Discrepancies of applying primary myelofibrosis prognostic scores for patients with post polycythemia vera/essential thrombocytosis myelofibrosis

Myelofibrosis (MF) is a clonal Philadelphia negative myeloproliferative neoplasm that is associated with cytopenias, splenomegaly, a heterogeneous symptom profile, and decreased overall survival.[1] Accurate prognostication of MF is essential for clinical decision making, as survival estimates often tip the scales toward or away from consideration of allogeneic stem cell transplant. As our biological and molecular understanding of MF has evolved over recent decades, so too have the prognostic classification systems associated with the disease. Current multiple prognostic scoring systems leave the clinician uncertain as to which system is most informative and clinically useful. In addition, it is still unclear whether the systems produce comparable scores if used interchangeably. Here we report on the agreement between two available risk prognostication tools in post-polycythemia vera and essential thrombocytosis (PV/ET) MF. We compare the Dynamic International Prognostic Scoring System (DIPSS),[2] developed for primary MF which is currently the most frequently used tool in clinical practice, with the post-polycythemia vera MF[3] risk stratification model, a model specific to secondary MF.

At a single academic medical center, a retrospective chart review was conducted for patients with post-PV/ET MF seen between 2000-2012. Descriptive statistics were used to describe patients' demographic and clinical variables in post PV/ET patients. One hundred and five patients were identified, with 61 patients (58%) harboring the diagnosis of post-ET MF and 44 patients (42%) with post-PV MF. The male to female ratio was 1:1. Median age was 65 years (range 25-87). Jak V617F positivity was noted in 68 patients (65.4%). Median hemoglobin was 10.9 g/dL (range 5.3-17.0), median platelet count was 287x10^9 (range 20-1864), and median white blood cell (WBC) count was 11.1 (range 1.1-165) (Table 1).

The DIPSS score was calculated at time of last follow up: age over 65 (1 point), hemoglobin less than 10 g/dL (2 points), leukocytes over 25x10^9 (1 point), circulating blasts 1% (1 point) and constitutional symptoms (1 point). The risk group was then assigned *per* published guidelines: low-risk (0 adverse points), intermediate-1 risk (1 adverse point), intermediate-2 risk (2-3 adverse points) and high-risk (4-6 adverse points). In the same patient cohort, and during the same time interval, post-PV risk scores were calculated at time of last follow up: hemoglobin level less than 10 g/dL (1 point), platelet count less than 100x10^9/L (1 point), and/or leukocyte count more than 30x10^9/L (1 point). The risk score was then assigned: low-risk (0 adverse points), intermediate-1 risk (1 adverse point), and intermediate-2 risk (2 adverse points), and high-risk (3 adverse points) (Table 2).

When DIPSS risk scores were applied, 11 patients were low, 48 were intermediate-1, 31 were intermediate-2, and 10 were high. When post-PV risk scores were applied 57 patients received score of 0, 31 patients scored 1, 9 patients scored 2, and 3 patients scored 3. Cross-tabulation of DIPSS score *versus* post-PV risk score at time of last follow up was conducted. Percent agreement and weighted κ coefficient were calculated. The overall agreement between DIPSS and post-PV risk scores was low, with 24% of cases in agreement. Weighted κ coefficient was 0.135 [95% confidence interval (CI) 0.047, 0.223], representing poor agreement beyond chance. (See Table 3 with agreement seen in highlighted cells.)

We found agreement for risk classification was poor when DIPSS and post-PV risk scores were applied to the

Table 1. Patients' characteristics.

Characteristic	Patients, n=105
Post ET MF (n, % of total)	61 (58%)
Post PV MF (n, % of total)	44 (42%)
Male to female (ratio)	1:1
Median age (years)	65 (range 25-87)
JAK *V617F* (n, % positivity)	68 (65%)
Median laboratory values	
Hemoglobin (g/dL)	10.9 (range 5.3-17.0)
Platelet (x10^9)	287 (range 20-1864)
WBC (x10^9)	11.1 (range 1.1-165)

ET: essential thrombocytosis; MF: myelofibrosis; PV: polycythemia vera; WBC: white blood cell count.

Table 2. Dynamic International Prognostic Scoring System and Post Polycythemia Vera Risk Scores calculation for myelofibrosis.

	Adverse point value		
DIPSS[2]	0	1	2
Age	≤65	≥65	
WBC (x10^9/L)	≤25	≥25	
Hemoglobin (g/dL)	≥10		≤10
Peripheral blood blast (%)	<1	≥1	
Constitutional symptoms (Yes/No)	N	Y	
Post PV[3]			
Hemoglobin (g/dL)		≤10	
Platelets (x10^9/L)		≤100	
WBC (x10^9)		≥30	
Total Point Score			
Risk category	DIPSS[2]	Post PV[3]	
Low	0	0	
Intermediate-1	1 -2	1	
Intermediate -2	3-4	2	
High	5-6	3	

DIPSS: Dynamic International Prognostic Scoring System; PV: polycythemia vera; WBC: white blood cell count.

Table 3. Dynamic International Prognostic Scoring System and Post Polycythemia Vera Agreement.

DIPSS	Post PV Risk Score 0	1	2	3	Total
Low	9 (75%)	3 (25%)	0	0	12
Int-1	31 (77.5%)	8 (20%)	1 (2.5%)	0	40
Int-2	17 (43.6%)	14 (35.9%)	6 (15.4%)	2 (5.1%)	39
High	0	6 (75%)	1 (12.5%)	1 (12.5%)	8
Total	57 (57.6%)	31 (31.3%)	8 (8%)	3 (3%)	99

PV: polycythemia vera; DIPSS: Dynamic International Prognostic Scoring System.

same post-PV/ET MF patients. Scores were calculated at fixed time interval and thus, the results are not simply representative of a change in clinical status over time. Interestingly, DIPSS was more likely to assign patients to a high-risk category than the post-PV risk assessment score.

This climate of risk prognostication has changed dramatically over the last two decades.

From the Lille[4] in 1996, International Prognostic Scoring System (IPSS)[5] in 2009, Dynamic International Prognostic Scoring System (DIPSS)[2] in 2010, DIPSS-plus[6] in 2011, to the most recent introduction of Mutation Enhanced International Prognostic Scoring System (MIPSS)[7] and the Genetics-based Prognostic Scoring System (GPS)[8] in 2014, accurate risk stratification within MF has been a moving target.[9] To complicate the issue further, the diagnosis of secondary myelofibrosis such as in post-polycythemia vera (PV) MF and post-essential thrombocytosis (ET) MF represents a unique prognostication challenge. Due to all prognostic models being developed from data obtained from primary MF alone, and stemming from the observation that secondary MF may represent a clinically unique entity,[10] Passamonti developed a separate dynamic scoring system for post-PV MF.[3] Subsequently, clinicians treating secondary forms of MF are forced to choose from competing prognostication models with no guiding data as to which model is superior or if the models correlate with one another. Our findings of poor agreement with DIPSS and post-PV/ET risk scores further highlight the need for studies in this area.

As we move forward in designing studies for better prognostic tools in post-PV/ET MF, the incorporation of molecular prognostic markers is essential. Calreticulin (CALR) and *ASXL1* mutations are recognized as prognostic indicators in ET and primary MF;[11] however, it is currently unknown if this prognostic value translates to post PV/ET myelofibrosis. In fact, it has been postulated that the molecular landscape of post-PV/ET MF differs from primary MF and thus molecular prognostic indicators will need to be carefully selected.[12]

Prognostic scoring systems are key to clinical success in post PV/ET MF patients, as they direct our medical decision making and suggest appropriate timing for use of high-risk therapies such as allogeneic transplant. As evidenced here, applying risk scores developed for primary MF such DIPSS may be suboptimal for the post-PV/ET patient population. As clinicians, we eagerly await a system that addresses the unique patient population of post PV/ET MF.

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