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"Agene": Using age and mutation status to accurately predict survival outcome in patients with primary myelofirborsis

Primary myelofibrosis (PMF) is a rare form of cancer of the bone marrow in which abnormal proliferation of blood-producing cells result in replacement of the marrow with a scar tissue ("fibrosis"). The course of PMF is variable. Some patients experience a rapidly progressive disease and die in less than one year whereas other patients live 10 years or more. Overall, the median survival of patients with PMF is 5 years.

Several investigators use various complicated prognostic measures to predict PMF patients' survival. The international prognostic scoring system (IPSS) stratify patients into 4 risk groups based on age more than 65 years, presence of constitutional symptoms, hemoglobin less than 10 g/dL, WBC more than 25 X 10^9/L and circulating blasts cells > 1%. Based on the IPSS, the dynamic IPSS (DIPSS) was developed and accounts for acquisition of risk factors over time. Another refinement of the model, proposed by the Mayo Clinic group, incorporates into this model adverse karyotype, transfusion dependency and thrombocytopenia.

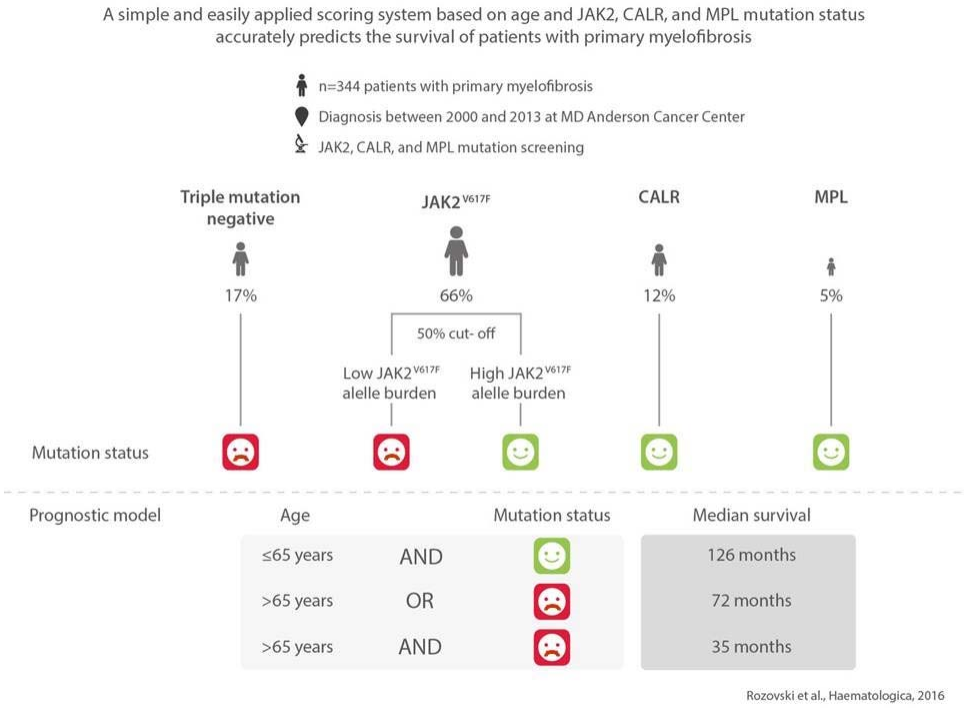

Fig. 1.

Hematopoietic cells of most PMF patients carry mutually exclusive mutations in one of 3 genes. An activating mutation in the Janus kinase-2 (*JAK2*) gene is detected in approximately 60% of patients. A frameshift mutations in exon 9 of the calreticulin (*CALR*) gene is detected in 20% of patients, and an activating mutation in the thrombopoietin receptor (*MPL*) gene is detected in 5% of PMF patients.

Conversely, none of those mutations can be identified in 15% to 20% of PMF patients. Those patients are termed “triple negative”. Overall, the survival of patients with mutated *CALR* is longer than that of patients with mutated *JAK2*. However, the survival of patients with mutated *JAK2* is not homogenous and is inversely correlated with the mutated *JAK2* allele burden. The higher the *JAK2* allele burden the shorter the patients’ survival.

Due to the heterogenous outcome of patients with mutated *JAK2*, mutation status *per se* is not a useful tool for patients’ classification. To develop a simple applicable prognostic model that incorporates genetic information, we analyzed the clinical and laboratory characteristics, including *JAK2*, *CALR* and *MPL* gene mutation status of 344 patients with PMF. Mutated *JAK2* was identified in 226 patients (66%). Mutated *CALR* in 43 patients (13%) and mutated MPL in 16 (4%). 59 patients (17%) were triple negatives. Based on the *JAK2* allele burden, our model split the heterogenous group of patients with mutated *JAK2* into two groups. The median survival of patients with mutated *JAK2* allele burden of 50% or higher was 80 months, whereas the median survival of patients with less than 50% was only 50 months. Based on *CALR* and *Mpl* mutation status and *JAK2* allele burden we split the entire cohort into two groups. Patients with mutated *MPL*, mutated *CALR* or high mutated *JAK2* allele burden had favorable prognosis. Conversely, patients with low mutated *JAK2* allele burden or triple negatives had unfavorable prognosis. Intriguingly, a prognostic model that incorporates only mutation status and age (“Agene”) surpassed the power of DIPSS to predict survival outcome in our cohort. Furthermore, none of the other components of the DIPSS improved the predictive power of our prognostic model. Patients with a favorable mutation status and age below 65 had a median survival of 126 months. Patients with one risk factor, either age above 65 or adverse mutation status had an intermediate survival expectancy. The two risk factors were additive: Patients older than 65 years with adverse mutation status had a median survival of only 35 months (Fig. 1).

Hence, in patients with PMF, age and *JAK2*/*CALR* /*Mpl* mutation status are independent predictors of survival. Based on these variables we developed the “Agene” prognostic model which stratifies PMF patients into 4 groups of equal size with distinct survival outcome.

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