemia at presentation. The

causes of anemia in PMF are multifactorial and may be due to decreased bone marrow production and varying degree of ineffective erythropoiesis. Moreover, it may be autoimmune in origin or due to hypersplenism.(7,8,13,18) Thrombocytosis and leukocytosis coincide with several other observations that raise the variability in the hematological profile of PMF in which they referred to both leucopenia and thrombocytopenia or thrombocytosis and leukocytosis or normal values which incorporated in the prognostic index (13) elevated platelet counts found at first in prefibrotic phase or proliferative phase which is then change to thrombocytopenia as the disease progresses. (7,13) In PMF Leukocytosis usually occurs less  $30 \times 10^9 / L$ (17) which is consistent with that described in this study ;Of particular note is the presence of teardrop-shaped red cells, immature myeloid cells ,and erythroblasts in the peripheral blood ( Leucoerythroblastic blood picture), which was observed in most patients (73%). This is consistent with results reported in other series (17-19). Twenty-three patients (77%) had an increase in the numbers of LDH serum, a finding that is in concordance with that described in the literature.(1,8) This increase in serum LDH is mainly attributed to high existing degree of ineffective erythropoiesis in PMF. (1, 8) The bone marrow biopsy is the mainstay in the diagnosis of PMF because it is useful to demonstrate and determine the pattern fibrosis histology.(8,20) In this study , most patients were in stage 2 fibrosis, this result disagree with other authors describing a predominance of cellular or prefibrotic stage at the time of diagnosis.(4,8) PMF has a chronic course and heterogeneous development: while few patients die within a short period after diagnosis, the majority have a survival of several decades.(1,13) The application of the scoring system Prognostic factors has considerable practical application as it enables increase the capacity of prognostic discrimination, as in other studies relationship was observed between patients who died and those most at risk.(1, 8,13) According to the international working group for study and treatment of PMF, low-risk patients have a median survival about 135 months, the intermediate risk group 1, 95 months, the 2 intermediate risk, 48 months, and the high risk of 27 months.20 , 23,36 Other authors describe the relationship of low-risk groups with a better median survival of 10-15 years.(1,21,22) PMF treatment should be based on two assumptions: First, the recognition that we are facing an incurable disease except perhaps for the minority of young patients who may benefit from stem cell transplantation. In the remaining patients, treatment is merely palliative and is intended to treat the complications of the disease and improve the quality of life rather than to try to prolong survival. Secondly, the marked heterogeneity in disease progression requires adjusting patients treatment according to their characteristics, taking in consideration this premise, the small

sample size and the diversity of therapeutic schemes used, it was not possible to reach conclusions regarding the influence of treatment on disease progression and which is better than other. (13,23) Because of short duration of follow-up, The median survival of 28 months (2.5 years) observed in this study which is consistent with that in other recent series, which ranges from 3 to 6 years ,(8,13,14,22,24) This prolonged survival compared to that of older series, attributed to the introduction of an effective treatment for t PMF . the explanation for this prolong survival ,first is the early diagnosis of the disease and, second, due to improvement in the supportive measures, the use of antifibrotic agents in all patients diagnosed, and lastly treatment with iron chelators in blood transfusion dependent .

#### Conclusion:

Primary myelofibrosis is part of myeloproliferative neoplasia; it usually runs chronic course. Till now none of the therapeutic modalities approved for treatment of primary myelofibrosis proved to be superior to others, yet the 5 year survival of this disease considered good.

#### References:

1. Ruben A, Tefferi A. Approach to chronic idiopathic myelofibrosis (with extramedullary hematopoiesis) . In: Sekeres M, Kalaycio M, Bolwell B editors. *Clinical malignant Hematology*. 1st ed. New york: McGraw-Hill, 2007. p. 475-9.
2. Mesa RA, Li CY, Ketterling RP, Schroeder GS, Knudson RA, Tefferi A. Leukemic transformation in myelofibrosis with myeloid metaplasia: a single-institution Experience with 91 cases. *Blood*. 2005 Feb 1; 105 (3) :973-7.
3. Arana-Yi C, Quintas-Cardama A, Giles F, Thomas D, Carrasco-Yalan A, Cortes J, et al. *Advances in the therapy of chronic idiopathic myelofibrosis*. *Oncologist*. 2006 Sep;11(8):929-43.
4. Al-Mashhadani A, Mansoor S, Sarhan F. subjective and quantitative evaluation of bone marrow trephine biopsy in idiopathic myelofibrosis. *Iraqi J Med Sci*, 2005; Vol. 4 (2): 214-219(www.iasj.net)
5. Tefferi A. Myelofibrosis with myeloid metaplasia. *N Engl J Med* 2000 April 27, 342 (17) :1255-65
6. Tefferi A. Primary myelofibrosis and its paraneoplastic stromal effects. *Haematologica*. 2007;92(5):577-9.
7. Cervantes F, Pereira A, Esteve J, Cobo F, Rozman C, Montserrat E. The changing profile of idiopathic myelofibrosis: a comparison of the presenting features of patients diagnosed in two different decades. *Eur J Haematol* 1998;60:101–105.
8. Cervantes F, Barosi G, Hernandez-Boluda JC, Marchetti M, Montserrat E. Myelofibrosis with myeloid metaplasia in adult individuals 30 years old or younger: presenting features, evolution and survival. *Eur J Haematol* 2001;66:324–327.

9. AL Mudallal S , Mukeef M. Evaluation of Angiogenesis in Idiopathic Myelofibrosis with CD31 and CD34 by Light Microscope and Computer-Aided Image Analysis System. *IRAQI J MED SCI*, 2010; VOL.8 (3):25-33(www.iasj.net)
10. Strasser-Weippl K, Steurer M, Kees M, Augustin F, Tzankov A, Dirnhofer S, Fiegl M. Age and hemoglobin level emerge as most important clinical prognostic parameters in patients with osteomyelofibrosis: introduction of a simplified prognostic score. *Leuk Lymphoma* 2006;47:441–50.
11. Cervantes F, Pereira A, Esteve J, Rafel M, Cobo F, Rozman C, Montserrat E . Identification of 'short-lived' and 'long-lived' patients at presentation of idiopathic myelofibrosis. *Br J Haematol* 1997;97:635–640
12. Dupriez B, Morel P, Demory JL, , Lai JL, Simon M, Plantier I, Bauters F . Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system. *Blood* 1996;88:1013–1018.
13. Cervantes F, Dupriez B, Pereira A, Passamonti F, Reilly JT, Morra E, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working. *Blood*. 2009 Mar 26;113(13):2895-901.
14. Linardi Cda C, Dalessandro T, Pracchia LF, Buccheri V. Evaluation of survival risk scores in primary myelofibrosis: A Brazilian experience from a single institution. *Leukemia & Lymphoma*. 2008 Aug;49(8):1641-3.
15. Okamura T, Kinukawa N, Niho Y, Mizoguchi H. Primary chronic myelofibrosis: clinical and prognostic evaluation in 336 Japanese patients. *Int J Hematol* 2001;73:194–198.
16. Chim CS, Kwong YL, Lie AK, Ma SK, Chan CC, Wong LG, et al. Long-term outcome of 231 patients with essential thrombocythemia: prognostic factors for thrombosis, bleeding, myelofibrosis, and leukemia. *Arch Intern Med*. 2005 Dec 12;165(22):2651-8.
17. Campbell PJ, Green AR. Mechanisms of disease in the myeloproliferative disorders. *N Engl J Med*. 2006 Dec 7;355(23):2452-66.
18. Hennessy BT, Thomas DA, Giles FJ, Kantarjian H, Verstovsek S. New approaches in the treatment of myelofibrosis. *Cancer*. 2005 Jan 1;103(1):32-43.
19. Tefferi A, Thiele J, Orazi A, Kvasnicka HM, Barbui T, Hanson CA, et al. Proposals and rationale for revision of the World Health diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. *Blood*. 2007 Aug 15;110(4):1092-7.
20. Barosi G, Bergamaschi G, Marchetti M, Vannucchi AM, Guglielmelli P, Antonioli E, et al. JAK2V617 F mutational status predicts progression to large splenomegaly and leukemic transformation in primary myelofibrosis. *Blood*. 2007 Dec 1;110(12):4030-6.
21. Tefferi A. How I treat myelofibrosis. *Blood*. 2011 Jan 3. [Epub ahead of print] PMID: 21200024
22. Cervantes F, Barosi G, Demory JL, Reilly J, Guarnone R, Dupriez B, et al. Myelofibrosis with myeloid metaplasia in young individuals: disease characteristics, prognostic and identification of risk group. *Br J Haematol*. 1998 Aug;102(3):684-90.
23. Vannucchi AM, Guglielmelli P, Tefferi A. Advances in understanding and management of myeloproliferative neoplasms. *CA Cancer J Clin*. 2009 May- Jun;59(3):171-91
24. Reilly JT. Prognosis and survivorship in primary myelofibrosis. *Am J Hematol*. 2010 Jan;85(1):4-5.