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ORIGINAL REPORT

DIPSS Plus: A Refined Dynamic International Prognostic Scoring System for Primary Myelofibrosis That Incorporates Prognostic Information From Karyotype, Platelet Count, and Transfusion Status

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ABSTRACT

Purpose
The Dynamic International Prognostic Scoring System (DIPSS) for primary myelofibrosis (PMF) uses five risk factors to predict survival: age older than 65 years, hemoglobin lower than 10 g/dL, leukocytes higher than 25×10^9/L, circulating blasts $\geq 1\%$, and constitutional symptoms. The main objective of this study was to refine DIPSS by incorporating prognostic information from karyotype, platelet count, and transfusion status.

Patients and Methods
Mayo Clinic databases for PMF were used to identify patients with available bone marrow histologic and cytogenetic information.

Results
Seven hundred ninety-three consecutive patients were selected and divided into two groups based on whether or not their referral occurred within (n = 428; training set) or after (n = 365; test set) 1 year of diagnosis. Multivariable analysis identified DIPSS, unfavorable karyotype, platelets lower than 100×10^9/L, and transfusion need as independent predictors of inferior survival. Hazard ratio (HR) –weighted adverse points were assigned to these variables to develop a composite prognostic model using the training set. The model was subsequently validated in the test set, and its application to all 793 patients resulted in median survivals of 185, 78, 35, and 16 months for low, intermediate-1 (HR, 2.2; 95% CI, 1.4 to 3.6), intermediate-2 (HR, 4.9; 95% CI, 3.2 to 7.7), and high-risk groups (HR, 10.7; 95% CI, 6.8 to 16.9), respectively ($P < .001$). Leukemia-free survival was predicted by the presence of thrombocytopenia or unfavorable karyotype (10-year risk of 31% *v* 12%; HR, 3.3; 95% CI, 1.9 to 5.6).

Conclusion
DIPSS plus effectively combines prognostic information from DIPSS, karyotype, platelet count, and transfusion status to predict overall survival in PMF. In addition, unfavorable karyotype or thrombocytopenia predicts inferior leukemia-free survival.

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INTRODUCTION

Primary myelofibrosis (PMF) is a clonal stem cell disorder currently classified as a myeloproliferative neoplasm (MPN).[1] The disease-causing mutation in PMF is not known. However, a number of novel mutations involving *JAK2*, *MPL*, *TET2*, *ASXL1*, *CBL*, *IDH*, *IKZF1*, *LNK*, or *EZH2* have recently been described in some patients with PMF, but also in those with other MPN.[2] The pathogenetic relevance of these mutations is currently under investigation. Patients with PMF also manifest aberrant cytokine milieu and bone marrow stroma that are incompletely characterized.[3] Median survival in PMF is estimated at 6 years,[4] but can range from months to several years. The disease course is complicated by progressive anemia, symptomatic splenomegaly, and severe constitutional symptoms.[5] Causes of death include leukemic transformation, progressive disease with marrow failure, and complications from thrombosis, bleeding, portal hypertension, or infections. Conventional drug therapy has not been shown to prolong survival in PMF. Allogeneic stem-cell transplantation (alloSCT) offers the only chance for cure, but it is associated with substantial morbidity and mortality.[6]

Treatment decisions in PMF are often challenging, particularly in regards to timing of alloSCT or participation in clinical trials. Therefore, accurate risk stratification of patients in terms of overall and leukemia-free survival is critical. In this regard, survival from the time of diagnosis is best assessed by the International Prognostic Scoring System (IPSS)[4] whereas a dynamic IPSS (DIPSS) model is used for estimating survival from any point in the disease course.[7] Both IPSS and DIPSS utilize the same five risk factors for survival (age $>$ 65 years, hemoglobin $<$ 10 g/dL, leukocyte count $>$ 25 $\times$ 10^9/L, circulating blasts $\geq$ 1%, and constitutional symptoms) in order to classify patients into four risk groups: low, intermediate-1, intermediate-2, and high risk. More recently, IPSS-independent prognostic factors for survival in PMF have been described and include red cell transfusion need,[8] unfavorable karyotype,[9,10] and thrombocytopenia.[11] The three main objectives of this study were to determine if the aforementioned IPSS-independent risk factors for survival are also DIPSS-independent; to develop a refined DIPSS model that incorporates DIPSS-independent prognostic factors; and to identify prognostic factors for leukemic transformation.

PATIENTS AND METHODS

Permission was obtained from the Mayo Clinic institutional review board to review the medical records of all patients with PMF referred to the Mayo Clinic during the time period 1970 through 2009. Only patients with available bone marrow and cytogenetic information at the time of their first referral to the Mayo Clinic were included in this study. The diagnoses of PMF and leukemic transformation were according to WHO criteria.[12] Cytogenetic results were interpreted and reported according to the International System for Human Cytogenetic Nomenclature.[13] The presence of fewer than 20 evaluable metaphases did not disqualify patients from study inclusion as long as $\geq$ 10 metaphases were examined in those patients with normal reports; patients with insufficient number of metaphases were excluded. None of the patients in this study were included in the original group of patients used to describe DIPSS.[7] In order to assure mature survival data, follow-up information was updated in July 2010 through review of patient histories and correspondence, social security death index, or a telephone call to the patient; date of last follow-up reflected this time point and not the last time a patient was seen at the Mayo Clinic. DIPSS risk categorization was as previously described.[7] Unfavorable karyotype included complex karyotype or single or two abnormalities including +8, −7/7q-, i(17q), −5/5q-, 12p-, inv(3) or 11q23 rearrangement.[9,10,14] The definition of transfusion dependency included both patients presenting with symptomatic anemia that necessitated treatment with RBC transfusion at the time of referral and those with history of RBC transfusions, for myelofibrosis-associated anemia, even before the time of their referral to the Mayo Clinic. In this regard, only those patients with an ongoing need for red cell transfusions were considered and not those who might have had isolated instances of transfusions in the remote past. The actual number of transfusions was not considered in labeling a patient transfusion dependent or not.

All statistical analyses considered parameters at time of first referral to the Mayo Clinic. Differences in the distribution of continuous variables between categories were analyzed by either Mann-Whitney (for comparison of two groups) or Kruskal-Wallis (comparison of three or more groups) test. Patient groups with nominal variables were compared by χ^2 test. Overall survival analysis was considered from the date of diagnosis to date of death (uncensored) or last contact (censored). Leukemia-free survival was calculated from the date of diagnosis to date of leukemic transformation (uncensored) or last contact/date of death (censored). Additional analyses that censored patients at time of alloSCT were performed for both overall and leukemia-free survival in order to avoid possible confounding of survival effect from the particular treatment modality. Overall and leukemia-free survival curves were prepared by the Kaplan-Meier method and compared by the log-rank test. Cox proportional hazard regression model was used for multivariable analysis. *P* values lower than .05 were considered significant. The Stat View (SAS Institute, Cary, NC) statistical package was used for all calculations.

RESULTS

Patients

Between January 1970 and 2009, a total of 923 consecutive patients with PMF were seen at our institution and underwent bone marrow examination. Cytogenetic studies were not done in 65 patients and resulted in insufficient mitotic figures in 40 patients. An additional 19 subjects with normal karyotype were excluded from the study because the number of metaphases analyzed was fewer than 10 (see Patients and Methods). Six more patients were excluded because of inaccurate diagnosis. Consequently, the study population included 793 patients with PMF of which 428 were referred within and 365 after their first year of diagnosis. These two groups of patients were respectively used as the training and test set of patients during the development of the DIPSS plus prognostic model. The clinical and laboratory characteristics of these two groups of patients as well as the entire cohort of 793 patients are outlined in Table 1.

Overall, median age at time of referral to the Mayo Clinic was 65 years (range, 14 to 92) and 63% were male. Considering all 793 study patients, DIPSS risk assignment at time of referral was low in 10% of the patients, intermediate-1 in 31%, intermediate-2 in 47%, and high in 13% (Table 1). The incidences of unfavorable karyotype, thrombocytopenia (platelets $<$ 100 $\times$ 10^9/L), and transfusion need at time of referral were 15%, 28%, and 39% (Table 1). *JAK2*V617F mutation studies were available in 332 patients and the mutation was detected in 66%. As expected, the group of patients seen after their first year of diagnosis had a more unfavorable clinical profile in terms of DIPSS/IPSS risk distribution, platelet count, karyotype, and transfusion need (Table 1). They were also more likely to have palpable splenomegaly and be on active therapy at the time of their referral (Table 1). The proportion of patients in each DIPSS risk category with red cell transfusion need, unfavorable karyotype, and thrombocytopenia were 0%, 7%, and 7% for low risk; 13%, 12%, and 18% for intermediate-1 risk; 56%, 17%, and 32% for intermediate-2 risk; and 69%, 23%, and 47% for high risk, respectively.

Survival, Leukemic Transformation, and Prognostic Factors

To date, 501 (63%) have died and leukemic transformation was documented in 52 patients (7%). Median follow-up of patients who are alive was 34 months (range, 0 to 339). Both univariate and multivariable analyses were performed separately on patients belonging to the training and test set (Table 2). In univariate analysis using the patient population in either the training or test set, higher DIPSS score, unfavorable karyotype, platelets lower than 100 $\times$ 10^9/L, and red cell transfusion need were each associated with inferior survival. Their prognostic significance was maintained during multivariable analysis limited to the patient population in the training set (Table 2). All but transfusion need also maintained their prognostic significance when analysis was performed using the patient population in the test set (Table 2).

Development of the DIPSS Plus Prognostic Model

Using hazard ratio (HR) –weighted scoring (Table 2), we used the patient population in the training set to devise a refined DIPSS

Table 1. Clinical and Hematologic Characteristics of Patients With Primary Myelofibrosis Stratified by Time of Referral to the Mayo Clinic (N = 793)

Variable	All Patients		Patients Referred Within 1 Year of Diagnosis		Patients Referred After 1 Year of Diagnosis		*P*
	No.	%	No.	%	No.	%	
No. of patients	793		428		365		
Median age at referral, years	65		65		65		.94
Range	14-92		14-92		26-88		
Male sex	501	63	265	62	236	65	.43
Median hemoglobin, g/dL	10		10.2		9.7		.18
Range	5-16.1		5-16.1		5.2-15.9		
Hemoglobin < 10 g/dL	427	54	220	51	207	57	**< .001**
Median No. of leukocytes, $\times 10^9$/L	8.8		8.3		10.4		**.01**
Range	0.9-236		0.9-113		1.4-236		
> 25	139	18	59	14	80	22	**.005**
< 4	130	16	70	16	60	16	.97
Median No. of platelets, $\times 10^9$/L	204		228		178		**.007**
Range	6-1,765		6-1,765		7-1,633		
Platelets < 100 $\times$ 10^9/L	218	28	110	26	108	30	.22
Circulating blasts ≥ 1%, No. evaluable = 760	452	60	217	51	235	64	**.0003**
Constitutional symptoms, No. evaluable = 789	274	35	151	36	123	34	.57
Palpable splenomegaly, No. evaluable = 710	559	79	266	73	293	84	**.0003**
Unfavorable karyotype*	121	15	56	13	65	18	**.07**
*JAK2*V617F, No. tested and % positive	332	66	174	60	158	68	.16
IPSS risk, No. evaluable = 752							
Low	67	9	46	11	21	6	
Intermediate-1	156	21	104	26	52	15	**< .001**
Intermediate-2	208	28	102	25	106	30	
High	321	43	149	37	172	49	
DIPSS risk							
Low	75	10	53	12	22	6	
Intermediate-1	248	31	154	36	94	26	**< .001**
Intermediate-2	370	47	173	40	197	54	
High	100	13	48	11	52	14	
Red cell transfusion need, No. evaluable = 791	307	39	143	33	164	45	**.001**
Any treatment, No. evaluable = 726	234	32	88	24	146	40	**< .001**
Cytoreductive therapy, No. evaluable = 725	128	18	35	10	93	26	**< .001**
alloSCT	29	4	17	4	12	3	.63
Deaths	501	63	270	63	231	64	.79
Leukemic transformation	52	7	35	8	17	5	.05

NOTE. Bold font indicates significant *P* values.
Abbreviations: IPSS, International Prognostic Scoring System; DIPSS, Dynamic International Prognostic Scoring System; alloSCT, allogeneic stem-cell transplantation.
*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include +8, −7/7q-, i(17q), −5/5q-, 12p-, inv(3), or 11q23 rearrangement.

model (DIPSS plus) that incorporated prognostic information from karyotype, platelet count, and transfusion status. Accordingly, 1 point each was assigned to DIPSS intermediate-1 risk, unfavorable karyotype, platelets lower than 100 $\times$ 10^9/L, and red cell transfusion need; DIPSS intermediate-2 and high risk were assigned 2 and 3 points, respectively. Each patient was subsequently assigned a sum score of 0 to 6 adverse points: 0 (n = 46), 1 (n = 114), 2 (n = 90), 3 (n = 87), 4 (n = 60), 5 (n = 28) and 6 (n = 3). The respective median survivals were 185, 81, 43, 30, 16, 14, and 4 months, respectively ($P < .001$). These six patient groups were then consolidated into four risk groups based on the margin of intergroup survival differences, in order to devise a refined DIPSS model (DIPSS plus) using the patient population in the training set (Fig 1): low risk (0 adverse points; median survival, 180 months), intermediate-1 risk (1 adverse point; median survival, 80 months), intermediate-2 risk (2 to 3 adverse points; median survival, 35 months), and high risk (4 to 6 adverse points; median survival, 16 months). The DIPSS plus model was subsequently validated in the patient population in the test set (Fig 2).

Figure 3 illustrates the application of DIPSS plus to the entire study population of 793 patients. Considering all 793 patients, median survivals were 185, 78, 35, and 16 months for low, intermediate-1 (HR, 2.2; 95% CI, 1.4 to 3.6), intermediate-2 (HR, 4.9; 95% CI, 3.2 to 7.7), and high risk groups (HR, 10.7; 95% CI, 6.8 to 16.9), respectively ($P < .001$). The overall results did not change when patients who received transplantation were censored at the time of their transplant or when the analysis was limited to patients that were on active treatment at the time of their referral (data not shown).

Prognostic Factors for Leukemia-Free Survival

All 793 patients were considered for the determination of prognostic factors for leukemic transformation. Multivariable

Table 2. Multivariable Analysis of Prognostic Factors for Overall and Leukemia-Free Survival in Patients With Primary Myelofibrosis (N = 793)

Survival	Patients Referred Within 1 Year of Diagnosis (n = 428)			Patients Referred After 1 Year From Diagnosis (n = 365)		
	95% CI	Hazard Ratio	*P*	95% CI	Hazard Ratio	*P*
Overall survival						
DIPSS risk						
High	4.0 to 13.3	7.3	**< .001**	2.9 to 15.9	6.8	**< .001**
Intermediate-2	2.1 to 6.0	3.6	**< .001**	2.1 to 10.3	4.6	**.0002**
Intermediate-1	1.2 to 3.1	1.9	**.01**	1.4 to 7.0	3.2	**.005**
Unfavorable karyotype*	1.7 to 3.4	2.4	**< .001**	1.2 to 2.3	1.7	**.001**
Platelets < 100 × 10^9/L	1.2 to 2.2	1.6	**.0009**	1.1 to 1.9	1.4	**.02**
Red cell transfusion dependent	1.1 to 2.0	1.4	**.01**	0.9 to 1.6	1.2	.16
Leukemia-free survival, N = 793						
DIPSS risk						
High	0.9 to 26	5.0	.06			
Intermediate-2	0.7 to 15	3.3	.12			
Intermediate-1	0.9 to 16	3.7	.08			
Unfavorable karyotype*	1.1 to 4.3	2.2	**.02**			
Platelets < 100 × 10^9/L	1.4 to 4.6	2.5	**.003**			
Red cell transfusion dependent	0.6 to 2.3	1.2	.65			

NOTE. Values were determined by the Cox regression model. Bold font indicates significant *P* values.
Abbreviation: DIPSS, Dynamic International Prognostic Scoring System.
*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include +8, −7/7q-, i(17q), −5/5q-, 12p-, inv(3), or 11q23 rearrangement.

analysis identified platelet count lower than 100 × 10^9/L ($P = .0007$) and unfavorable karyotype ($P = .04$), but not DIPSS or transfusion status as independent predictors of leukemia-free survival (Table 2). Accordingly, we utilized these two variables, to construct a prognostic model to predict leukemic transformation: low risk (none of the adverse factors present) and high risk (at least one adverse factor present). The respective 5- and 10-year risk of leukemic transformation were 6% and 12% for the low-risk group versus 18% and 31% for the high-risk group ($P < .001$; HR, 3.3; 95% CI, 1.9 to 5.6; Fig 4).

DISCUSSION

The IPSS is the most widely used prognostic scoring system in PMF and was developed by the International Working Group for Myeloproliferative Neoplasms Research and Treatment.[4] IPSS utilizes five

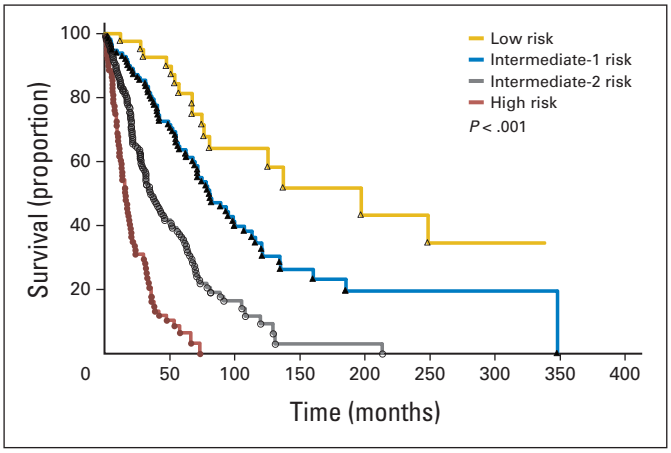

Fig 1. Survival data of 428 patients with primary myelofibrosis evaluated within 1 year of their diagnosis and stratified by their Dynamic International Prognostic Scoring System (DIPSS) + karyotype + platelet count + transfusion status prognostic scores. Low risk, zero adverse points; n = 46; median survival, approximately 180 months. Intermediate-1 risk, one adverse point; n = 114; median survival, approximately 80 months. Intermediate-2 risk, two or three adverse points; n = 177; median survival, approximately 35 months. High risk, four to six adverse points; n = 91; median survival, approximately 16 months. Scale for DIPSS: high risk, three adverse points; intermediate-2, two adverse points; intermediate-1, unfavorable karyotype, platelets < 100 x 10^9/L, and transfusion need, one adverse point.

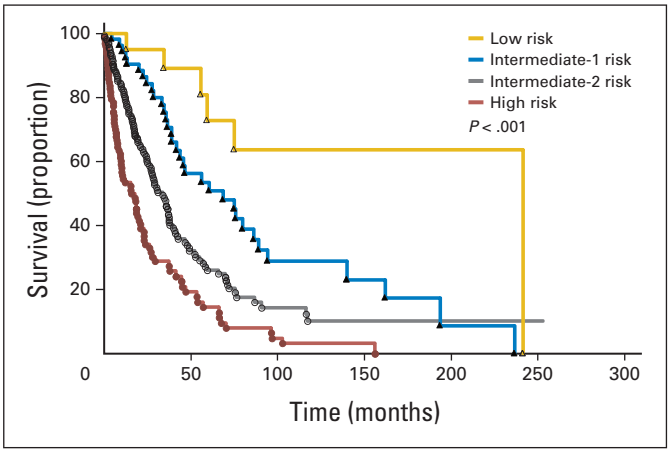

Fig 2. Survival data of 365 patients with primary myelofibrosis evaluated beyond the first year of their initial diagnosis and stratified by their Dynamic International Prognostic Scoring System (DIPSS) + karyotype + platelet count + transfusion status prognostic scores. Low risk, zero adverse points; n = 20; median survival not reached. Intermediate-1 risk, one adverse point; n = 60; median survival, approximately 63 months. Intermediate-2 risk, two or three adverse points; n = 183; median survival, approximately 33 months. High risk, four to six adverse points; n = 102; median survival, approximately 16 months. Scale for DIPSS: high risk, three adverse points; intermediate-2, two adverse points; intermediate-1, unfavorable karyotype, platelets < 100 x 10^9/L, and transfusion need, one adverse point.

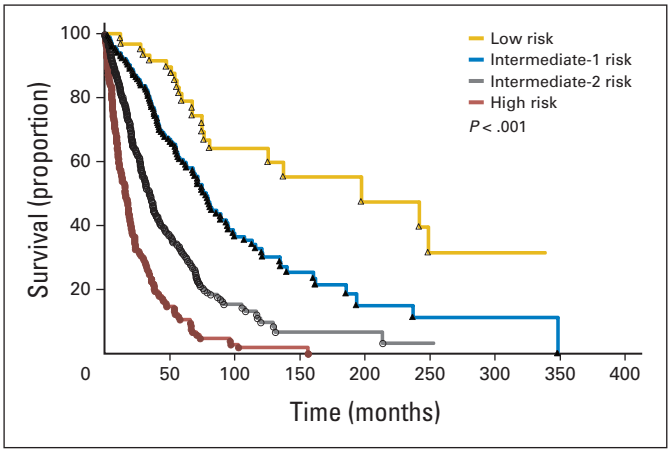

Fig 3. Survival data of 793 patients with primary myelofibrosis evaluated at time of their first Mayo Clinic referral and stratified by their Dynamic International Prognostic Scoring System (DIPSS) + karyotype + platelet count + transfusion status prognostic scores. Low risk, zero adverse points; n = 66; median survival, approximately 185 months. Intermediate-1 risk, one adverse point; n = 174; median survival, approximately 78 months. Intermediate-2 risk, two or three adverse points; n = 360; median survival, approximately 35 months. High risk, four to six adverse points; n = 193; median survival, approximately 16 months. Scale for DIPSS: high risk, three adverse points; intermediate-2, two adverse points; intermediate-1, unfavorable karyotype, platelets < 100 x 10^9/L, and transfusion need, one adverse point.

adverse risk factors measured at time of diagnosis: age older than 65 years, hemoglobin lower than 10 g/dL, leukocyte count higher than 25×10^9/L, circulating blasts ≥ 1%, and constitutional symptoms. Each one of these risk factors is assigned 1 adverse point. The presence of 0, 1, 2, and ≥ 3 adverse points defines low, intermediate-1, intermediate-2, and high-risk disease with corresponding median survivals of 11.3, 7.9, 4, and 2.3 years.[4] The International Working Group for Myeloproliferative Neoplasms Research and Treatment subsequently developed the DIPSS model that utilizes the same prognostic variables as IPSS, but can be applied at any time during the disease

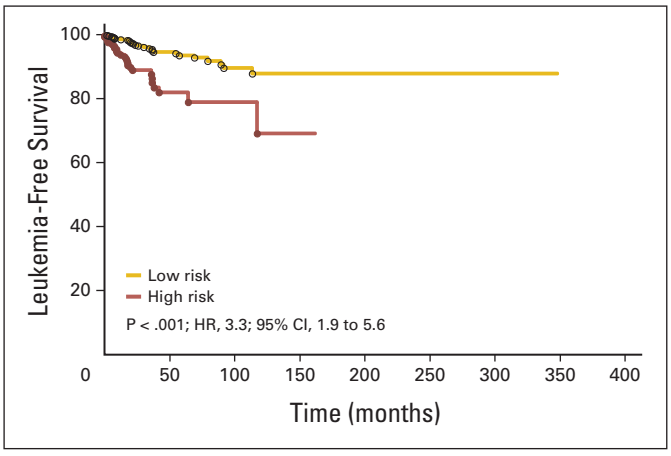

Fig 4. Leukemia-free survival data of 793 patients with primary myelofibrosis evaluated at time of their first Mayo Clinic referral and stratified by their Dynamic International Prognostic Scoring System + karyotype + platelet count + transfusion status prognostic scores. Low risk for leukemic transformation (favorable karyotype and platelets ≥ 100 x 10^9/L), n = 515; 5-year risk of leukemic transformation, 6%; 10-year risk, 12%. High risk for leukemic transformation (unfavorable karyotype or platelets < 100 x 10^9/L), n = 278; 5-year risk of leukemic transformation, 18%; 10-year risk, 31%.

course.[7] DIPSS assigns 2, instead of 1, adverse points for hemoglobin lower than 10 g/dL and risk categorization is accordingly modified to low (0 adverse points), intermediate-1 (1 or 2 points), intermediate-2 (3 or 4 points), and high (5 or 6 points); the corresponding median survivals were not reached, 14.2, 4, and 1.5 years. IPSS-independent risk factors for survival in PMF have since been described and include unfavorable karyotype (ie, complex karyotype or sole or two abnormalities that include +8, −7/7q-, i(17q), −5/5q-, 12p-, inv(3), or 11q23 rearrangement),[10] red cell transfusion need,[8] and platelet count lower than 100×10^9/L.[11] The proportion of patients with PMF with these additional risk factors, within a given DIPSS risk category, is not trivial. For example, in this study, 7%, 12% and 17% of patients categorized as low, intermediate-1, and intermediate-2 risk by DIPSS displayed unfavorable karyotype whereas the respective figures for patients with platelets lower than 100×10^9/L were 7%, 18%, and 32%.

In this study, we show that the above-mentioned IPSS-independent risk factors for survival in PMF are also DIPSS independent. Such prognostic information was effectively inserted into the DIPSS model in order to identify otherwise lower risk patients with unfavorable outcome and higher risk patients with favorable outcome (Appendix Table A1, online only). For example, the median survival of DIPSS low-risk patients with unfavorable karyotype or thrombocytopenia was 6.5 years as opposed to longer than 15 years in the absence of these two additional risk factors. Similarly, DIPSS high-risk patients with one or more of the above-mentioned risk factors carry an extremely poor prognosis with a median survival of shorter than 1.5 years as opposed to approximately 3 years otherwise. Also, according to the new prognostic model, transfusion-dependent patients are compulsorily assigned to an intermediate-2 risk category with a median survival of approximately 3 years; in the DIPSS model, such patients would have been included in intermediate-1 risk category with an expected median survival of 14 years.[7] These observations make it evident that the new prognostic model greatly enhances the ability to select the appropriate patient for a specific treatment modality. For example, the risk of alloSCT is fully justified for DIPSS plus high-, but not for DIPSS plus low-risk patients. alloSCT is also advised for DIPSS plus intermediate-2 risk patients whereas experimental drug therapy might be more appropriate for intermediate-1 risk patients with symptomatic disease.

This study also provides prognostic information for leukemia-free survival in PMF by demonstrating a respective 5- and 10-year risk of leukemic transformation at approximately 6% and 12%, for low-risk group (ie, absence of both unfavorable karyotype and platelets < 100×10^9/L). The corresponding values in the presence of one or both of these risk factors were 18% and 31%. These observations are consistent with our recent report on the prognostic value of cytogenetic studies in newly diagnosed patients where the 5-year leukemic transformation rate for unfavorable versus favorable karyotype were 46% and 7%.[10] The detrimental effect of unfavorable karyotype on leukemia-free survival in PMF has also been noted by other investigators.[15] Furthermore, in a recent MD Anderson Cancer Center study, a survival of shorter than 1 year and leukemic transformation were predicted by the presence of platelet count lower than 50×10^9/L or chromosome 17 abnormalities.[16] Similarly, in an earlier study, leukemic transformation in PMF was associated with a platelet count of lower than 100×10^9/L.[17] Transfusion need in PMF has also been

associated with an increased risk of leukemic transformation;[18] although, the particular observation was not confirmed in this study. Regardless, the additional prognostic information on leukemia-free survival in PMF might influence one to consider earlier use of alloSCT in intermediate-1 risk patients and AML-like induction chemotherapy in high-risk patients.

There are other variables of potential prognostic importance in PMF. Most noteworthy in this regard are peripheral blood blast percentage and CD34-positive cell count. In an earlier study, for example, we had shown that peripheral blood blast count of at least 3% affected both overall and leukemia-free survival.[17] This observation was consistent with the findings from a Japanese study where the presence of $\geq$ 3% circulating blasts was shown to be an independent predictor of inferior survival.[19] Similarly, in the aforementioned study from MD Anderson Cancer Center, the presence of $\geq$ 10% circulating blasts was associated with significantly shortened overall and leukemia-free survival.[16] In this study, we did not investigate the additional prognostic value of excess peripheral blood blasts because of the subjective nature of the test. The prognostic relevance of peripheral blood CD34-positive cell count is at best controversial,[20,21] and its desirability is further undermined by the lack of test standardization and questionable additional value in the context of current prognostic models.[4] Finally, recent data suggest inferior survival in PMF associated with nullizygosity for *JAK2* 46/1 haplotype[22,23] and also in patients with low *JAK2*V617F allele burden.[24,25] The value of the latter in routine clinical practice is undermined by the lack of standardized assays for measuring *JAK2*V617F allele burden. The prognostic influence of *JAK2* 46/1 haplotype was shown to be IPSS independent.[22] In contrast, the presence or absence of *JAK2*V617F[24,25] or other PMF-associated mutations, such as *IDH*[23] or *TET2*[26] mutations, did not correlate with altered survival. Regardless, it is likely that future prognostic models in PMF will include molecular or biologic markers, especially in light of recent progress in understanding disease pathogenesis.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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