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The underappreciated risk of thrombosis and bleeding in patients with myelofibrosis: A review

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Abstract

Bleeding and thrombosis are long recognized complications of myelofibrosis (MF) and contribute significantly to its morbidity and mortality. However, so far, few studies have evaluated the frequency of these events, their characteristics, and their prognostic impact. Based on these studies, thrombotic events in MF are about as common as in essential thrombocytemia (ET) but less common than in polycythemia vera (PV), while bleeding events are relatively more common in MF than in ET or PV. The emergence of the concept of prefibrotic primary MF (PMF), which is associated with a higher frequency of thrombohemorrhagic complications than ET, and the growing evidence that prefibrotic PMF may also have a different thrombotic and bleeding risk profiles than fibrotic (overt) PMF, have emphasized the need for a reappraisal of the risk of thrombosis and hemorrhage in patients with MF. In this review, we discuss the frequency of thrombosis and bleeding in patients with MF, including prefibrotic PMF and their established and potential risk factors.

Keywords

myelofibrosis; thrombosis; bleeding; prefibrotic; risk factors

Introduction

Myelofibrosis (MF) belongs to the group of Philadelphia-negative myeloproliferative neoplasms (MPN), diseases characterized by the clonal proliferation of myeloid cells with variable morphological maturity associated with progressive marrow failure. According to the 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia, major diagnostic criteria for overt (fibrotic) PMF include 1) presence of megakaryocytic proliferation and atypia, accompanied by reticulin and/or collagen fibrosis of grades 2 or 3; 2) not meeting WHO criteria for essential thrombocythemia (ET), polycythemia vera (PV), *BCR-ABL1* positive chronic myeloid

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leukemia (CML), myelodysplastic syndrome, or other myeloid neoplasms and 3) presence of *JAK2*, *CALR* or *MPL* mutations or presence of another clonal marker, or absence of reactive fibrosis. Minor criteria, include a) anemia not attributed to a comorbid condition, b) leukocytosis $\geq 11 \times 10^9$, c) palpable splenomegaly, d) lactate dehydrogenase (LDH) level above normal limit of institutional reference range and e) leukoerythroblastosis, all to be confirmed in 2 consecutive determinations. For prefibrotic PMF, all criteria remain the same except the major criteria on bone marrow morphology which has been mentioned as "megakaryocytic proliferation and atypia, without reticulin fibrosis > grade 1, accompanied by increased age-adjusted bone marrow (BM) cellularity, granulocytic proliferation, and often decreased erythropoiesis", and no leukoerythroblastosis as a minor criterion. The diagnosis of both prefibrotic and fibrotic PMF requires meeting all three major and at least 1 minor criteria [1]. Another entity that contributes to a large pool of patients with MF is MF secondary to ET or PV. Regarding diagnosis of post-ET MF and post-PV MF, as stated by International Working Group for Myelofibrosis Research and Treatment (IWG-MRT), major criteria are: a) documentation of a previous diagnosis of either ET or PV as defined by World Health Organization and b) presence of increased bone marrow fibrosis. The minor criteria are: a) progressive anemia or loss of phlebotomy requirement, b) leukoerythroblastic blood picture, c) increasing degree of splenomegaly, d) development of constitutional symptoms such as weight loss, fever and night sweats and e) increased serum LDH (post-ET MF only). The diagnosis requires both major and at least 2 minor criteria [2]. The pathogenesis of MF is thought to involve hyper-activation of the JAK-STAT intracellular signaling pathway, via mutually exclusive mutations of the *JAK2*, *CALR* or *MPL* gene. These result in the abnormal expression and activity of a number of pro-inflammatory cytokines leading to abnormal deposition of excess collagen and reticulin [3,4]. Clinical manifestations of MF include cytopenia, fatigue and constitutional symptoms such as low-grade fever, weight loss and night sweats. The complications that can occur in the disease natural history are infections, end-organ failure, manifestations of extra-medullary hematopoiesis, thrombohemorrhagic events, and leukemic transformation, which affect short- and long-term morbidity and patient survival [5].

Because malnutrition, cytopenias, infections and leukemic transformation largely account for the significantly worse outcomes associated with MF compared to the other MPN, the risk of thrombotic and/or hemorrhagic events may be underappreciated in this patient population. However, it is important to understand their pathophysiology, frequency, and risk factors, to formulate an appropriate treatment plan and reduce the associated morbidity and mortality. The classic MPN (MF, ET and PV) have been frequently studied together and the characteristics of bleeding and thrombosis in these patients share commonalities [6–9]. Neverthless the differences exist.

The pathomorphological entity of prefibrotic PMF has been considered a new category of PMF in the latest revision of the WHO classification [1], whereas in the 2001 version it was categorized as subcategory [10]. It is being increasingly recognized that patients with prefibrotic PMF may have a distinct thrombohemorrhagic risk profile, that might be different from that of either ET or overt PMF patients [11,8].

Thrombotic complications in myelofibrosis

Descriptive epidemiology

Table 1 provides the summary of the types and frequency of major thrombotic events in patients with PMF as reported in published studies. Both arterial and venous thrombotic events are not uncommon in patients with PMF [6,12,13]. Arterial events typically include stroke/transient ischemic attack (TIA), peripheral vascular disease (PVD), coronary artery disease (CAD) or acute coronary syndrome (ACS) and central retinal artery occlusion (CRAO), whereas venous thromboses include deep venous thrombosis (DVT)/pulmonary embolism (PE), portal vein thrombosis (PVT), Budd-Chiari Syndrome (BCS) and cerebral venous sinus thrombosis (CVST). The overall frequency of thrombosis appears to be similar to that observed in ET, but lower than in PV [6,13–15]. Elliot et al. reported an incidence of thrombotic events of 13.2% at, or prior to diagnosis, and 10.7% over a median follow-up of 31 months in a series of 208 patients [12]. In another single institution series of 155 patients, 11.6% had thrombotic events during a median follow-up of 4.2 years [6]. In a study of 707 patients with PMF, fatal and nonfatal thromboses were diagnosed in 7.2% patients with a rate of 1.75% patient-years. Remarkably, there were 31 cases of venous thrombotic events out of which 9 were fatal. The overall death rate due to cardiovascular (CV) events was low at 2%, accounting for 0.39 deaths per 100 patient-years. The large majority of deaths were due to other causes, including leukemia, infections and complications of stem cell transplantation. When the deaths from non-CV causes were considered as competing events, the estimated adjusted rate of major thrombotic events would have been 2.2% patient-years [13]. This is comparable to what is seen in ET, where the annual rate of fatal and non-fatal thrombosis was 1.9% patient-years in a series of 891 patients. The overall frequency of arterial and venous thrombosis in the same ET population was 12% after a median follow-up of 6.2 years [16]. On the other hand, the frequency of thrombotic complications in patients with PMF is significantly lower than in those with PV. Indeed, in the Efficacy and Safety of Low dose Aspirin in Polycythemia Vera (ECLAP) observational study, the cumulative rate of CV deaths and nonfatal thrombotic events was 5.5 events per 100 patient-years [17].

It should be noted that the rate of thrombosis in PMF could likely be obscured by other fatal and nonfatal non-CV competing events including transformation to acute leukemia. A large Swedish population-based study reported increased 10-year probability of dying from cardiovascular and cerebrovascular diseases in young MPN (ET, PV and PMF) patients aged 50 to 59 years (4.2% for cardiovascular disease vs 2.1% for controls and 1.9% for cerebrovasvcular disease vs 0.4% for controls), whereas no difference was observed in MPN patients versus controls aged 70 to 79 years (16.8% vs 15.2% for cardiovascvular disease and 5.6% vs 5.2% for cerebrovascular). Once again, the large majority of overall deaths in MPN were due to hematologic malignancies with HR of 92.8 (95% CI, 70.0 to 123.1) [18]. In the series by Cervantes et al., 5 out of 104 deaths (4.8%) were directly attributable to thrombotic events which included BCS (2 patients), and PVT, stroke and pulmonary thromboembolism (1 each) [6].

Venous events commonly occur in unusual sites in patients with MPN, including MF. In a series of 155 patients by Cervantes et al., out of 31 thromboembolic events, 6 (20%) were

splanchnic vein thrombosis (SVT) and 1 was cerebral venous sinus thrombosis [6]. The proportion of SVT was 6 out of 34 (18%) in PMF patients in the German SAL-MPN-registry, a non-interventional prospective study [19]. A meta-analysis by Smalberg et al. of 1062 patients with BCS demonstrated that, out of 440 patients who underwent a complete diagnostic workup for MPN, including *JAK2* mutation analysis, 40.9% were diagnosed with MPN; 6.7% of whom had PMF, and 80% being *JAK2*-positive. In the same analysis, out of a total of 855 patients with PVT, MPNs were found in 188 of 615 (31.5%) patients who underwent complete diagnostic workup. PMF contributed to 12,8% of MPN patients. [20].

Pathophysiology

The mechanism underlying thrombosis in patients with MPN is incompletely understood. Platelet activation leading to platelet-leukocyte adherence, endothelial activation and consequent initiation of the coagulation cascade (similar to what happens in ET or PV) have been suggested to play a central role in the pathogenesis of MF-associated thrombosis [21,22,14,23]. In general, platelet-leukocyte interactions at the site of vascular injury have been implicated in the balance between hemostasis and thrombosis [24,25]. A similar mechanism may come into play in thrombogenesis in MF patients. PMF patients have increased baseline platelet activation compared to controls, as evidenced by higher level of soluble and platelet P-selectin expression and higher percentage of platelet-monocyte complexes [23]. Platelet membrane abnormalities, leading to persistent activation and alpha-granule depletion, have also been demonstrated in PMF. In addition, CD11b overexpression and plasma levels of F1+2, a marker of clotting activation, have shown correlation with the presence of the *JAK2V617F* mutation[26]. The role of the later in thrombosis in patients with MPN has been increasingly recognized. A mutated *JAK2* may not only increase the platelet number but also alter the platelet function thereby playing a role in thrombogenesis. *JAK2V617F* mutation has been reported to cause intrinsic changes in the process of platelet formation from megakaryocytes in a knock-in mouse model of ET resulting in increased differentiation, as well as increased migratory ability and proplatelet formation. The platelets were found to be prothrombotic and demonstrated enhanced reactivity to different agonists, with consequent increase in platelet aggregation *in vitro* and decreased duration of bleeding *in vivo* [27]. These findings have not ben replicated in the setting of MF and further research will be needed to clarify the pathogenesis of thrombosis in patients with MF.

Risk factors

There are only a few established risk factors of thrombosis in MF patients; a number of other putative risk factors have not shown a consistent predictive power across studies, as demonstrated in Table 2. Cervantes et al. reported that thrombocytosis (i.e., platelet count $>450 \times 10^9$/L), cellular phase of MF, presence of CV risk factor and Hb >11g/dL were independently predictive of thrombosis in a study of 155 patients with PMF [6]. *JAK2V617F* positivity and age over 60 years were the only risk factors for thrombosis in another retrospective series. The investigators also demonstrated a borderline association between leucocytosis and thrombosis. The highest number of events were observed when *JAK2V617F* mutation was present along with leukocytosis [13]. Finazzi et al. reported association of *JAK2V617F* with risk of thrombosis while *CALR*-mutated, *MPL*-mutated and “triple-negative” patients had favorable risk [28]. A systematic review by Lussana et al.

showed a tendency towards an increased risk of thrombosis in PMF patients with *JAK2V617F* mutation, which did not reach statistical significance (it did in ET patients) [29]. Another recent meta-analysis reported a lower risk of thrombosis in *JAK2V617F* negative patients when compared with the *JAK2* mutated ones [30].

Other risk factors may contribute to thrombosis in patients with MPN. In a retrospective analysis of 205 patients, up to 71% of thromboses were temporally associated with factors like recent surgery, estrogen-based therapy or placement of central lines [12]. Information on the association between inherited or acquired thrombophilia and thrombosis in MF patients is presently limited. The *MTHFR-C677T* polymorphism was demonstrated to increase the risk in univariate analysis in a study of 68 patients, which included only 3 patients with PMF [31]. Some studies have attempted to unfold the additional risk secondary to thrombophilic states in a *JAK2V617F*-positive MPN patient poulation. In a small cohort of 192 patients, which included 60 PMF patients, Tevet et al. conducted thrombophilia screening of 62 patients. The “wild type” and *JAK2*-mutated patients had a relative risk of thrombosis of 0.93 and 2.94, respectively. In addition, the co-presence of *JAK2V617F* and inherited thrombophilia carried a relative risk of thrombosis of 3.56 (95% CI 2.41–7.34) compared to patients with neither risk factor, suggesting an additive interaction between the two [32]. The impact of CV risk factors on the frequency of thrombotic events in MF patients was examined in very few studies and has not been firmly established. A study by Cervantes et al. demonstrated that diabetes mellitus, smoking, hypertension and dyslipidemia were independent predictors of thrombosis in PMF patients [6]. The thrombogenic potential of thalidomide, which is often used for the treatment of anemia in MF patients, has been well documented in studies of multiple myeloma (MM) [33]. Similarly, lenalidomide, which has been used to treat cases of MF associated with the rare 5q deletion, carried with higher risk of thrombosis when used in combination with high-dose dexamethasone for the treatment of MM [34]. The data on the potential thrombogenic role of either agent in MF patients are not yet available. Splenomegaly was a significant risk factor for thrombotic events in univariate analysis in the German SAL-MPN-registry with ET, PV, MF and MPN-unclassifiable patients [19].

Management

There is scarcity of data on the management of vascular events specifically in patients with MF. However, some generalizations can be made. As a rule, treatment should be individualized, factoring in the higher risk of bleeding of patients with MF relative to those with other MPN (see below). Management strategies are often based on sound clinical judgement, expert opinion and extrapolation of data from studies of other MPN subtypes. The cardiovascular events are managed with antiplatelet agents and deep vein thrombosis with anticoagulation, as would be the case in other non-MPN clinical settings. The duration of anticoagulation for secondary VTE prevention (time-limited vs. indefinite) is unclear, as MPN represents a persistent risk factor [35]. BCS and PVT may require life-long anticoagulation and co-management of the patient together with the liver team. The management can be invasive in the most severe cases and include transjugular intrahepatic portosystemic shunt, angioplasty, surgical shunts and liver transplantation. Hydroxyurea should generally be used to normalize platelet counts as able [36]. It currently remains

unknown if cytoreductive therapy with hydroxyurea decreases the risk of thrombosis in MF as it does in high risk PV or ET. Neverthless, several experts recommend hydroxyurea and low-dose aspirin in MF patients with established risk factors (i.e, age over 60 years and/or history of thrombosis) [37].

Thrombosis in prefibrotic PMF

Prefibrotic PMF may have a different thrombotic risk profile than that of ET or overt (fibrotic) PMF (Table 1). There were few studies dedicated to this entity, which attempted to define its associated risk of thrombosis. In a population of 264 patients by Buxhofer-Ausch and colleagues, 41 (15.5%) and 17 (6.4%) had an arterial and venous event respectively, before diagnosis. After a median follow up of 6.28 years, 42 (16%) had nonfatal events at a rate of 2.1% patient-year and 13 (4%) had fatal thrombotic events. The arterial events occurred at a rate of 1.7% patient-year, as compared to venous events of 0.6% patient-year. On multivariate analysis using all parameters as metric variables, leukocytosis at diagnosis was a significant risk factor for overall (P=0.005, HR 1.15) and arterial thrombosis (P=0.047, HR 1.12). Lower hemoglobin level at diagnosis predicted increased risk of venous thrombosis (P=0.007, HR 0.59). A multivariate analysis repeated using only relevant categorical variables, revealed that platelet count lower than 870×10^9/L and WBC higher than 11.2×10^9/L remained independently predictive of overall thrombosis [14]. Another study focused on the impact of leukocytosis on thrombotic events over time. Among 189 ET and prefibrotic PMF patients, elevated baseline WBC count at diagnosis was a significant risk factor for thrombosis both in univariate and multivariate analysis (P=0.005 and P= 0.017 respectively), but WBC count during follow up had no impact. This result mainly applied to prefibrotic PMF since majority of ET patients had normal WBC count. The platelet counts and hemoglobin level were not significant risk factors of thrombosis both at diagnosis and during follow up [38]. A comparative study between 61 patients with ET and 72 with “early” PMF (26 prefibrotic and 42 with grade 1 or 2 fibrosis) demonstrated that, at or before diagnosis, “early” PMF patients had higher frequency of thrombosis than ET patients (22% vs 8% before diagnosis and 15.2% vs 1.2% at diagnosis). Similarly, patients with prefibrotic PMF had higher 15-year risk of thrombotic events (48 %) compared to WHO-defined ET (17%) or fibrotic PMF patients (16%). By multivariate analysis, age >60 years and prefibrotic PMF were significant risk factors for developing thrombotic complications at 20 years [8]. Barosi et al. demonstrated a significantly higher incidence of splanchnic vein thrombosis in prefibrotic PMF as compared to fibrotic PMF [39].

The current expert opinion is to treat prefibrotic PMF like true ET. Thus, prefibrotic PMF patients should receive cytoreductive therapy only if they are at high risk of thrombosis secondary to age >60 years and/or a history of thrombotic events [37]. However, since prefibrotic PMF patients may have a different thromboembolic profile and the entity itself was shown to be an independent risk factor for thrombosis, a case could be made for the creation of separate prefibrotic PMF-specific risk model. Further research will be needed to solidify and elaborate information on the thrombotic risk of this novel entity.

Bleeding in myelofibrosis

Descriptive epidemiology

Bleeding events in MF may affect survival outcomes and impact quality of life [40,41]. Many MF patients have a degree of anemia that is often transfusion-dependent, especially in the more advanced stages of disease. Major bleeding episodes would, therefore, worsen pre-existing anemia and precipitate adverse outcomes. Indeed, hemorrhagic events can be fatal and are one common cause of death in PMF [42].

Table 3 depicts how the frequency of bleeding events vary widely across reported studies. However, most of them have demonstrated it to be higher than in ET or PV [11,7]. The available studies have generally been small in size and reported the frequency of events during follow-up rather than at or before diagnosis. In a small cohort of 25 patients, 57% had the bleeding events as compared to a frequency of 23% in PV, 20% in CML, and 16 % in ET [7]. An analysis from the German SAL-MPN-registry reported only 2 out of 36 bleeding events before the diagnosis of MPN which suggested that major bleeding occurred as a consequence of MPN or its treatment. Collectively, there were 10 bleeding events among 109 PMF patients, 4 in 21 post-PV MF patients and 1 in 19 post-ET MF patients at or before diagnosis and during follow up [19].

Life-threatening bleeding complications in patients with MF include variceal bleeding secondary to portal hypertension and intracranial bleeding, among others. Upper gastrointestinal bleeding was the most common cause of major bleeding among PMF patients with 6 out of 10 events reported in one study [19]. In the same series, 3 events of intracranial hemorrhage were recorded [19]. Other minor bleeding manifestations in MF include echymosis, gingival hemorrhage, menorrhagia and epistaxis.

Pathophysiology

There are several possible causes of bleeding in a MF patient. Progressive thrombocytopenia secondary to marrow failure, and functional abnormalities of platelets are common findings in MF patients[43]. Mild acquired factor V deficiency was found in some MPN patients, but did not significantly correlate with bleeding events. It was shown in one of the largest case series of 33 MPN patients out of which 21 (64%) had MF that included 13 PMF patients (40%) [44]. Acquired von Willebrand’s syndrome secondary to very high platelets may cause bleeding in MF, as it does in other MPN [45]. Extreme thrombocytosis in MPN patients can also cause clot fragility secondary to a mechanical effect of the high platelet count, or to inhibition of fibrin polymerization by platelet glycoprotein 1b [46]. Massive splenomegaly and splanchnic vein thromboses are commonly found in MF and can lead to portal hypertension and development of gastric and/or esophageal varices [47,48]. Other causes of bleeding in MF patients include use of antiplatelets and/or anticoagulants. In most cases, multiple bleeding risk factors are at play in any given MF patient, further complicating the clinical picture and management.

Risk factors

There have been limited studies dedicated to evaluating the hemorrhagic complications of MF. Moreover, analyses have been heterogenous in terms of number of patients, subtypes of MF and duration of follow-up [7,19,9,11]. Most series, as displayed in Table 4, included MPN patients in general, rather than MF specifically, further complicating the interpretation of data [5, 7, 10, 15]. Using a multivariable logistic regression, Kander et al. reported that bleeding events did not vary significantly by MPN subtype (10 % in ET, 19.1% in MF, 30% in MPN-U and 15.3% in PV). In addition, the study failed to show a correlation between bleeding risk and leukocyte count at presentation, platelet count at presentation, aspirin use, presence of *JAK2V617F* mutation, gender, or prior thrombosis history. There was an association between bleeding and older age at diagnosis [9]. Similarly, a retrospective analysis by Wehmeier et al. of 260 MPN patients reported that elevated platelet count and patient age were not risk factors of bleeding [7].

Management

The prevention and management of bleeding in MF patients is generally centered on the judicious use of antiplatelet agents and anticoagulants, and platelet transfusions when clinically indicated. In cases of major hemorrhage, the acute blood loss is managed with volume expansion, with or without the use of blood products as necessary, whereas chronic anemia in MF may be managed with the use of androgens, erythropoeitin stimulating agents, prednisone or immunomodulating agents, such as thalidomide or lenalidomide [49–53], recognizing that these agents have an intrinsic potential to cause or precipitate a thrombotic event and thus demand frequent monitoring of the patient and hemoglobin response. The role of thrombocytapheresis in management of bleeding secondary to extremely high platelet counts is not well defined in MF patients. However, like any other thrombocytosis in general, it may be considered on case by case basis, if urgent platelet reduction is desired in bleeding secondary to acquired von Willebrand's syndrome [54]. Per current ASFA guidelines, thrombocytapheresis is a category 2 (second line therapy either as a standalone treatment or in conjunction with other modes of treatment), grade 2C recommendation (weak recommendation, low quality or very low quality evidence) for symptomatic thrombocytosis [55].

Bleeding in prefibrotic PMF

The definition of bleeding risk in patients with prefibrotic PMF is evolving as this is a relatively new entity. In a large international study, among 1104 patients who were initially diagnosed as having ET, 891 were found to have true ET and 180 were revised as prefibrotic PMF patients. During follow-up, major bleeding occurred in 55 (6%) WHO-defined ET and 21 (12%) prefibrotic PMF patients (p=0.009), at the rate of 0.79 and 1.39 patient-year, respectively. Independent predictors of bleeding included the diagnosis of prefibrotic PMF, previous hemorrhage, leukocytosis and aspirin therapy [11]. The reticulin grade was found to be an independent risk factor of bleeding during follow-up in a study of ET patients (P=0.05) [56], raising the question of whether those patients had thrombocythemic manifestations of prefibrotic PMF. In a retrospective analysis of 565 ET patients diagnosed between 1977 and 2010, Palandri et al. described significant correlation between total

bleeding events and baseline splenomegaly (P <0.0001), history of hemorrhage (P =0.005), platelet count higher than 1000 × 10^9/l (P<0.0001) and leukocyte count >11 × 10^9/l (P<0.0001) in a univariate analysis. The patients were further stratified, based on presence of 3 risk factors for hemorrhage (splenomegaly, leukocyte count 11 ×10^9/l, platelet count >1000 ×10^9/l), into high risk (total 66 patients, 60 with 2 and 6 with 3 risk factors), intermediate risk (160 patients with 1 risk factor) and low risk (no risk factors). The cumulative risk of hemorrhage at 10 years was 8.8% in the low risk, 16.4% in the intermediate risk (P=0.09) and 45.8% in the high risk (P<0.001)[57]. Interestingly, the 3 high risk factors were typical of a subgroup of 'PVSG-diagnosed ET', now recognized as prefibrotic PMF [15].

Conclusion

The exact pathogenesis of vascular events in MF remains poorly understood and requires further investigation. Age >60 and prefibrotic PMF are consistently associated with higher risk of thrombosis while thrombocytosis and *JAK 2* positivity are consistently not associated with risk of bleeding. The other proposed risk factors have not shown consistent relationship across studies. The interaction of MPN, specifically MF with other hereditary and acquired thrombophilic states, including the use of oral contraceptives, is virtually unknown. There is lack of prospective studies and data are derived mostly from heterogeneous retrospective studies. The predictive value of the currently known factors is rather limited and the development of a scoring system for risk stratification remains a challenge. Moreover, the optimal use of antiplatelet agents for the secondary prevention of cardiovascular events, especially in light of increased risk of bleeding in these patient population, is still unclear. Data informing clinical decision has often been extrapolated from studies examining MPN in general, that may not necessarily apply to MF as an individual entity. The pro-thrombotic role of *JAK2V617F* mutation in PV or ET is well established and is included in the thrombotic risk model for ET [58], but remains to be clarified in patients with MF. The newly formalized definition of prefibrotic MF emphasized the need for re-exploration of the thrombohemorrhagic risk profile of this group of patients. Available studies suggest that the risk of these events may be different in prefibrotic PMF versus overt PMF.

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Table 1

Studies reporting types and frequency of major thrombotic events in patients with primary myelofibrosis

Characteristics	Cervantes et al. [6]	Kaifie et al. [19]	Rupoli et al. [8]	Barbui et al. [13]	Elliot et al. [12]	Buxhofer-Ausch et al. [14]	Buxhofer-Ausch et al. [38]	Barosi et al. [39]
Total no. of pts.	155 (Included fibrotic PMF)	109 (Included fibrotic PMF)	72 (26 prefibrotic and 42 fibrotic PMF)	707 (Included fibrotic PMF)	205 (Included fibrotic PMF)	264 (Early/prefibrotic PMF)	77 (Prefibrotic PMF)	132 (prefibrotic PMF) 551 (Fibrotic PMF)
F/u duration	4.2 yrs. (mean)	25 yrs.**	7.08 yrs. (median)	35 yrs.	2.6 yrs. (median)	6.2 yrs. (median)	9.5 yrs.	At or in the year before diagnosis
No. of patients with thrombotic events (%)	18 (11.6)	NR	NR	47 (6.64) nonfatal and 12 fatal (1.69)	22 (10.7)	42 (15.91) nonfatal 13 (4.92) fatal	NR	40 (30.3) Prefibrotic PMF 37 (6.7) Fibrotic PMF
No. of events	31	34	22	59	33	NR	21	NR
VTE*	11	17	11	31	24	NR	NR	36 (90) Prefibrotic PMF 34 (92) Fibrotic PMF
ACS	4	7	4	7	4	NR	NR	NR
Stroke/TIA	7	7	3	13	4	NR	NR	NR
PVD	7	NR	NR	7	1	NR	NR	NR
Others	1(CRAO) 1 (cerebral thrombosis)	NR	3 (CRAO) 1 (cerebral thrombosis)	1 (sudden death)	NR	NR	NR	2 (5) cerebral thrombosis and 2 (5) arterial thrombosis Prefibrotic PMF 3 arterial thrombosis Fibrotic PMF

*VTE included DVT/PE, portal vein thrombosis and Bud-Chiari syndrome.

** Also included events at diagnosis and follow up. NR = not reported.

Table 2

Studies reporting risk factors for thromboembolism in MPN

Risk Factors	**Cervantes et al.[1,2] (included PMF) [6]**	**Keife et al.[2] (included PV, ET, PMF, post-ET-MF, post-PV-ME, MPN-U [19]**	**Rupoli et al.[1] (included ET, early/prefibrotic MF) [8]**	**Barbui et al.[1] (included PMF) [13]**	**Ellot et al.[1] (included fibrotic PMF) [12]**	**Buxhofer-Ausch et al.[1](included prefibrotic MF) [14]**
Age >60	NR	NR	+	+	NR	−
JAK2 V617F	NR	NR	NR	+	NR	−
Leukocytosis >15 × 10^3	NR	NR	NR	−	−	+*
Platelets >450 × 10^9/l	+[2]	NR	NR	−	NR	NR
History of thrombosis	NR	NR	NR	NR	+	−
Splenomegaly (palpable)	NR	+	NR	−	NR	NR
Hb>11 g/dl	+[2]	NR	NR	−	NR	NR
Post PV MF	NR	+	NR	NR	NR	NR
Any cardiovascular risk factor	+[1]	NR	NR	NR	NR	−
Prefibrotic MF	+[1]	NR	+	NR	NR	NR
Cytoreductive therapy	NR	NR	NR	NR	NR	−
Platelets<870 ×10^9	NR	NR	NR	NR	NR	+

+ denotes significant association and − denotes no significant association.

*Leukocytosis >11.2 × 10^9/L.

[1]denotes multivariate analysis,

[2]denotes univariate analysis. NR = not reported

Table 3

Studies reporting frequency of bleeding in myelofibrosis

Characteristics	Kander et al. [9] (Myelofibrosis)	Wehmeier et al. [7] (Myelofibrosis)	Finazzi et al. (prefibrotic PMF) [11]
Number of patients	63	25	180
No. of bleeding pts during the follow up, n (%)	12 (19)	14 (56)	21(12)

Table 4

Studies reporting risk factors for bleeding in MPN

Risk factors	Wehmeier et al.[1] (included ET, PV, PMF and CML) [7]	Kaife et al.[2] (included PV, ET, PMF, MPN-U, post-ET-MF and post-PV-MF) [19]	Kander et al.[1] (included PV, ET, PMF, MP PV, ET, PMF, MPN-U, post-ET-MF, post-PV-MF and MDS/MPN) [9]	Finazzi et al.[1] (included ET and prefibrotic MF) [11]
Age at diagnosis	−	NR	+	−
Thrombocytopenia	−	NR	NR	NR
Thrombocytosis	−	−	NR	−
JAK 2 positivity	NR	NR	−	−
Aspirin use	NR	−	−	+
Anticoagulation	NR	−VKA and Rivaroxaban + Heparin	NR	NR
Thrombotic/thromboembolic event in medical history	NR	+	−	−
Palpable splenomegaly	NR	+	NR	−
MPN subtype	NR	NR	−	+ (prefibrotic MF>ET)
Leukocytosis (WBC=or> 11K)	NR	NR	NR	+
History of bleeding	NR	NR	NR	+
Decreased RBC number	+	NR	NR	NR
Decreased Hemoglobin	+	NR	NR	NR
Decreased percentage of segmented neutrophils	+	NR	NR	NR

+ denotes significant association, − denotes no significant association. NR = not reported.

[1] denotes multivariate analysis,

[2] denotes univariate analysis.