A DYNAMIC PROGNOSTIC MODEL TO PREDICT SURVIVAL IN POST-POLYCYTHEMA VERA MYELOFIBROSIS.

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Short title: Prognosis in post-PV MF

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Abstract

Post-polycythemia vera myelofibrosis (post-PV MF) is a late evolution of PV. Within 647 patients with PV we found that leukocytosis (white blood cell count >15 x10^9/L) at diagnosis is a risk factor for the evolution in post-PV MF. In a series of 68 patients who developed post-PV MF median survival was 5.7 years. Hemoglobin level <10 g/dL at diagnosis of post-PV MF was an independent risk factor for survival. The course of post-PV MF, however, is a dynamic process that implies a progressive worsening of clinical parameters. Using a multivariate Cox proportional hazard regression with time-dependent covariates, we found that a dynamic score based on hemoglobin <10 g/dL, platelet count <100 x10^9/L, and white blood cell count >30 x10^9/L is useful to predict survival at any time from diagnosis of post-PV MF. The resulting hazard ratio of the score was 4.2 (95% CI: 2.4-7.7; \( P < .001 \)), meaning a 4.2-fold worsening of survival for each risk factor acquired during follow-up. In conclusion, leukocytosis at diagnosis of PV is a risk factor for evolution in post-PV MF. A dynamic score based on hemoglobin level, platelet and white blood cell count predicts survival at any time from diagnosis of post-PV MF.
Introduction

Post-polycythemia vera myelofibrosis (post-PV MF) is a recently named condition,\(^1\) that represents the natural evolution of patients with polycythemia vera (PV).\(^2\) The criteria proposed for the diagnosis of post-PV MF\(^1\) set the time-point of evolution along the natural history of the disease. Patients’ survival after transition to MF, as well as the prognostic factors for survival, are not defined.

Post-PV MF is a delayed event in the course of PV. No risk factors for this condition have been identified so far. In patients with PV, the 15-year risk of evolution to myelofibrosis is estimated at 6% and the incidence is 5.1 x1000 person-years.\(^3\) A similar figure is reported in young patients with PV.\(^4\) Patients with post-PV MF have a high rate of detection of the JAK2 (V617F) mutation ranging from 91%\(^5\) to 100%.\(^6\) Concerning the JAK2 (V617F) mutation burden, patients with post-PV MF have the highest proportion of mutant alleles within patients with chronic myeloproliferative disorders (CMD).\(^6\) An abnormal stem cell trafficking has been reported in patients with post-PV MF.\(^7\)-\(^9\) JAK2 (V617F) may activate circulating granulocytes playing a role in the constitutive mobilization of CD34\(^+\) cells into peripheral blood. This phenomenon is particularly evident in patients with PV and post-PV MF.\(^6\)

Current treatments for patients with post-PV MF do not affect survival and are considered palliative.\(^1^0\) Allogeneic hematopoietic stem-cell transplantation is the only curative treatment for post-PV MF. Only few patients, however, have been treated with fully ablative\(^1^1\) or reduced-intensity conditioning allogeneic transplantation.\(^1^2\) Clinical trials on JAK2 inhibitors are still under way.\(^1^3\)

Within a cohort of 647 patients with PV, 68 developed post-PV MF according to the criteria of the International Working Group on Myelofibrosis Research and Treatment (IWG-MRT).\(^1\) The aim of this study is to define survival of patients with post-PV MF and to identify prognostic factors for survival. We developed a dynamic prognostic model useful to predict survival at any time from diagnosis.
Patients, materials, and methods

Patients

Within 76 consecutive patients previously diagnosed as post-PV MF, systematic revision of clinical and histopathologic records identified 68 patients fitting diagnostic criteria for post-PV MF established by the IWG-MRT. Patients were followed from 1982 to 2007 at the Division of Hematology of the Fondazione Policlinico San Matteo, University of Pavia, and at the Division of Hematology of the Niguarda Ca’ Granda Hospital, Milan, Italy. Patients of the two Institutions were well matched with regard to baseline demographic and disease characteristics. The diagnosis of PV and of primary myelofibrosis (PMF) was made in accordance with the criteria in use at the time of first observation. The study was approved by the institutional ethics committee of Pavia, and the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Samples for molecular analysis were obtained after patient provided written informed consent.

JAK2 (V617F) mutational analysis

Granulocytes were obtained from the neutrophil fraction by osmotic lysis of red cells. Genomic DNA was obtained by using the Puregene Blood DNA isolation kit (Gentra Systems, Minneapolis, MN). A quantitative real-time polymerase chain reaction-based allelic discrimination assay was used to detect the V617F mutation of JAK2 gene.

Flow cytometric analysis of circulating CD34+ cells

Circulating CD34+ cells were enumerated by flow cytometry using a single-platform assay as previously described, following the cell-gating guidelines recommended by the International Society for Hematotherapy and Graft Engineering (ISHAGE) and the subsequent modifications of the European Working Group of Clinical Cell Analysis (EWGCCA). Daily instrument quality control, including fluorescence standardization, linearity assessment, and spectral compensation were performed to ensure identical operation from day to day.
Statistical analysis

The cumulative probability of survival was estimated using the Kaplan-Meier method. Comparison between survival curves was performed using the Gehan-Wilcoxon test. Survival analysis was performed using Cox models with time-dependent covariates to assess the effect of the variables of interest on overall survival (OS). Cox regression models were also applied to carry out multivariate survival analyses. Standardized mortality ratios (SMR) were calculated to compare the patients’ mortality with the mortality of the general population in Italy. The Italian mortality rates by age, sex, and calendar year were provided by the Istituto Nazionale di Statistica (ISTAT). Statistical analyses were performed using Microsoft Excel 2000 (Redmond, Washington), Statistica 7.1 (Stat-Soft Inc., Tulsa, Oklahoma), and Stata 9.2 (StataCorp, College Station, Texas).

Results

Disease information prior to post-PV MF

A total of 647 patients with PV were evaluated at the two Institutions between 1970 and 2007. The median interval between the diagnosis of PV and that of post-PV MF was 13 years (range, 2.4-29.6 years). We found that the longer the follow-up of patients with PV, the higher the risk of developing post-PV MF (P < 0.001). During PV, myelosuppressive agents were given to 65 (96%) of 68 patients who developed post-PV MF and to 501 (86.4%) of 579 patients who did not, while the remaining patients received phlebotomy alone. The rate of patients receiving myelosuppression was significantly higher among those who developed post-PV MF (P = 0.01). On the other hand, patients receiving myelosuppression had a significantly longer follow-up than those treated with phlebotomy alone (7.1 years and 2.9 years, respectively; P < 0.001).

To investigate potential risk factors of transformation in post-PV MF present at diagnosis of PV, we evaluated the clinical features at diagnosis in the whole cohort of patients (n= 647). Parameters taken into account were: age, hemoglobin level, platelet count, white blood cell count, spleen size, (all considered as continuous numerical variables), leukocytosis (white blood cell count >15 x10^9/L), calendar year at diagnosis and institutional location. Univariate survival analysis showed that white blood cell count as numerical variable (P
<0.001) and white blood cell count >15 x10^9/L (P = 0.002) were significant risk factors for transformation in post-PV MF.

**Clinical features at diagnosis of post-PV MF**

Table 1 summarizes clinical and hematological data at diagnosis of 68 patients with post-PV MF. IWG-MRT criteria and patients’ distribution per single criterion are outlined in Table 2. Regarding spleen, one patient underwent splenectomy before diagnosis of post-PV MF. Another patient with no spleen enlargement at diagnosis of post-PV MF showed anemia and leuko-erythroblastic peripheral picture in addition to required criteria. Among 47 patients studied for the JAK2 (V617F) mutation at different intervals from diagnosis, all carried the mutation. Within 27 patients evaluated at diagnosis, 21 (78%) had more than 50% mutant alleles. In all patients, the number of circulating CD34+ cells and serum lactate dehydrogenase (LDH) level exceeded the upper reference value (10 cells /µL for CD34+ cells and 450 mU/mL for LDH).

**Disease complications and outcome**

Patients with post-PV MF were observed for 181 person-years of follow-up after diagnosis and received palliative treatments. During follow-up, the incidence of thrombosis was 42 x1000 person-years (95% CI: 19-93.5): three patients had deep venous thrombosis, two had stroke and one myocardial infarction. Two patients had splenic infarction. The incidence of leukemia was 50 x1000 person-years (95% CI: 26-115) and the 3-year leukemia-free survival was 82%. Univariate analysis performed on clinical parameters at diagnosis of post-PV MF identified as significant risk factors for leukemia the low platelet count (P = .041) and the high circulating CD34+ cell count (P = .016). In a multivariate Cox proportional hazard regression, only circulating CD34+ cell count retained a significant impact on leukemia-free survival (P = .036).

The median survival of patients with post-PV MF was 5.7 years. The standardized mortality ratio (SMR) was 6.5 (95% CI: 4.2-10.1), indicating a significantly higher mortality for patients with post-PV MF in comparison with the general Italian population matched for age, sex, and calendar year (P < .001). We compared the survival of patients with post-PV MF (mortality: 11.1 per 100 person-years) with the survival of 291 patients with PMF...
(mortality: 10.1 per 100 person-years). Gehan-Wilcoxon test showed that survival of patients with post-PV MF was not significantly different from that of patients with PMF \( (P = .32) \). Also after adjustment for white blood cell count, hemoglobin level, platelet count, spleen size and age in a multivariate Cox proportional hazard regression model, there was no difference in survival between the two conditions.

Finally, to evaluate whether transformation to myelofibrosis affects the overall survival of patients with PV, a Cox proportional hazard regression model with transformation to myelofibrosis as time-dependent covariate was applied to the whole series of PV patients. We found that survival of patients with PV was significantly worsened after progression to post-PV MF \( (HR= 2.17; 95\% \text{ CI}: 1.27-3.72; P = .005) \). This finding retained statistical significance also after adjustment for age, white blood cell count, hemoglobin level, platelet count, spleen size in a multivariate Cox proportional hazard regression model.

**Prognostic factors at diagnosis of post-PV MF**

The parameters we evaluated at diagnosis of post-PV MF to investigate potential predictors of survival were: age, hemoglobin level, platelet count, white blood cell count, spleen size, year-duration of PV, serum lactate dehydrogenase level, granulocyte JAK2-V617F mutation burden, circulating CD34+ cells (all considered as continuous numerical variables), hemoglobin value <10 g/dL, white blood cell count <4 x10^9/L, platelet count <100 x10^9/L, platelet count >30 x10^9/L, platelet count <100 x10^9/L, karyotype (according to the categorization in use for PMF). Univariate survival analysis showed that hemoglobin value <10 g/dL \( (P < .001) \) and circulating CD34+ cell count \( (P = .009) \) were significant risk factors for survival. Multivariate Cox regression model including the parameters available in all patients at diagnosis of post-PV MF (hemoglobin value, white blood cell count, platelet count, spleen size, age) indicated that only hemoglobin <10 g/dL was an independent risk factor for survival \( (P < .001) \). Using this hemoglobin level as cut-off, patients could be stratified into two risk categories with significantly different survival: 6.6 years for those with hemoglobin value ≥10 g/dL and 1.9 years for those with hemoglobin value <10 g/dL \( (P = .0001) \).

**Time-dependent analysis of prognostic factors**
Sixty-four patients with post-PV MF had longitudinal blood cell count measurements at regular intervals from diagnosis. We studied this cohort of patients to assess whether variation of hematological parameters during follow-up may further help in predicting survival at any time from diagnosis. The acquisition of the following parameters was studied: hemoglobin level <10 g/dL, platelet count <100 x10^9/L, white blood cell count <4 x10^9/L or >30 x10^9/L. Modification of therapy was not involved in the acquisition of risk factors. During follow-up of post-PV MF, hemoglobin level dropped below 10 g/dL in 17 (26%) patients, platelet count below 100 x10^9/L in 23 (36%), white blood cell count below 4 x10^9/L in 7 (11%) and above 30 x10^9/L in 14 (22%).

As a first step, we evaluated univariate survival analysis with Cox regression models using hemoglobin value <10 g/dL, platelet count <100 x10^9/L, white blood cell count <4 x10^9/L and white blood cell count >30 x10^9/L as time-dependent covariates. The HRs were 5.8 (95% CI: 2.2-15.2; \( P < 0.001 \)) for hemoglobin, 4.5 (95% CI: 1.67-12, \( P = .003 \)) for platelets, 8.2 (95% CI: 3-22; \( P <.001 \)) for white blood cells >30 x10^9/L, while white blood cells <4 x10^9/L did not significantly affect survival (\( P = .115 \)). After adjustment for age in a multivariate Cox proportional hazard regression with time-dependent covariates, hemoglobin value <10 g/dL, platelet count <100 x10^9/L and white blood cell count >30 x10^9/L retained statistical significance on survival.

So, we defined a dynamic scoring system based on these three independent risk factors. As the 95% CIs of the three HRs did not differ, we assigned the same weight (presence = 1; absence = 0) to the three factors. As a consequence, the resulting score can be easily calculated by simply counting the number of risk factors acquired at any time during follow-up. The lower risk group includes patients who never acquire risk factors during follow-up (i.e. hemoglobin \( \geq \) 10 g/dL, platelets \( \geq \) 100 x10^9/L and white blood cells <30 x10^9/L). Conversely, higher risk categories include patients with one, two, or three risk factors, respectively. To assess the impact on survival of this dynamic scoring system, we analyzed the score as a continuous time-dependent covariate in a Cox survival regression model, obtaining a HR of 4.2 (95% CI: 2.4-7.7; \( P < .001 \)). This implies a 4.2-fold increase of risk when the patient acquires one risk factor at any time from the diagnosis of post-PV MF. The time-dependent prognostic model retained statistical significance after adjustment for age (HR: 6.7, 95% CI: 3-14.7; \( P < .001 \)). Figure 1 exemplifies the impact of this
dynamic prognostic model on survival, showing the estimated survival curves for the resulting four risk groups according to the Cox time-dependent model.

Discussion

In this study we evaluated 68 patients who developed post-PV MF within a cohort of 647 patients with PV. Diagnosis of post-PV MF is based on distinctive criteria, recently proposed by the IWG-MRT. These criteria combine histopathological (bone marrow fibrosis), clinical (splenomegaly, constitutional symptoms), and hematological findings (anemia, leukoerythroblastic peripheral blood picture).

In this series of 647 patients with PV, the analysis of risk factors that may predict transformation to post-PV MF showed that the presence of leukocytosis (white blood cell count $> 15 \times 10^9$/L) at diagnosis of PV significantly correlates with post-PV MF occurrence. A correlation between leukocytosis and risk of acute leukemia has been recently reported in patients with PV. These data indicate that PV patients with leukocytosis are at higher risk of disease evolution. This suggests that within PV patients those with leukocytosis are the most appropriate candidates for clinical trials with JAK2 inhibitors.

A not yet defined issue in the natural history of PV concerns whether the development of post-PV MF has adverse prognostic implication on survival. Using a Cox proportional hazard regression model, with transformation to post-PV MF as time-dependent covariate, our data indicates a worsening of overall survival of patients with PV after fibrotic transformation.

Studying the 68 patients of this series who developed post-PV MF, we found that all patients with available JAK2 (V617F) status carried the mutation with a high mutational burden. In fact, 78% of patients at diagnosis of post-PV MF had more than 50% mutant alleles, as previously reported. In PMF, the rate of homozygosity for JAK2 (V617F) has been recently reported to be 28%. Constitutive mobilization of CD34+ cells into peripheral blood represents a frequent phenomenon in post-PV MF and all patients tested in this study had high circulating CD34+ cell count. Serum LDH measurement has been recently introduced in the proposed revision of WHO criteria for CMD as additional criterion to
diagnose PMF. All patients in this series with post-PV MF had high levels of serum LDH, highlighting the clinical utility of this parameter in these patients.

Regarding disease complications of patients with post-PV MF, this study shows that thrombosis remains a relatively frequent complication in PV patients also after transition to myelofibrosis. Leukemia occurs with an incidence of 50 \times 1000 \text{ person-years} and circulating CD34$^+$ cell count at diagnosis of post-PV MF may predict leukemia-free survival. The frequency of leukemic transformation in patients with post-PV MF seems higher than that reported in patients with PMF.

In this study, the median survival of patients with post-PV MF was 5.7 years, slightly lower than that reported in a study including patients with post-PV and post-essential thrombocythemia MF. To better stratify patients, we studied potential risk factors for survival at diagnosis of post-PV MF. Using a multivariate Cox proportional hazard regression, we found that an hemoglobin level $<10$ g/dL is an independent risk factor for survival. In fact, patients with hemoglobin value $\geq 10$ g/dL had a median survival of 6.6 years, while those with hemoglobin value $<10$ g/dL had a median survival of 1.9 years. The cut-off of 10 g/dL for hemoglobin is also considered useful in the risk stratification of patients with PMF. Another common behaviour between patients with post-PV MF and those with PMF is survival, that we found similar in the two conditions. Regarding the adverse impact of unfavourable karyotype on survival reported in a prior study, we did not find a significant correlation in our series of patients with post-PV MF. This may probably reflect the small number of patients with unfavourable karyotype or the different patient population.

The course of post-PV MF is a dynamic process during which progressive deterioration of clinical parameters occurs. This may imply the acquisition of additional risk factors. In fact, hemoglobin and platelets progressively tend to decrease, while leukocytes tend either to increase or to decrease. On this ground, we developed a time-dependent scoring system that can be used to predict survival at any time after diagnosis. According to this model, patients are classified into a risk group at diagnosis and remain in the same group until the acquisition of new risk factors. At this time-point patients enter a higher risk category. We provide evidence that a dynamic scoring system based on hemoglobin $<10$ g/dL, platelet count $<100 \times 10^9$/L and white blood cell count $>30 \times 10^9$/L is useful to predict survival at any
time from diagnosis. In fact, the score predicts a 4.2-fold worsening of survival for each risk factor acquired at any time during follow-up of post-PV MF. The survival curves resulting from this dynamic model have to be interpreted differently from traditional survival curves. In fact, the survival curves of the dynamic model represent an estimated survival as long as the patient remains in the same risk group. A more accurate prediction of survival has potential clinical implications, as these patients are JAK2 mutated and may be candidates to clinical trials with JAK2-inhibitors.

In conclusion, this study demonstrates that patients with PV showing a white blood cell count >15 x10^9/L at diagnosis have higher risk of developing post-PV MF. When patients with PV develop post-PV MF, a dynamic prognostic model based on hemoglobin level, platelet count, and white blood cell count may predict survival at any time after diagnosis.

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Contributions. F.P. and M.L conceived the study, collected, analyzed, interpreted data, wrote the paper; E.M. and M.C. analyzed and interpreted data; E.R. collected and analyzed data; M.C., C.E., L.A., C.D. collected clinical data; E.B: performed bone marrow evaluation; D.P. performed JAK2 mutation analysis; L.V. performed CD34+ cell count; P.B. performed cytogenetic analysis; C.P. did statistical analyses.

The authors have no potential conflict of interest to disclose.
Table 1: Demographic and hematological characteristics at diagnosis of 68 patients with post-polycythemia vera myelofibrosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>Median (range)</th>
</tr>
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<tbody>
<tr>
<td>No. of patients</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, years, median (range)</td>
<td>65 (44-81)</td>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
<td>45/23</td>
<td></td>
</tr>
<tr>
<td>WBC count, x 10^9/L, median (range)</td>
<td>12.2 (2.3-98)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin level, g/dL, median (range)</td>
<td>12.3 (7.8-14.8)</td>
<td></td>
</tr>
<tr>
<td>PLT count, x 10^9/L, median (range)</td>
<td>369 (50-1827)</td>
<td></td>
</tr>
<tr>
<td>Spleen size, cm below left costal margin</td>
<td>7 (0-25)</td>
<td></td>
</tr>
<tr>
<td>Bone marrow findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median marrow cellularity, % (range)</td>
<td>90 (70-100)</td>
<td></td>
</tr>
<tr>
<td>Reticulin fibrosis, grade 2 : grade 3</td>
<td>3 : 1</td>
<td></td>
</tr>
<tr>
<td>MK cluster, loose : dense</td>
<td>0.6 : 1</td>
<td></td>
</tr>
<tr>
<td>Median marrow myeloblast, % (range)</td>
<td>0 (0-5)</td>
<td></td>
</tr>
<tr>
<td>Lactate dehydrogenase, mU/mL, median (range) (n=41)</td>
<td>837 (460-3151)</td>
<td></td>
</tr>
<tr>
<td>Circulating CD34^+ cells/µL, median (range) (n=39)</td>
<td>44.3 (12.1-1005)</td>
<td></td>
</tr>
<tr>
<td>No. JAK2 (V617F)-positive, (%) (n=27)</td>
<td>27 (100%)</td>
<td></td>
</tr>
<tr>
<td>Proportion of JAK2 (V617F) alleles, % median (range)</td>
<td>87 (10-100)</td>
<td></td>
</tr>
<tr>
<td>*Bone marrow karyotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable</td>
<td>20 (80%)</td>
<td></td>
</tr>
<tr>
<td>Unfavourable</td>
<td>5 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

*Bone marrow karyotype:
- Favourable: normal, 20q-; 13q-23;
- Unfavourable: other than favourable;
- normal range of circulating CD34^+ cells: <10/µL;
- normal range of LDH: < 450 mU/mL.
Table 2: International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria for the diagnosis of post-polycythemia vera myelofibrosis (post-PV MF) and the distribution of meeting criteria in 68 patients with post-PV MF.

<table>
<thead>
<tr>
<th>IWG-MRT required criteria</th>
<th>N. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Previous diagnosis of polycythemia vera (WHO criteria)</td>
<td>68 (100%)</td>
</tr>
<tr>
<td>2. Bone marrow fibrosis grade 2–3 (on 0–3 scale)</td>
<td>68 (100%)</td>
</tr>
</tbody>
</table>

**IWG-MRT additional criteria (two are required)**

| 1. Anemia* or | Sustained loss of requirement of phlebotomy or cytoreduction | 43 (63%) |
| 2. Leukoerythroblastic peripheral blood picture | 68 (100%) |
| 3. Increasing splenomegaly: | 66/67 (98%)** |
| Palpable spleen >5 cm from left costal margin | 54 (82%) |
| Appearance of a newly palpable splenomegaly | 12 (18%) |
| 4. Development of ≥1 of three constitutional symptoms** | 26 (38%) |

* defined as hemoglobin value <12 g/dL for female and <13.5 g/dL for male

** one patient underwent splenectomy before diagnosis: so, the calculation was provided on 67 patients

*** defined as: ≥10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)
Legend to Figure

Figure 1. Time-dependent survival estimation in post-polycythemia vera myelofibrosis.
Survival curves estimated from the Cox proportional-hazard regression with time-dependent covariates. According to the model, each patient is initially assigned to a risk group and followed in that group as long as no changes in risk factors take place. The patient is reassigned to another risk group whenever further risk factors are acquired. So, each patient may contribute with some observation time to the estimate of survival in different risk groups. Therefore, the upper curve includes patients who did not acquire any risk factors during the whole follow-up (i.e. hemoglobin level ≥10 g/dL, platelet count ≥100 x10^9/L, white blood cell count <30 x10^9/L). The other curves include patients who acquired one, two, or three factors during follow-up.
References


A dynamic prognostic model to predict survival in post-polycythemia vera myelofibrosis

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