CLINICS

CLINICAL SCIENCE

Primary myelofibrosis: risk stratification by IPSS identifies patients with poor clinical outcome

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OBJECTIVES: To evaluate whether risk scores used to classify patients with primary myelofibrosis and JAK-2 V617F mutation status can predict clinical outcome.

METHODS: A review of clinical and laboratory data from 74 patients with primary myelofibrosis diagnosed between 1992 and 2011. The IPSS and Lille scores were calculated for risk stratification and correlated with overall survival.

RESULTS: A V617F JAK2 mutation was detected in 32 cases (47%), with no significant correlation with overall survival. The patients were classified according to the scores: Lille - low, 53 (73.%); intermediate, 13 (18%); and high, 5 (7%); and IPSS – low, 15 (26%); intermediate-1, 23 (32%); intermediate-2, 19 (26%); and high, 15 (31%). Those patients presenting a higher risk according to the IPSS (high and intermediate-2) had a significantly shorter overall survival relative to the low risk groups (intermediate-1 and low) ($p = 0.02$).

CONCLUSIONS: These results emphasize the importance of the IPSS prognostic score for risk assessment in predicting the clinical outcome of primary myelofibrosis patients.

KEYWORDS: Primary Myelofibrosis; IPSS; Prognosis.

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INTRODUCTION

Primary myelofibrosis (PMF) is a clonal hematopoietic stem cell disorder characterized by bone marrow fibrosis, extra-medullary hematopoiesis with splenomegaly and leukoerythroblastosis in the peripheral blood (1,2). The clinical manifestations of PMF include severe anemia, marked hepatosplenomegaly and constitutional symptoms. Ineffective erythropoiesis and extra-medullary hematopoiesis are the main causes of anemia and organomegaly, respectively. Approximately 20% of patients diagnosed with PMF may present progression to acute leukemia, but most patients die of other conditions, such as cardiovascular events, or as a consequence of cytopenias, such as infections or bleeding (3).

The diagnostic criteria for this disease have been revised since the discovery in 2005 of the acquired mutation V617F in the JAK2 gene, which is found in 50-60% of patients with PMF (4). The JAKs, which include JAK1, JAK2, JAK3 and TYK, are a family of cytoplasmic tyrosine kinases that are essential for cytokine signaling and gene transcription. The JAK2V617F mutation results in the constitutive activation of JAK2 tyrosine kinase and its downstream targets, which leads to increased signaling of associated cytokine receptors and the subsequent proliferation of hematopoietic cells harboring these receptors (5). The clinical significance of the mutation is evident in that homozygosis for JAK2 V617F results in a more symptomatic illness relative to heterozygous patients. However, the prognostic significance of the mutation is controversial, including its implication in poor clinical outcomes and the risk of progression to leukemia (6).

Until recently, the most widely used prognostic classification of PMF was the Lille score, which categorizes patients into three risk groups based on the hemoglobin level and leukocyte count at diagnosis (7). However, the Lille score fails to clearly discriminate between intermediate- and high-risk prognostic categories.

Recognition of these limitations led to a multicenter study aimed at building a new International Prognostic Scoring

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System (IPSS) for PMF, in which seven European and American centers contributed data from more than 1,000 PMF patients. In the multivariate analysis, the initial features independently associated with a poor prognosis were an age older than 65 years, the presence of constitutional symptoms, hemoglobin <10 g/dL, WBC count $>25\times10^9$/L and the presence of blasts in the peripheral blood. These prognostic factors formed the basis for four risk groups with clear-cut, non-overlapping survival curves: no factors (low risk), one factor (intermediate risk-1), two factors (intermediate risk-2) or three or more factors (high risk) (8).

The IPSS demonstrated a higher discriminatory power than previous scoring systems and showed a high degree of replicability and predictive accuracy. The IPSS is based on prognostic factors recorded at the diagnosis of PMF that are not necessarily stable over the course of the disease. To address this shortcoming, a dynamic prognostic model (DIPSS) was subsequently developed, and it utilizes the same prognostic variables used in IPSS but can be applied at any time during the course of the disease (9). The DIPSS assigns two, rather than one, adverse points for hemoglobin <10 g/dL, and the risk categorization is accordingly modified: low (0 adverse points), intermediate-1 (1 or 2 points), intermediate-2 (3 or 4 points) and high (5 or 6 points).

As many patients are elderly at diagnosis or present several comorbidities, most PMF patients are managed with supportive care only. Thus, a high degree of prognostic certainty is desired to permit the recommendation of more aggressive or high-risk therapeutic procedures, and the patient's classification by prognostic score enables better therapeutic planning, especially for patients who are younger and eligible for bone marrow transplantation. Furthermore, the development of methods to assess and validate measures for clinical outcome becomes crucial in the era of targeted therapies, in which the therapeutic potential of JAK inhibitor molecules has emerged (10-12).

Thus, the aim of our study was to analyze the clinical and laboratory data of consecutive PMF cases diagnosed in a single center, focusing on the Lille and IPSS prognostic scores and comparing their applicability to predict a poor outcome.

PATIENTS AND METHODS

Seventy-four consecutive patients with primary myelofibrosis diagnosed between January 1992 and August 2011 were included in this study for retrospective analysis. The local ethics committee approved this study. All cases were reclassified according to the WHO classification. In all cases, the presence of increased reticulin and/or collagen bone marrow content without any apparent cause (such as chronic myeloid leukemia, PV, myelodysplasia, lymphoproliferative disorders, scleroderma and primary pulmonary hypertension) was required in addition to the presence of features typical of this disease, including palpable splenomegaly, leukoerythroblastosis or histological demonstration of myeloid metaplasia.

The variables selected for their prognostic significance were assessed at diagnosis and included the following: peripheral blood counts (hemoglobin, total leukocytes, platelets and circulating blasts), splenomegaly, constitutional symptoms (weight loss greater than 10% of the baseline value in the year preceding the PMF diagnosis and/or unexplained persistent fever or excessive sweating) and myelofibrosis grade on a bone marrow biopsy based on the Baumeister scale and karyotype obtained from the marrow aspirate. JAK-2 mutation status was analyzed at diagnosis or during the follow-up. The Lille and IPSS prognostic scores were also calculated (Table 1).

Table 1 - Risk models for myelofibrosis applied in the current study.

Risk model	Risk factors	Point per factor	Risk stratification
Lille	Hb <10 g/dL	1	Low: 0 points
	WBC <4 or $>30\times10^9$/l	1	Intermediate: 1 points
			High: 2 points
IPSS	Age >65 years		Low: 0 points
	Hb <10 g/dL	1	Intermediate-1: 1 points
	WBC $>25\times10^9$/l	1	Intermediate-2: 2 points
	Circulating blasts ≥1%	1	High: 3 or more points
	Constitutional symptoms	1	

Statistical analysis

Overall survival (OS) was calculated from the diagnosis until the last follow-up or death, and transformation-free survival (TFS) was calculated from diagnosis until the progression to acute myeloid leukemia, last evaluation or death. Survival curves were calculated using the log-rank test (software Winstat 3.11 Statistics for Windows, version 3.1, Kalmia Co. Inc). Correlations between thrombosis and the JAK2 mutation and between the myelofibrosis grade in the bone marrow and IPSS were evaluated using the chi-square test.

RESULTS

Patient features at presentation

The main clinical and laboratory data of the 74 patients in this study are summarized in Table 2. The median age at diagnosis was 71.5 years. The hemoglobin level was <10 g/dL in 13 patients, the WBC was $>25\times10^9$/l in eight patients and splenomegaly was found in 31 patients (42%). Cytogenetic analysis was performed in 34 patients (46%), and one case showed a partial deletion of chromosomes 13 and 15. The myelofibrosis grade based on the Baumeister scale was available in 54 patients: 13 (24%) were classified as grade 2, 27 (50%) as grade 3, and 14 (26%) as grade 4.

Treatment

Sixty-six patients (89%) received hydroxyurea (HU), which was discontinued in six cases: three patients switched

Table 2 - Clinical data of the primary myelofibrosis patients (n = 74).

Demographics/Characteristics	N
Age (median and range)	71.5 (31-92)
Presence of V617V JAK2 mutation	32 (47%)
Splenomegaly at diagnosis	31 (42%)
Hb (g/dL) (median and range)	12.2 (5.4-16.9)
Leucocytes/mm^3 (median and range)	11.4 (0.9-47.3)
>30,000/mm^3	2
<4000/mm^3	6
Platelets (median and range)	456 (76-1.545)

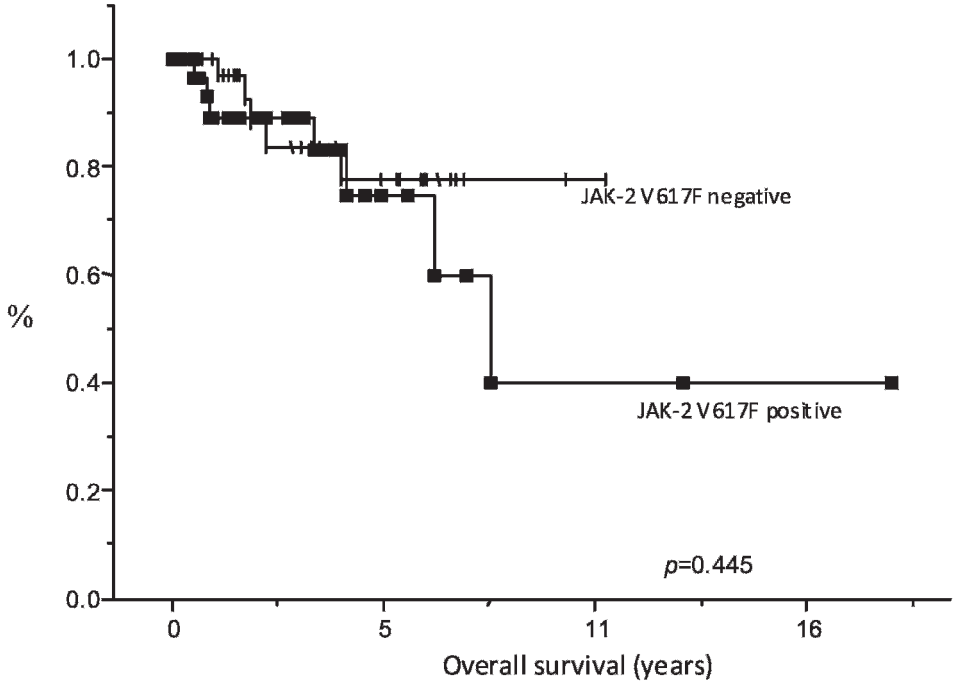

Figure 1 - Overall survival of patients according to V617F JAK2 mutation status.

to anagrelide because of toxicity (lower limb ulcers), and three patients switched to thalidomide and prednisone because of therapeutic failure. Three patients were treated only with supportive care (transfusion). Three patients received no specific treatment during the course of this study because they presented as clinically stable and had blood counts similar to the normal range.

A splenectomy was performed in two patients, and three others received splenic radiotherapy to control the symptoms. Only one patient was eligible for allogeneic bone marrow transplantation, and he achieved complete remission, which was maintained by the end of this study (15 months of disease-free survival).

Thrombotic events were observed in 13 (18%) patients (arterial occlusion in seven and venous thrombosis in six); only one event occurred during thalidomide treatment. There was no other relationship between these events and the therapy applied or any other clinical or laboratory variable.

V617F JAK2 mutation analysis

A V617F JAK2 mutation was detected in 32 cases (47%). Patients with the mutation presented a shorter overall survival (39% *vs.* 77%), although this difference was not significant ($p = 0.448$) (Figure 1).

Risk stratification and clinical endpoints

According to the Lille score, most patients presented a low risk (73.5%) (Table 2). The IPSS classification is described in Table 3.

During the analysis period, 15 deaths were recorded: nine due to infectious complications, three after a blast crisis (occurring a median of 45 months after the diagnosis), and three others by causes not related to the disease.

According to the Lille classification, no significant difference was observed in overall survival (Figure 1). However, in the IPSS data, 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) ($p = 0.02$) (Figure 2).

There was no significant difference in overall survival when patients were stratified according to myelofibrosis grade ($p = 0.81$). We did not find a correlation between myelofibrosis grade and IPSS score ($p = 0.59$).

DISCUSSION

Myelofibrosis is a myeloproliferative stem cell disorder that is curable exclusively by allogeneic hematopoietic stem cell transplantation. It also has substantial patient morbidity and mortality, which results in an important need for improved therapies. Recent advances in the understanding of the pathogenetic mechanisms underlying this disease have led to many clinical trials evaluating novel therapies, such as ruxolitinib, which is the first JAK2 inhibitor approved by the FDA for the treatment of patients with intermediate- or high-risk myelofibrosis (13-15). Clinical trials of these compounds have demonstrated improvement

Table 3 - Risk stratification according to the Lille and IPSS scores.

IPSS	N
Low	15 (26%)
Intermediate-1	23 (32%)
Intermediate-2	19 (26%)
High	15 (31%)
Lille	
Low	53 (73.5%)
Intermediate	13 (18%)
High	5 (7%)

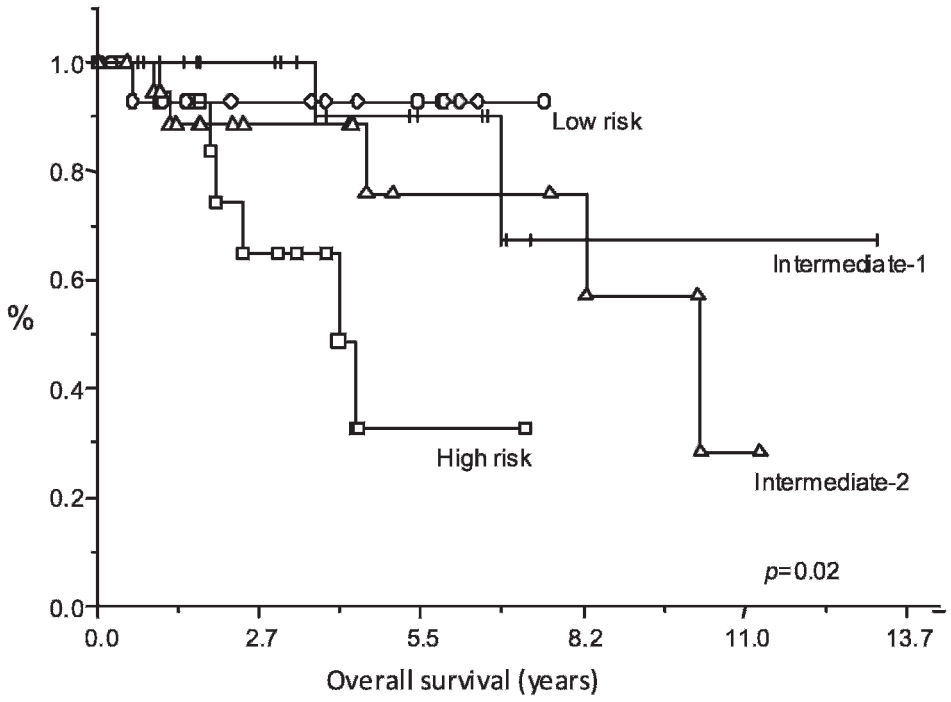

Figure 2 - Overall survival of patients according to the IPSS.

in constitutional symptoms and splenomegaly in patients with both mutated and wild-type JAK2 PMF (16,17).

However, the development and validation of useful tools to determine the prognosis and estimate survival is necessary for better management of these patients. Although the association was not significant, our findings suggest that positivity for the JAK2 (V617F) mutation in our group of patients may be associated with poorer survival. Published data regarding the role of the *JAK2* (V617F) mutation in the prediction of the survival of PMF patients reveal contradictory results. Campbell et al. showed that patients positive for the mutation had a shorter overall survival, even after correction for confounding factors ($p = 0.01$) (18). However, a recent study showed that a positive qualitative test for the V617F mutation does not predict survival but that patients with a lower V617F allele burden presented a worse survival, which most likely indicates the presence of an overriding V617F-negative clone that confers a more aggressive disease phenotype (19,20).

Although important for the differential diagnosis of PMF with ET, the myelofibrosis grade based on the Baumeister scale was not correlated with survival or the IPSS score. Most of our patients presented with grade 3 or 4 (76%).

Our study also demonstrated that the IPSS is an appropriate method for identifying patients with a worse overall survival, which agrees with data from other studies (8,9,21). Patients classified as high-risk (high and intermediate-2 scores) showed a significantly lower overall survival than low-risk patients (intermediate-1 and low scores). In addition to demonstrating the efficacy of the IPSS for prognosis evaluation in myelofibrosis, our results also demonstrate the limitations of the Lille score in determining risk for patients with a more severe disease. The Lille score model was initially designed using 195 patients with PMF. As described in other studies, the Lille score is capable of identifying a well-defined group of patients with a good prognosis but fails to clearly identify patients with a very poor prognosis and those with an intermediate prognosis. This issue may be partially explained by the reliance of the score on the hemoglobin level because leukopenia and leukocytosis greater than 30×10^9/L are infrequent at the time of the PMF diagnosis (8,22). In fact, in our population, only two patients presented leukocytosis greater than 30×10^9/L, and six presented with leukocytosis $<4\times10^9$/L at diagnosis.

These findings corroborate the evidence indicating that the IPSS must be evaluated for all patients recently diagnosed as having PMF. In addition to predicting survival, it is a helpful tool to evaluate therapeutic options; it is easy to calculate and requires the evaluation of only simple clinical and laboratory data. Other clinical trials should be encouraged to better evaluate the influence of the IPSS score in predicting the response to the new drugs available for the treatment of PMF.

In summary, this study confirmed the importance of the IPSS for risk factor stratification. Adjunctive treatment with hydroxyurea is able to control low-risk patients in the cellular phase of the disease. However, patients with intermediate- and high-risk disease are candidates for other therapeutic approaches, such as bone marrow transplantation or experimental drug therapies.

AUTHOR CONTRIBUTIONS

Benites BD contributed to the study conception and design, data collection, analysis and interpretation. Pagnano KB and Lorand-Metze I contributed to the study conception and design, data analysis and interpretation. Lima CS contributed to data collection, analysis and interpretation. Delamain MC, Oliveira GB, Souza CA and Vassallo J contributed to data analysis and interpretation. Almeida D contributed to the JAK2 mutation analysis. All authors helped in the collection or assembly of data, analysis and

interpretation of data and critical revision of the article for important intellectual content.

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