Genomic profiling for thrombosis risk prediction in myeloproliferative neoplasms

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ABSTRACT

The main *BCR-ABL*-negative myeloproliferative neoplasms consist of polycythemia vera, essential thrombocythemia and primary myelofibrosis. They have been associated with an overall elevated risk of thromboembolism, including both venous and arterial events. Different risk factors for thrombosis have been identified in this patient population, including clinical but also molecular predictors. Accurate estimation of thrombotic risk could potentially allow for identification of patients who are the best candidates for pharmacological prophylaxis with an antiplatelet or anticoagulant agent. The genes for which most data on associated risk of thromboembolism are available are *JAK2*, *CALR* and *MPL*. The *JAK2* V617 mutation is the most common driver alteration for polycythemia vera and has been clearly associated with approximately a doubling in the risk of venous thromboembolism compared with *JAK2*-negative myeloproliferative neoplasms. It is also found in about half of cases of essential thrombocythemia. *CALR*-mutated essential thrombocythemia has been associated with a lower risk of thromboembolic event, while there is less data about MPL given it low frequency of alterations. In later years more knowledge has emerged about mutations found in other genes altered in the blood and marrow of individuals with a myeloproliferative neoplasm. Risk stratification schemes have been derived using basic patient characteristics but so far no well validated model or clinical prediction rule includes any molecular predictor besides the *JAK2* V617F mutation. Additional work is needed to validate associations for markers other than *JAK2* and integrate this knowledge into clinically useful prediction models.

Key words: myeloproliferative neoplasm; thrombosis.

Introduction

Polycythemia (PV), essential thrombocythemia (ET) and primary myelofibrosis (MF) are the main *BCR-ABL*-negative myeloproliferative neoplasms (MPNs). They usually feature a blood or bone marrow somatic mutation in one of three driver genes: *JAK2*, *CALR* and *MPL*. PV is characterized by an elevated hemoglobin level, MF is associated with evidence of bone marrow fibrosis and ET is diagnosed in the presence of an elevated platelet count, a typical driver gene mutation and the exclusion of a PV or MF diagnosis.[1] ET and PV tend to be associated with a normal life expectancy, while MF is characterized by a high risk of transformation to acute myeloid leukemia.[2] Increases in the availability of next generation sequencing (NGS) have resulted in growing numbers of patients undergoing extensive genotyping of their disease, leading to an improved understanding of the molecular landscape for those MPNs.[3]

The association between *BCR-ABL*-negative MPNs and thromboembolism was described early on.[4] Both venous and arterial events were noted to be increased and the risk is highest shortly after diagnosis.[5] Clinical risk factors for thromboembolism were identified, including older age, prior thromboembolism and general cardiovascular risk factors including a history of smoking. In more recent years, individual driver gene mutations were also found to be associated with the risk of thromboembolism.[6] Venous and arterial thromboembolic events are associated with significant morbidity and mortality in this patient population. The administration of aspirin has been shown to decrease the risk in patients with PV.[7] Several clinical prediction rules were devised to help stratify MPN patients and identify those at higher risk of thromboembolic events and better guide pharmacological prophylaxis. The most recent thromboembolism models include molecular information, but much remains to be done to improve the accuracy of predictions, especially in terms of integrating information about genes beyond *JAK2*, *CALR* and *MPL*.

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Genomic alterations in myeloproliferative neoplasms

Classical driver mutations

Almost all cases of PV exhibit the *JAK2* V617F mutation or the less common *JAK2* exon 12 mutation. About half of individuals with ET and MF also have the *JAK2* V617F mutation, a quarter possess a *CALR* mutation and only about 5% have a mutation in the *MPL* gene.[8] Activation of the JAK-STAT pathway is a common finding for all those molecular variants.[9] This results in clonal bone marrow proliferation of myeloid precursors and an increase in peripheral blood red cells and platelets.

Other mutations

Several other genes have been found to be variably altered in patients with an MPN, including: *ASXL1*, *CBL*, *DNMT3A*, *EZH2*, *IDH1*, *IDH2*, *IKZF1*, *KMT2C*, *LNK*, *NFE2*, *PPMD1*, *SF3B1*, *SRSF2*, *TET2*, *TP53* and *U2AF1*. Somatic mutations in those non-classical driver genes have been shown to influence disease progression.[3]

Effect of alterations on thrombotic risk

The studies assessing the risk of thromboembolism as a factor of somatic genetic alterations are heterogenous. Selected original articles reporting on this topic are presented in Table 1. The endpoint in most studies consists of combined arterial and venous events, but in some cases risk estimates are provided separately. The risk is typically confounded by prevalent cardiovascular risk factors. Adjustments are often made for the existence of prior thrombotic events, a common finding in patients diagnosed with an MPN. Most studies are retrospective in nature.

JAK2, CALR and MPL

The classical MPN driver mutations are by far the most studied genetic alterations. Most patients with a *JAK2* alteration will have the V617F mutation and often no mention will be given of whether or not exon 12 mutations were assessed. It is well established that the presence of the *JAK2* V617F mutation in ET or PV confers an approximate doubling of the risk of arterial and venous thromboembolism compared with a *CALR* or *MPL* mutation.[10] Interestingly, the type of *CALR* mutation matters, as type 2 appears to be associated with a lower risk.[11] Intuitively, the *JAK2* V617F allele burden should be correlated with the risk of thromboembolism, which was noted for arterial and/or venous thrombosis in four studies.[12-15] However other studies did not demonstrate this association.[16] A variant allele frequency (VAF) threshold of 50% was used in most cases to make the assessment. Notably, it has been shown that in PV the *JAK2* V617 VAF is a predictor of transformation to MF.[17] The increased risk of thrombosis associated with a *JAK2* mutation has also been described for MF.[18] Interestingly, triple negative MPN (i.e., no *JAK2*, *CALR* or *MPL* mutation) seems to be associated with a low risk of thromboembolism, even though the number of patients in this category is low.[19]

Other genes

The advent of next-generation sequencing has allowed the genotyping of MPN cases for a large extent of genes other than the three classical driver genes. However, since this technology is newer in implementation there is comparatively less data. Non-classical alterations are more common in MF than in PV or ET. There is ample evidence that TET2, DNMT3A mutations and other myeloid alterations present at a low level increase the risk of arterial events in patients with clonal hematopoiesis, as defined by a variant allele frequency of at least 2%.[20] This association was not reliably demonstrated for venous thromboembolism. Data for MPNs suggest that *ASXL1*, *BCOR/BCORL1*, *DNMT3A*, *TET2* and *TP53* alterations might be associated with a higher risk of thromboembolism in individuals with an MPN, however confirmation studies will be necessary.[21-23]

Splanchnic vein thrombosis

The association between MPN and thrombosis of a splanchnic vein (portal, splenic, superior mesenteric, inferior mesenteric or hepatic vein) has been well described.[24] The main genetic risk factor in this case is the presence of the *JAK2* V617F mutation. Patients presenting *de novo* with splanchnic vein thrombosis and without an overt precipitating factor should be evaluated for possible PV or ET. The typical disease features (e.g., elevated blood counts) can be inconspicuous in those patients, so routine screening for the *JAK2* V617F mutation has been advocated.[25] Other genetic alterations have not been consistently associated with splanchnic vein thrombosis.

Existing risk models

The main thromboembolism risk stratification scheme used for patients with ET is the IPSET-thrombosis score, which has gone through updates over the years (Table 2).[26] It is based on age, genotype (*JAK2* mutated vs not) and presence or absence of a prior history of thrombosis. Patients are classified as very low, low, intermediate or high risk of thromboembolism. The existence of prior thrombosis or the combination of an age >60 years and mutated *JAK2* places an individual in the high-risk group. In a recent study, the yearly incidence of thromboembolism was found to be 0.72%, 0.73%, 0.78% and 1.96% for the very low-, low-, intermediate- and high-risk groups respectively.[27] The risk score was able to discriminate satisfactorily for the risk of arterial events but failed to do so for venous events. Machine learning models are being evaluated in order to integrate genomic data to predict thromboembolic event in individuals with an MPN but none has been reliably validated in large external cohorts.

The current models still tend to feature a combined endpoint of venous and arterial thromboembolism, the latter dominating outcomes. There exists no well validated model to accurately predict VTE events for patients with an MPN. Separating the two outcomes using distinct models would be relevant to clinical practice, since optimal pharmacological prophylaxis modalities differ for arterial vs venous events. It is unclear if other genetic loci besides *JAK2* will explain enough of the variability of VTE incidence in this population to justify including them in a dedicated model.

Table 1. Selected original articles reporting on the risk of thromboembolism associated with specific somatic alterations in individuals with a myeloproliferative neoplasm.

Author, Year	Disease(s)	Gene / alteration	Thrombotic event type	Effect of alteration on risk of thromboembolism
Carobbio *et al.*, 2009[12]	ET, PV	*JAK2* V617F allele burden	Arterial and venous	Higher allele burden was associated with higher risk of thrombosis in both ET and PV.
Passamonti *et al.*, 2010[16]	PV	*JAK2* V617F allele burden	Arterial and venous	Higher *JAK2* allele burden was not associated with an increased risk of thrombosis.
Rumi *et al.*, 2014[10]	ET, PV	*JAK2*, *CALR*, *MPL*	Arterial and venous	The risk of thrombosis for patients with a *JAK2* mutation was about double that of individuals with a *CALR* mutation.
Tefferi *et al.*, 2014[30]	ET	*JAK2*, *CALR*	Not specified	*CALR*-mutated ET was associated with a lower thrombotic risk compared with *JAK2*-mutated ET.
Alvarez-Larrán *et al.*, 2016[31]	ET	*JAK2* V617F, *CALR*	Arterial and venous	Aspirin decreased thrombotic risk in *JAK2*-mutated ET; a lower baseline risk of thrombosis was noted in patients with *CALR*-mutated ET.
De Stefano *et al.*, 2016[32]	ET, PV, MF	*JAK2* V617F	Splanchnic venous thrombosis (recurrence)	The presence of a *JAK2* V617F mutation was not associated with recurrent thrombosis.
Pietra *et al.*, 2016[11]	ET, MF	*JAK2* V617F and *CALR* mutation subtype	Not specified	Type 2-like *CALR* mutations were associated with a lower thrombosis than type 1-like or *JAK2*.
Pérez Encinas *et al.*, 2020[33]	ET	*JAK2* V617F and *CALR* mutation subtype	Arterial and venous	Type 2 *CALR* mutations were associated with a lower thrombosis risk than type 1 or *JAK2* V617F.
Zhang *et al.*, 2020[13]	ET, PV, MF	*JAK2* V617F	Arterial and venous	A *JAK2* V617F variant allele frequency above 50% was associated with an increased risk of thrombosis.
Cattaneo *et al.*, 2021[19]	ET	triple-negative (no *JAK2*, *CALR* or *MPL* mutation)	Arterial and venous	Triple-negative ET was associated with a low thrombotic risk.
Guglielmelli *et al.*, 2021[14]	PV	*JAK2* V617F	Arterial and venous	A *JAK2* V617F variant allele frequency above 50% was associated with an increased risk of venous thrombosis.
Soudet *et al.*, 2022[15]	ET, PV, MF	*JAK2* V617F	Arterial and venous	A *JAK2* V617F variant allele frequency above 50% was associated with an increased risk of venous thrombosis.
Wang *et al.*, 2022[34]	ET, PV	*JAK2*, *CALR*, *MPL* and non-driver mutations	Arterial and venous	The presence of a *TET2* mutation was associated with a higher risk of thrombosis in patients with ET.
Gu *et al.*, 2023[21]	PV	Non-driver mutations	Arterial and venous	Alterations of *ASXL1*, *DNMT3A* and *BCOR/BCORL1* were associated with a higher risk of thrombosis.
Pasquer *et al.*, 2023[23]	ET, PV, MF	Non-driver mutations	Arterial and venous	The presence of a *TET2* or *DNMT3A* alteration was associated with a higher risk of arterial event.
Furuya *et al.*, 2024[22]	ET	Non-driver mutations	Arterial and venous	Alterations of *ASXL1* and *TP53* were associated with a higher risk of thrombosis.
Özdemir *et al.*, 2024[35]	ET	*JAK2* V617F, *CALR*	Arterial and venous	The *JAK2* V617 alteration was associated with a higher risk of thrombosis than a *CALR* mutation.

Table 2. Revised IPSET-thrombosis score. Reproduced from: Barbui *et al.* Blood Cancer J 2015;5:e369; with permission.

Risk category	Characteristics
Very low	Age ≤60 years, *JAK2* unmutated, no prior thrombosis
Low	Age ≤60 years, *JAK2* mutated, no prior thrombosis
Intermediate	Age >60 years, *JAK2* unmutated, no prior thrombosis
High	Age >60 years and *JAK2* mutated, or prior thrombosis history regardless of other factors

Application to clinical practice

In patients with PV most mitigation of the risk of thromboembolism is performed through cytoreduction and administration of aspirin. All patients should undergo therapeutic phlebotomy to decrease the hematocrit below 45%. Low-dose aspirin is recommended for all except for those with an elevated risk of bleeding.[28] Cytoreduction with hydroxyurea is indicated for high-risk individuals, i.e., those aged 60 years and older or with a history of prior thrombosis. In the case of ET, aspirin is typically administered to most individuals. High-risk ET patients should also be treated with cytoreduction.[29] There is no validated risk score for MF and the overall risk of thromboembolism is lower than for PV and ET, so there are no specific recommendations for pharmacological prophylaxis.

Conclusions

The only MPN somatic genetic alteration which has been strongly associated with an increase in the risk of arterial and venous thromboembolism is the *JAK2* V617F mutation. It is also the only one incorporated in an accepted risk stratification system, the IPSET-thrombosis score. The latter applies only to ET and is only moderately effective at discriminating risk levels. Given the significant burden of thromboembolism in patients with *BCR-ABL* negative MPNs, new risk stratification schemes are needed in order to better guide pharmacological prophylaxis, especially considering the increased risk of bleeding from aspirin in this population. Besides known risk factors in these patients, improved knowledge of the effect of non-driver genes on thrombosis risk could lead to better models.

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