useful biomarkers. Future studies will need to uncover the underlying mechanisms driving the observed changes in circulating relevant miRNAs in the disease, and how immunosuppression modulates such levels.

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Risk stratification in myelofibrosis: the quest for simplification

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doi:10.3324/haematol.2016.158865

Risk-stratification systems in hematologic malignancies can serve a myriad of clinical and research purposes. They facilitate rational bedside discussion regarding the likely trajectory of a disease, provide an objective screen to ensure clinical trial enrollment reproducibility, and help guide decision-making with regard to risky interventions.

The ideal prognostic model would be that derived from the experience of patients very similar to those who are seen in your clinic; thus, generalizable. It would utilize data that you have at hand, or at least can easily and accurately obtain, and it would reliably predict the future clinical course of your patient's health condition, providing greater precision when discussing sometimes highly heterogeneous diseases.

Myeloproliferative neoplasms (MPNs) are a group of malignant conditions known for such heterogeneity. For essential thrombocythemia and polycythemia vera, two of the lower-risk subtypes of MPNs, risk-stratification models have always been remarkably simple – perhaps due to the limited number of therapeutic interventions employed. A thorough patient history, complete blood count, and, in the case of essential thrombocythemia, knowledge of the *JAK2V617F* mutation status, allow the physician to sort patients into standard and high-risk categories, and assign therapy accordingly.

However, in primary myelofibrosis (PMF), a disease where survival can range from months to over a decade, there has been continuous re-evaluation of the prognostic models used. Initially, those utilized in myelodysplastic syndrome, such as the International Prognostic Scoring System (IPSS), were opted for. In the last few years, two PMF-specific models have become the standard of care: dynamic IPSS (DIPSS), and DIPSS-plus. Each of these works with relatively easy to obtain inputs including age, blood count, symptoms, peripheral blood blast percentage, transfusion history, and karyotype. Typically, clinicians use the system that best fits the situation at hand – for example, if one were discussing transplantation with a younger than average patient, one might calculate the DIPSS score since the retrospective results published by Nicolaus Kröger *et al.*, comparing transplant to non-transplant outcomes, were stratified using that same score.[1] For a patient under consideration for Ruxolitinib therapy, one might use the IPSS score since it was the model chosen for eligibility in the pivotal registration studies for this agent.[2,3]

Since 2005, when a mutation in the *JAKV617F* gene was first identified as a seminal pathologic event in polycythemia vera, an increasing number of somatic mutations have been described in association with PMF. In general, *JAK2*, *CALR* and *MPL* are considered driver mutations, though there are elegant studies examining how acquisition order dictates phenotypic destiny.[4] Additional somatic mutations found in the disease include *LNK*, *CBL*, *TET2*, *ASXL1*, *IDH1/2*, *IKZF1*, *EZH2*, *DNMT3A*, *TP53*, *SF3B1*, *SRSF2*, and *U2AF1*, a list that is likely not exhaustive. While we await additional research on the mechanistic consequences of these aberrations, retrospective studies are already looking into the prognostic importance of mutations, or groups of mutations, in patients. How these molecular mutations should be integrated into pre-existing scores, such as the DIPSS, remains a significant conundrum

for both the practitioner and their patients. Two stratification systems, the Mutation-Enhanced International Prognostic Scoring System (MIPSS)[5] and the Genetics-Based Prognostic Scoring System (GPSS),[6] have been presented; however, they are not yet the standard of care.

In this issue of Haematologica, a group of researchers from the MD Anderson Cancer Center put forth a model for prognosis in primary myelofibrosis that attempts to cut through some of the noise.[7] They have provided a simple model, based on a large number of patients, which uses relatively easy to obtain, objective and reproducible data. It incorporates quantitation of the JAK2 allele burden, but does not require patients to undergo next generation sequencing – a test which has highly variable reimbursement patterns and is financially out of reach for many patients. Indeed, the only features needed to classify patients are age, JAK2 allele burden (dichotomized at 50%), and *CALR* and *MPL* status.

Their model is based on 13 years' worth of patient data; 344 individuals were included in the analysis, ranging in age from 26-86 years. The researchers were able to establish two patient profiles: one with high-risk mutation status, the other with low-risk mutation status. Notably, this was possible by testing the presence or absence of *MPL* and *CALR*, but they needed to quantify the allele burden of the *JAKV617F* mutation. Whilst the presence of higher V617F allele burden describes a more dangerous phenotype in polycythemia vera, the opposite is true in myelofibrosis, where a low allele burden has been associated with reduced survival.[8] In addition, in myelofibrosis, patients with a higher *JAK2617F* allele burden are more likely to achieve clinical benefit when treated with Ruxolitinib therapy.[9]

Therefore, combining age, presence of *MPL* or *CALR*, and *JAK2V617F* allele burden, researchers established a highly discriminant scale that could separate patients into four categories of median overall survival – ranging from 35 to 126 months.

Will we adopt this new system for clinical use? Perhaps eventually. Firstly, however, it needs to be validated in a large, independent patient population. Secondly, clinicians and third-party payers need to acknowledge that baseline calculation of the *JAK2V617F* allele burden is of significant clinical relevance to patients with this devastating disease – data such as that presented here makes a compelling argument.

Should the above happen, the prognostic scale proposed by Dr. Rozovski *et al*. has great clinical potential; most notably in that it is highly objective. One of the downfalls of the DIPSS is the categorization of "constitutional symptoms," which can be subjective, depending on the evaluator. With this system, the clinician can avoid having to sort out whether fatigue or some other "not quite severe enough symptom" merits a point on the DIPSS scale. Secondly, it is transportable; a patient seen at one institution will have the same risk features when referred to a tertiary care center for a transplant consultation. Finally, this analysis most likely includes patients who were treated with Ruxolitinib. As such, this data becomes more generalizable to the contemporary patient, where Ruxolitinib or an investigational equivalent is administered.

Of course, there is still much to learn: Does risk, with this scale, change over time? How might somatic mutations like *TP53* or *ASXL1* be integrated? Can we use this data to assess timing of allogeneic stem-cell transplantation? How do we weigh findings like ascites, splenomegaly or a progressive failure to thrive – findings that portend, in clinical judgement and experience, worse outcomes? Such findings are poorly captured in charts, and are therefore difficult to integrate into scales that are derived from retrospective data, such as this one.

As our clinical community struggles to advance the field, prognostic scales like the one proposed here can provide uniformity, reproducibility and clinical precision for our patient encounters and future research. They represent an important tool for patient care and management. Kudos for reaching toward the ideal.

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