The classical Philadelphia chromosome-negative myeloproliferative neoplasms (MPN) of polycythaemia vera (PV), essential thrombocythaemia (ET), and primary myelofibrosis (PMF) are myeloid disorders characterized by clonal expansion of mature hematopoietic cells, extramedullary hematopoiesis and clinically by increased incidence of thrombosis, hemorrhage and the potential to transform to acute leukemia (1). The mainstay of MPN therapy has been phlebotomy, antiplatelet drugs and cytoreductive agents to control constitutional symptoms and prevent thrombotic events and leukemic transformation. More recently targeted therapies have shown considerable efficacy in these malignancies (2).

Current MPN disease models envisage PV, ET and PMF as part of a continuum of phenotypes, reflected in the prevalence of the main MPN genotypic driver mutations which are generally found in a mutually exclusive manner across subtypes and which contribute to phenotype through convergent activation of intracellular JAK-STAT signalling (3). The most common of these driver mutations is the JAK2 V617F, present in more than 95% of PV patients and in 50–60% of ET and PMF patients. Up to 40% of patients with splanchnic vein thrombosis (SVT), which encompasses Budd Chiari syndrome, portal and mesenteric vein thrombosis, are subsequently diagnosed with either an overt or latent MPN (4,5). This high incidence compels molecular testing for the JAK2 V617F mutation to be the primary investigation as to whether an MPN is the underlying cause of the SVT. Other risk factors for SVT including pregnancy, abdominal disorders, an inherited thrombophilic state, hormone therapy, autoimmune disorders or paroxysmal nocturnal hemoglobinuria with further investigations for acquired and hereditary thrombophilia warranted in those cases where the JAK2 V617F mutation is absent. Other, less common driver mutations of MPN, namely those within MPL exon 10 and JAK2 exon 12, are generally absent in patients with SVT (6,7). It should also be noted that ethnic differences in the etiology of diseases such as Budd-Chiari syndrome have been reported (8).

In 2013 insertion and/or deletion mutations of the CALR gene, that encodes the intracellular, calcium binding protein calreticulin, were discovered in 20–30% of patients with ET and PMF (9,10). As previously mentioned, CALR mutations occur in a virtually mutually exclusive manner of the JAK2 V617F necessitating detection to be incorporated into the routine molecular diagnostic algorithm for MPN (11). Interestingly, those MPN patients with CALR mutations have a significantly lower risk of thrombotic events than their JAK2 V617F-positive counterparts (12,13).

Initial investigations into the frequency of CALR mutations in patients with SVT revealed a low frequency (<2%) or absence in European cohorts (14,15). These
findings were borne out by several subsequent studies with conflicting opinion as to whether CALR mutation screening should be part of the diagnostic algorithm for SVT: both clinical and laboratory-orientated arguments exist for screening all JAK2 V617F-negative cases, not screening at all, or for screening only those cases with other clinical or hematological features of an MPN also present (16). In an effort to resolve this screening issue, Poisson and colleagues have analysed an extended cohort of more than 500 SVT patients in order to identify those with the highest likelihood of harboring CALR mutations (17). From an initial test cohort of 312 SVT patients, five CALR positive patients (1.6%) were identified, all of whom had a spleen height of 16 cm or larger and a platelet count greater than 200×10^9/L. These indices, chosen on the basis of previous findings of low sensitivity but high specificity for detection of underlying MPN in SVT patients in the pre-JAK2 era (18), were extended into a validation cohort of SVT patients and enabled identification of a further 2 of 6 (33.3%) CALR mutated cases. Despite resulting in a positive predictive value of only 46.6%, perhaps more importantly from a molecular diagnostic perspective, a negative predictive value of 99.7% for CALR mutation detection was obtained across both cohorts indicating who not to screen. Whilst the platelet count threshold appears arbitrary (the normal range for platelets in adults being 150×10^9–400×10^9/L) this threshold may account for the effects of portal hypertension such as hypersplenism and hemodilution which can lead to red cell and platelet counts below MPN diagnostic criteria (18). Poisson et al. (17) go on to propose an algorithm for MPN diagnosis in SVT based on these results and recommend CALR mutation screening should only be considered in those JAK2 V617F-negative SVT patients with splenomegaly and a platelet count >200×10^9/L thereby limiting subsequent further bone marrow biopsy analysis to those patients where a JAK2 V617F or CALR mutation is not detected.

Inclusion of these basic hematological and clinical indices, in addition to molecular data, into an easily adopted model has the potential to rapidly exclude suspected MPN and to minimise invasive bone marrow evaluation to appropriate patients, thereby enhancing diagnosis and improving overall clinical management in SVT patients. As the prevalence of CALR mutations in SVT becomes more clearly defined, it will be interesting to speculate if CALR genotype (19) influences phenotype, outcome, or response to therapy as observed in overt MPN.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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