Leukemia Research 136 (2024) 107420

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

The molecular landscape of myeloproliferative neoplasms associated with splanchnic vein thrombosis: Current perspective

Carlo Pescia [a,*], Gianluca Lopez [a,f], Daniele Cattaneo [b,c], Cristina Bucelli [b], Umberto Gianelli [d,e], Alessandra Iurlo [b]

[a] Unit of Anatomic Pathology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[b] Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[c] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[d] Department of Health Sciences, University of Milan, Milan, Italy
[e] Unit of Anatomic Pathology, ASST Santi Paolo e Carlo, Milan, Italy
[f] Department of Biomedical, Surgical and Dental Sciences, University of Milan, Italy

ARTICLE INFO

Keywords:
Myeloid neoplasms
Myeloproliferative neoplasms
Splanchnic vein thrombosis
Molecular biology

ABSTRACT

BCR::ABL1-negative myeloproliferative neoplasms (MPNs) are classically represented by polycythemia vera, essential thrombocythemia, and primary myelofibrosis. *BCR::ABL1*-negative MPNs are significantly associated with morbidity and mortality related to an increased risk of thrombo-hemorrhagic events. They show a consistent association with splanchnic vein thrombosis (SVT), either represented by the portal, mesenteric or splenic vein thrombosis, or Budd-Chiari Syndrome. SVT is also a frequent presenting manifestation of MPN. MPNs associated with SVT show a predilection for younger women, high association with *JAK2V617F* mutation, low *JAK2V617F* variant allele frequency (generally <10 %), and low rates of *CALR*, *MPL*, or *JAK2* exon 12 mutations. Next-Generation Sequencing techniques have contributed to deepening our knowledge of the molecular landscape of such cases, with potential diagnostic and prognostic implications. In this narrative review, we analyze the current perspective on the molecular background of MPN associated with SVT, pointing as well future directions in this field.

1. Introduction

BCR::ABL1-negative myeloproliferative neoplasms (MPNs) are clonal myeloid neoplasms defined by the absence of *BCR::ABL1* fusion transcript and by the aberrant proliferation of differentiated myeloid cells in the bone marrow and peripheral blood. They are classically represented by Polycythemia Vera (PV), Essential Thrombocythemia (ET), Primary Myelofibrosis (PMF, either in the pre-fibrotic or overt fibrotic stage), and myeloproliferative neoplasms, unclassifiable (MPN-U) [1–4].

BCR::ABL1-negative MPNs are molecularly defined by alterations of the *JAK-STAT* pathway. *JAK2*V617F mutation leads to a constitutively activated *JAK/STAT* signaling; it is found in more than 95 % of PV patients, and up to 60 % of ET and PMF cases. *JAK2 exon 12* mutations are found in almost all *JAK2*V617F-negative PV cases while being absent in ET and PMF. On the other hand, *MPL* mutations, leading to an activation of the thrombopoietin receptor, are found in 5 %−10 % of patients with ET and PMF and not in PV. Last but not least, calreticulin (*CALR*) mutations are found in up to 35 % of ET and PMF cases, but again not in PV patients [1,3,5]. About 20 % of ET and 10 % of PMF cases do not show any of the above-mentioned driver mutations and are therefore termed "triple negative"; instead, they exhibit non-driver mutations as surrogate markers of clonal hematopoiesis [6]. Concomitant mutations in other genes, such as *TET2*, *ASXL1*, *IDH1/2*, *EZH2*, *SRSF2*, *U2AF1*, and *DNMT3A* can be variably encountered across *BCR::ABL1*-negative MPNs, especially within PMF in the overt fibrotic phase or MPN accelerated/blast phase [7]. *ASXL1, IDH1/2*, *EZH2*, *SRSF2*, and *U2AF1* mutations portend poorer prognosis as they guide disease progression and are therefore termed "High Molecular Risk" (HMR) mutations. Moreover, the acquisition of *TP53* mutation is a well-known leukemogenic factor in MPNs [1,8].

BCR::ABL1-negative MPNs show a consistent association with thrombosis, also involving unusual sites, such as cerebral veins and splanchnic vessels (SVT). SVT is an unusual thromboembolic

* Corresponding author.
E-mail address: carlo.pescia@unimi.it (C. Pescia).

https://doi.org/10.1016/j.leukres.2023.107420
Received 26 June 2023; Received in revised form 30 October 2023; Accepted 3 November 2023
Available online 10 November 2023

phenomenon that manifests as portal (PVT), splenic, or mesenteric vein thrombosis, or Budd-Chiari syndrome (BCS), defined as hepatic venous outflow obstruction [9]. PVT is the most common SVT with a prevalence esteemed around 1 % [10], while BCS is, on the other hand, the least frequent (Fig. 1) [11]. *BCR::ABL1*-negative MPNs hold almost a 5-fold higher risk of venous thrombosis compared to controls [12], with a particular increase in SVT incidence; radiographic evidence of SVT is found in almost 1/3 of MPNs [13]. On the other hand, a *BCR::ABL1*--negative MPN diagnosis is made in 15 %−30 % of patients presenting with PVT and in up to 50 % of those with BCS [10,14,15].

This narrative review aims to describe current insights on specific molecular alterations of *BCR::ABL1*-negative MPNs associated with SVT (from now on, MPN-SVT), and their relationship with clinical and pathological features.

2. Epidemiology and natural history of MPN-SVTS

While other thrombotic events are more frequently reported in the elderly, MPN-SVT shows a distinct and unexplained predilection for female patients younger than 45 years old. Moreover, SVT risk is significantly higher within the first year of MPN diagnosis among younger patients compared to older ones [12]. This is probably due to a combination of environmental factors (i.e. oral contraceptive assumption), co-occurrence of thrombophilia disorders, low intensity of treatment, and/or higher prevalence of the *JAK2 46/1* haplotype, which is associated with a higher risk of MPN-SVT development and a presumed higher frequency among females [17–24]. The co-existence of hypercoagulable/thrombophilia disorders might have been an underestimated factor in the past, and it is found in almost 40 % of MPN-SVT [25].

Despite its significant association with MPNs, SVT risk is not uniformly distributed among different MPN subtypes. SVT shows in fact the strongest association with PV (37.1 % of MPN-SVT), followed by ET (34.4 %), PMF (17 %), and MPN-U (10.6 %) [25]. Accordingly, SVT prevalence among PV patients is significantly higher than in other MPNs (76 % vs. 26 %) [26], while PMF exhibits the lowest SVT prevalence, estimated at around 1 % [27]. However, MPNs should be suspected in all patients presenting with non-cirrhotic/non-malignant SVTs. BCS is associated with PV in 52.9 % of cases, with ET in 24.6 % and with PMF in 6.7 %, while PVT is associated with PV in 27.5 % of cases, with ET in 26.2 % and with PMF in 12.8 % [15].

Of interest, vascular complications, including SVT, seem to occur frequently within two years before MPN diagnosis, therefore assuming the role of a presenting sign of disease [28], especially in the context of MPN-U [16,29]. De Stefano et al. [30] have in fact identified SVT as the heralding manifestation of MPN in 58 % of their cohort composed of 181 patients. Interestingly, however, the reported association between MPN-U and SVT might be partly biased by the hypersplenism and hemodilution caused by the SVT itself, which hinders the expression of a full-blown MPN phenotype. Therefore, a consistent subset of MPN-SVT might be incorrectly termed as “unclassifiable” due to the inability to meet specific clinical criteria (such as hemoglobin and hematocrit thresholds for PV), an occurrence seen in about 40 % of MPN-SVT patients [15,16,30,31]. It should be noted, however, that tools such as red cell mass measurement and plasma volume measurement (with Cr^{51}-labeled RBC and $I1^{25}$-labeled albumin respectively) consistently help in excluding hemodilution and/or hypersplenism and might be valuable in augmenting diagnostic accuracy for MPN-SVT, especially in the case of PV; unluckily, they are not commonly used and are available at few centers [32–34].

According to some authors [35], MPN-SVTs might have shorter age-corrected survival compared to conventional MPNs due to vascular complications (such as liver failure and major bleeding) and higher incidence of second cancers rather than to actual MPN progression. With specific regards to hemorrhagic complications, a multicenter study on chronic non-cirrhotic, non-tumoral PVT reported an incidence of newly developed varices of 2 % at 1 year and 22 % at 3 years, and a probability of worsening of existing esophageal varices of 13 % and 40 % at 1 and 3 years, respectively. The same study reported a probability of bleeding in patients with large esophageal varices of 9 % and 20 % at 1 and 3 years [36]. MPN-SVTs show high recurrence of thrombotic events, with an esteemed risk of 2.55 % per year; BCS, history of thrombosis, splenomegaly, and leukocytosis are all factors independently associated with SVT recurrence [30]. However, most studies agree on the general benign clinical behavior of MPN-SVT with low rates of leukemic evolution [25,29,31,37–39]. A panoramic on epidemiologic and molecular features associated with MPN-SVT is offered in Fig. 2.

3. Pathogenesis of SVT IN BCR::ABL1-Negative MPNS

The exact mechanism leading to SVT in MPNs is yet to be fully understood. Higher hematocrit levels and increased platelet count (>400

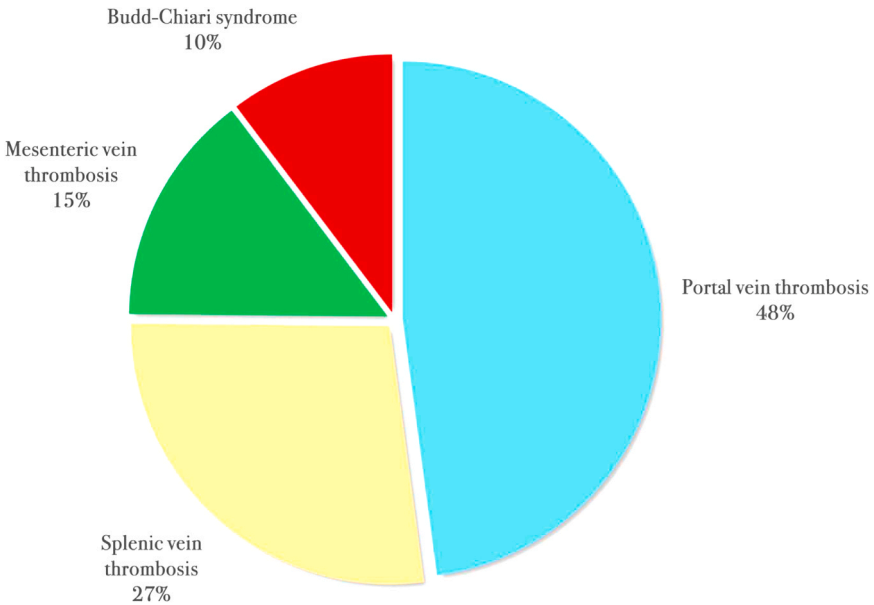

Fig. 1. Percentual distribution of different types of MPN-SVT based on the experience at our center [16].

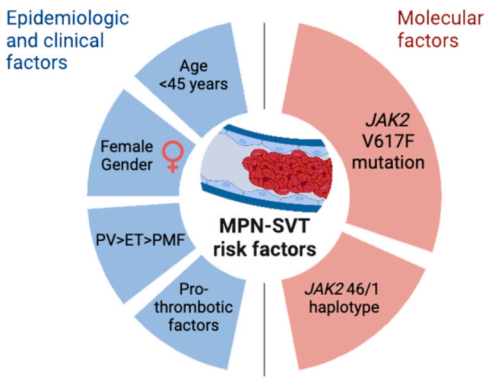

Fig. 2. Epidemiologic, clinical, and molecular features associated with MPN-SVT. (PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis). Image created with Biorender.com.

x10^9/L) have been predictably linked to thrombotic diathesis in MPN patients [40], thus representing important risk factors to be monitored. Hence, lowering hematocrit and platelet count represents one of the most important therapeutic interventions in MPNs. However, blood counts are not the only variable determining MPN-SVT. Several studies have demonstrated *JAK2*V617F mutation also in endothelial cells, which play a pivotal role in coagulation homeostasis [41–43]. This fascinating observation confirms a common cell of origin for hematopoietic and endothelial cells and provides further insights regarding the pro-thrombotic implications of *JAK2* mutations. Indeed, *JAK2*V617F mutations lead to an increased endothelial expression of von Willebrand factor (vWF) and P-selectin, which exhibit adjuvant functions in platelet adhesion and aggregation at sites of injury [44,45], and to a pro-coagulative endothelial phenotype as demonstrated by means of transcriptomic analysis [46].

Another significant aspect contributing to SVT might be represented by slow flow gradients within the splenic vein system [14] and the increase in circulating endothelial cells in MPN patients [47], which may both play additive pro-coagulative roles.

Lastly, several studies have highlighted a reduced bioavailability of nitric oxide (NO), increased cell adhesion molecules expression, and decreased fibrinolysis via *STAT* pathway activation in *JAK2*-mutated MPNs, deranging the hemostatic balance and therefore contributing to thrombosis [48–54].

Pathogenetic mechanisms involved in MPN-SVT are summarized in Fig. 3.

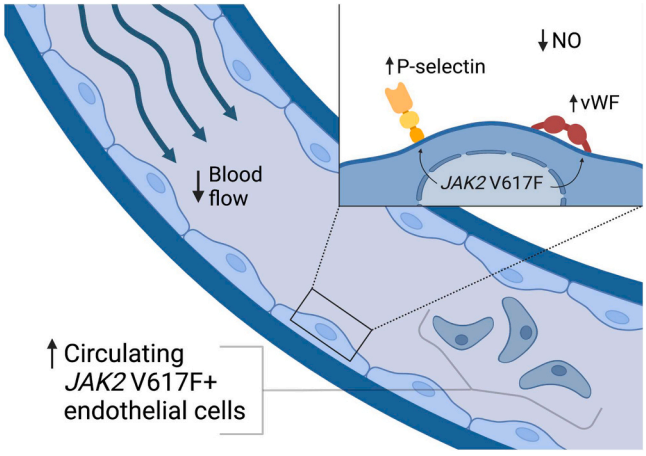

Fig. 3. Mechanisms involved in MPN-SVT pathogenesis include decreased blood flow in splanchnic veins, increase in circulating *JAK2*-mutated endothelial cells, and up-regulation of P-selectin and von Willebrand factor and downregulation of NO production by *JAK2* mutated endothelial cells. Image created with Biorender.com.

4. Molecular insights on *BCR::ABL1*-NEGATIVE MPNS associated with SVT

4.1. *JAK2 mutations in SVT: a molecular driver and a predictor of MPN?*

*JAK2*V617F mutation is detected employing polymerase chain reaction (PCR) techniques in 4 %−32 % of SVTs, depending on different population samples [55–57], while its prevalence is significantly lower (less than 10 %) in non-SVT vascular complications. *JAK2*V617F mutation confers indeed a higher risk of SVT, with an odds ratio of 53.98 [55], and its screening reveals an underlying MPN in 17.1 % of BCS patients and 15.4 % of those with PVT [15]. Overt MPNs complicated with SVT seem to show even higher *JAK2*V617F mutation prevalence, ranging from 71 % to 100 % [25,58]. Moreover, the frequency of *JAK2*V617F mutation is significantly higher in ET and PMF associated with SVT compared to their control counterparts (85.1 % vs. 60.6 % and 84.6 % vs. 65.2 % respectively). No differences in this regard have been observed in PV patients, while MPN-U associated with SVT harbor the *JAK2*V617F mutation in almost 94 % of cases [25].

*JAK2*V617F variant allele frequency (VAF) has been studied by several authors in conventional MPNs with interesting results. First, PV patients show higher although heterogeneous *JAK2*V617F VAF compared to ET patients, with a median value of around 50 %. A VAF higher than 50 % in PV has been correlated by several studies with a higher risk of arterial and venous thrombotic events [59–61] and the development of secondary myelofibrosis [62]. On the other opposite of the spectrum, cases with low VAF (<1 %) might harbor additional genetic abnormalities such as *CALR* exon 9 or *MPL* mutations [63]. *JAK2*V617F VAF varies widely in MPN-SVT patients, with a mean value of 27 % [64]. Quite surprisingly, MPN-SVTs show a significantly lower *JAK2* allele burden compared to conventional MPNs. How *et al.* [65] found a median VAF value of 5 % in MPN-SVTs compared to a median of 36.3 % in MPNs ($p = 0.019$), with no patients showing a VAF greater than 10 %. This finding was subsequently confirmed by other authors [39,66,67]. In the large MPN-SVT cohort studied by Sant'Antonio et al. [25], however, median *JAK2*V617F VAF was 47.7% in PV, 29.5 % in ET, 30 % in overt PMF, 43 % in pre-fibrotic PMF, and 19.2 % in MPN-U. Moreover, the authors highlighted a higher *JAK2* allele burden among ET-SVT compared with ET controls (29.5 % vs. 22 %, $p = 0.029$), while results regarding other MPN-SVT phenotypes were not statistically significant.

*JAK2*V617F mutation is found in about 30 % of SVT without overt MPN [68,69]. In this regard, as mentioned in the epidemiology section, many authors have highlighted the inadequacy of peripheral blood count criteria for MPN diagnosis in the setting of MPN-SVT, mainly due to hypersplenism, bleeding from gastro-esophageal varices, and hemodilution: all these factors modify blood counts hampering the fulfillment of diagnostic clinical criteria and lead to underdiagnosis of MPN and/or overdiagnosis of MPN-U [16,25]. Hence, Yonal et al. [68] have suggested specific cut-off values for platelet (>190 x10^9/L) and white blood cell count (>8.15 x10^9/L) that may improve *JAK2*V617F diagnostic significance and therefore MPN diagnosis in SVT clinical setting: according to their study, these two parameters were the only ones that positively correlated with *JAK2*V617F mutational status. During the last twenty years, WHO classifications have progressively lowered PV hemoglobin/hematocrit thresholds and ET platelets cutoff to improve MPN diagnosis; however, the debate concerning the correct classification of *JAK2*V617F mutated SVTs without "overt" MPN is still ongoing. In this regard, the scientific community suggests performing *JAK2*V617F testing in the diagnostic workup of SVTs outside the cirrhotic or oncologic setting, as a useful tool to identify "latent" MPNs [64,66,70–75].

Of note, *JAK2 exon 12* mutations are extremely rare in MPN-SVT and have been documented only by means of Next-Generation Sequencing (NGS) or high-resolution melting (HRM) techniques (see paragraph *4.5*)

[66,72,76,77].

4.2. The JAK2 46/1 haplotype and its role in MPN-SVT

As mentioned above, *JAK2 46/1* (GGCC) haplotype on chromosome 9p.24.1 might have particular implications in MPN-SVT development. *JAK2 46/1* haplotype is found in up to 45 % of the general population and is associated with a predisposition towards *JAK2* mutations, leading to a 5 times higher risk of MPN development. Interestingly, the *46/1* haplotype has also been linked to *MPL*-mutated MPNs, inflammatory diseases, and reduced defense against infections [22,78–80].

Different studies have explored the association between this haplotype and SVT or MPN-SVT. Colaizzo *et al.* have discovered a significantly higher frequency of the *46/1* haplotype among *JAK2*-unmutated SVTs [81], while Smalberg *et al.* demonstrated its higher expression among patients with *JAK2*-mutated BCS and *JAK2*-negative SVT associated with a documented MPN [21]. Additionally, Villani *et al.* observed a significantly higher prevalence of the *46/1* haplotype across MPN-SVTs compared to the normal population, while its frequency was not increased in idiopathic SVTs not associated with MPN [82].

In conclusion, *JAK2 46/1* haplotype plays an important role as a susceptibility factor for MPN and therefore for MPN-SVT, while it is not presumably associated with SVT *per se* [83,84].

4.3. CALR mutations

Calreticulin (*CALR*) exon 9 mutations are the second most common driver mutation found in MPNs and determine a ligand-independent activation of the thrombopoietin receptor. *CALR* frameshift mutations lead to a novel C-terminal protein sequence, either represented by a 52-bp deletion (type 1 mutation) or a 5-bp insertion (type 2 mutation). Type 1 mutation is the most commonly found and presents a more favorable prognosis in PMF [1,85,86]. The prevalence of *CALR* mutations among MPN-SVT is deemed to be really low. Turon *et al.* [87] report a 1.9 % prevalence of *CALR* mutations among SVT patients and a 5.4 % prevalence in cases with an underlying MPN. Similar results have been reported in more or less wide cohorts by different authors [25,88–91]. In the work by Poisson et al. [88], all *CALR*-mutated patients had a spleen height $\geq$16 cm and a platelet count $>200 \times 109$/L; these criteria had a low positive predictive value but a 100 % negative predictive value and can be used to choose those patients who may benefit from *CALR* testing.

In light of these findings, *CALR* testing is not strongly recommended in the SVT diagnostic workup, with the obvious exception of *JAK2*-negative cases with features highly suggestive of MPNs as those reported by Poisson et al. [64,88,92]. Interestingly, a reason for *CALR*'s inconsistent association with MPN-SVT might be represented by lower thrombotic risk and lower platelet reactivity observed in *CALR*-mutated ETs [93–95].

4.4. MPL mutations

Missense *MPL* mutations represent the third most common molecular alteration in MPN. The most common *MPL* mutations (either W515L or W515K) lead to an amino acid substitution at the 515 position and to subsequent constitutive activation of thrombopoietin receptor signaling. *MPL* mutations in MPNs have been linked to older age at presentation and lower cell counts, although with no significant prognostic implications [96–98].

In a similar fashion to *CALR*, *MPL* mutations are infrequent among MPN-SVTs, with a presumed prevalence inferior to 1 % according to different cohorts and reports; these results probably reflect its overall low prevalence among all MPNs [25,64,72,76,99,100]. Bergamaschi et al. [76] identified 3/93 (3 %) SVT patients showing *MPL*W515 mutations: however, they were all confirmed ET and one harbored also a concomitant *JAK2*V617F mutation with *MPL* and *JAK2* VAF both inferior to 50 %.

4.5. Triple-negative cases and additional mutations. The role of Next-generation sequencing in MPN-SVTs

While triple-negative cases account for 10 %−15 % of MPNs, a precise evaluation of their contribution to the molecular background of MPN-SVTs is difficult, although some authors have reported a 3.5 % prevalence among MPN-SVTs [16].

Conventional quantitative polymerase chain reaction (qPCR) and digital droplet PCR (ddPCR) are the routinely used techniques to perform *JAK2*V617F evaluation in suspected MPNs, as they allow sensitive detection of low VAF. On the other hand, *CALR* and *MPL* mutations are usually detected by Sanger sequencing or PCR techniques in *JAK2*V617F-negative cases [101,102]. However, PCR does not permit the simultaneous complex screening of genetic variants, which is instead enabled by Next-Generation Sequencing (NGS). NGS has been applied to conventional MPNs with interesting results, although at present its use is still mainly considered for investigational purposes. NGS provides diagnostic improvements, especially in triple-negative cases, supplying molecular proof of clonal hematopoiesis [6,103–106]. Clonal markers alternative to classical driver mutations suggested for MPN diagnosis by the present classifications include *ASXL1*, *EZH2*, *TET2*, *DNMT3A*, *IDH1*, *IDH2*, *SRSF2*, and *SF3B1* mutations, and/or translocations such as those involving *ABL1* [1,4]. Many of these mutations, implied in spliceosome or chromatin remodeling, have been also linked to a more aggressive disease course in MPNs.

Likewise, NGS techniques have been suggested to improve the diagnosis of underlying MPNs in SVT patients lacking conventional MPN molecular alterations. Magaz *et al.* showed that 2/5 (40 %) cases originally categorized as triple negative MPN-SVT harbored *JAK2 exon 12* mutations [107]. Moreover, they highlighted additional mutations in *TET2*, *DNMT3A,* and *ASXL1* genes in more than 1/3 of SVT patients, supporting a putative role as predictors of thrombotic events. Indeed, *TET2* mutations might be an independent thrombotic risk factor in PV [108] and in the study by Magaz et al. patients with additional mutations in the above-mentioned genes exhibited a trend towards recurrent thrombosis. *TET2* mutations have been previously documented in almost 15 % of SVT patients [109,110]. However, despite being more frequent than *CALR* and *MPL* mutations in MPN-SVT, *TET2* alterations co-occur frequently with *JAK2V617F* mutations, and their contribution to thrombosis and prognosis is yet to be fully understood. More recently, in a single-center experience evaluating the clinical-morphological and molecular data of 58 consecutive patients with MPN-SVT, the authors showed a high prevalence of *TET2* mutations (28.5 %) compared with other previous studies (roughly 14 %) [111]. This evidence, together with a reported increased prevalence of cases with homozygous *JAK2*V617F mutations, which have been shown to precede those of *TET2* in the majority of subjects, allowed the authors to hypothesize a genetically determined prothrombotic phenotype in MPN patients affected by SVT.

In contrast with these findings, Kiladjian et al. [112] failed to highlight any additional mutations in triple-negative SVTs by means of NGS, although they were able to prove clonal hematopoiesis for 1 case out of 5 triple-negative MPN-SVT (20 %) harboring a *DNMT3A* mutation.

Ultradeep NGS, which consists of multiple repetitions of genomic region sequencing, has been able to detect *JAK2*V617F and *MPL*W515R mutations in about 30 % of blood samples from an SVT cohort composed of 44 patients, including 7 mutations whose VAF was under the conventional NGS detection threshold of 2 % and a co-occurrence of both *JAK2* and *MPL* mutations [67]. Ultradeep NGS has high sensitivity, and it might therefore predict MPN diagnosis and increase MPN prevalence among SVT patients by identification of low and ultra-low driver mutation allele burdens.

Finally, Debureaux *et al.* [39] illustrated a molecular profiling scheme for MPN-SVT delineating a high-risk subset of patients defined by the presence of at least one of the following: (a) *JAK2*-mutant allele burden $\geq$50 %, (b) chromatin, spliceosome or *TP53* mutations detected

by NGS. These patients showed worse event-free and overall survival, representing 29 % of the analyzed cohort. This elegant study parallels analogous results found in conventional MPN, where additional mutations affecting chromatin or spliceosome (i.e., *TET2, DNMT3A*, and *ASXL1* mutations) negatively impact survival [113]. NGS might therefore identify high-risk patients who might benefit from disease-modifying therapies. However, due to conflicting pieces of evidence, the prognostic value of *TET2* mutations in MPN has been significantly downsized by current WHO and ICC classifications, which identify only *EZH2*, *IDH1*, *IDH2*, *SRSF2*, *ASXL1*, and *U2AF1* alterations as "high molecular risk" (HMR) mutations [1,4].

4.6. Practical recommendations on laboratory and molecular testing in MPN-SVTs

To summarize, considering the scientific evidence and expert recommendations, the initial assessment of suspected MPN-SVTs involves physical examination, complete blood counts, and ultrasounds or CT scans. These serve as the fundamental tools for disease characterization and the localization of SVTs, helping to point toward a potential MPN diagnosis. If the blood counts do not raise suspicion of MPN, additional tests such as red cell mass or plasma volume measurements, available in selected centers, can be useful in ruling out the effects of hypersplenism and hemodilution [34].

When confronted with clinical indicators suggestive of MPN-SVT, it is essential to conduct *JAK2* V617F testing using conventional PCR methods. A positive result necessitates a bone marrow biopsy for the classification of the underlying MPN. In cases of negative results, patients should be screened for *MPL, CALR* and *JAK2* exon12 mutations [72,88]. If any of these mutations is present, a bone marrow biopsy is always required for MPN characterization. However, if these tests yield negative results and there is a strong suspicion of an underlying MPN (indicated for example by a spleen height of $\geq$16 cm and a platelet count $>200 \times 10^9$/L), further investigations, ranging from bone marrow biopsy to NGS or Ultradeep NGS, may be considered to detect extremely low *JAK2* VAF or surrogate markers of clonality, with potential prognostic implications. It is however important to note that, as of now, NGS use in MPN is mainly limited to scientific research and is not currently applied to routine clinical practice. Testing for the *JAK2* haplotype 46/1 does not have clinical implications and is not recommended, either for individual cases or for familial screening purposes [34,39,64].

5. Treatment of MPN-SVTS

MPN-SVT treatment, although poorly defined, must be focused on two main tasks: (a) thrombosis management via anticoagulation, and (b) MPN management via cytoreduction.

5.1. Anticoagulation therapy

Anticoagulation is the main therapeutic intervention in patients with SVT and MPNs, as it may promote vascular recanalization and prevent thrombosis recurrence, and in the acute phase it does not differ from that of patients without MPNs [114]. Anticoagulation with full-dose low molecular weight or unfractionated heparin followed by vitamin K antagonists (VKA) should be initiated as soon as possible in MPN-SVT patients, with the *caveat* of patients showing frank portal hypertension (especially in BCS), for whom it may increase bleeding risk [14,115]. During past years, oral anticoagulation choices have been almost exclusively restricted to VKA; however, newer direct oral anticoagulants have been safely and successfully tested in SVT as well as in MPNs, and they might be preferable in terms of patient convenience. Anticoagulation therapy should be continued indefinitely in MPN-SVT, considering the presence of a permanent risk factor for thrombosis, such as underlying MPN[116,117], and patients should be monitored for portal hypertension and gastro-esophageal varices [14,118–120]. In fact, in a multicenter prospective registry of SVT patients, anticoagulant drugs were used in almost all MPN patients [121], as recommended by the American College of Chest Physicians guidelines [122]. The addition of anti-platelet drugs such as aspirin or clopidogrel to anticoagulants is of little use, but it should be considered in patients with SVT recurrence while on anticoagulation or suffering from arterial thrombosis, although it may increase major bleeding occurrence [14,30,123]. In this context, it should also be considered that hemorrhagic events not related to portal hypertension occur in approximately 10 % of patients with cirrhosis treated with anticoagulants [124]. This rate does not appear to be higher than that observed in patients with cirrhosis and PVT not receiving anticoagulation nor in patients without cirrhosis receiving anticoagulation [124,125], although in cirrhotic patients treated with VKA, a PLT count < 50 x10^9/L was predictive of bleeding [126]. Unexpectedly, bleeding events related to portal hypertension are less frequent in patients receiving anticoagulation than in those without anticoagulation, possibly due to a beneficial effect of anticoagulation on intrahepatic vascular resistance [124,125,127]. Therefore, the administration of anticoagulants does not imply more frequent screening for gastroesophageal varices nor more intense prophylaxis for portal hypertension-related complications [128].

Additionally, if there is clinical worsening despite anticoagulation, cytoreductive therapy, and supportive care, including sodium restriction, diuretic therapy, and paracentesis, patients with BCS should be considered for invasive procedures, such as angioplasty with or without stenting, or transjugular intrahepatic portosystemic shunt (TIPS) [116]. The latter might be applied to those patients with a high risk of liver failure secondary to SVT. Predictably, TIPS improves recanalization rates, especially in *JAK2*V617F mutated SVTs that show the lowest recanalization rates [129,130]]. Liver transplantation should be considered an effective treatment for rapidly progressive BCS after failure of conventional strategy or portosystemic shunting, occurring in 10–20 % of patients [14,121].

5.2. Cytoreductive treatment

The second pillar of MPN-SVT management is MPN cytoreductive treatment. Cytoreduction is generally obtained through hydroxyurea, pegylated interferon, or *JAK1/2* inhibitor ruxolitinib, and should be adapted to specific MPN subtypes [131,132]. In detail, PV patients with SVT are classified at high risk of thrombosis recurrence, even if they are young and have only a moderate increase of hemoglobin or hematocrit [14]. Therefore, cytoreductive therapy is indicated, in addition to phlebotomy, with the goal of maintaining hematocrit $<$45 % [133] and, possibly, PLT count $\leq 400 \times 10^9$/L and WBC count $<10 \times 10^9$/L [134]. According to current recommendations [131], either hydroxyurea (HU) or pegylated interferon (PEG-IFN) represent first-line cytoreductive therapy at any age. In PV patients resistant or intolerant to HU [135], both the *JAK1/2* inhibitor ruxolitinib and PEG-IFN can be appropriate second-line therapies [72,131,136–138]. Current guidelines also favor HU as first-line therapy for ET patients requiring cytoreduction, including those with SVT [131,139], while anagrelide or PEG-IFN are the recommended second-line therapies in case of resistance or intolerance to HU [131,136,140–142]. Regarding PMF, current prognostication systems are based on the risk of mortality rather than thrombosis [143–145]; consequently, the presence of SVT does not change the risk classification of PMF patients. Regardless of risk categories, if cytoreductive treatment is indicated to reduce leukocytosis or thrombocytosis, the first-line drug of choice is HU [131]. In the subgroup of PMF patients with SVT ruxolitinib could also represent an effective therapeutic option, reducing disease-related symptoms and spleen size, as well as the resistivity indices of the hepatic and splenic intraparenchymal arteries, with a substantial stabilization of esophageal varices grade [146]. This compares favorably with a prospective study of non-cirrhotic, non-tumoral PVT, in which the probability of worsening of existing esophageal varices at 1 year was 13 % [36].

That said, the most difficult context is represented by MPN-U patients with SVT who present with normal blood counts, therefore not satisfying all the diagnostic criteria required for another MPN, and for whom the need for cytoreduction is still uncertain [114]. Indeed, since approximately half of these patients will not develop an overt MPN during follow-up [16,25,29,111], and exhibit an indolent clinical course [147], there is no evidence to prescribe cytoreductive regimens [114, 132]. An expert panel identified the appropriateness of myeloproliferative-targeted therapy in patients with SVT-associated MPN as an unmet clinical need and provided methodological suggestions to address this issue [148].

It should also be kept in mind that, despite reaching MPN control, there is no evidence that cytoreductive therapies significantly impact SVT recurrence [146,149,150].

6. Conclusions and future perspectives

MPN-SVT represents a unique and fascinating subset of *BCR::ABL1*-negative MPN that poses diagnostic and therapeutic challenges. MPN-SVT molecular biology has been partly unraveled during the last few years, revealing a strong association with *JAK2*V617F mutation, although with a lower allele burden compared to conventional MPNs. On the other hand, *JAK2 exon 12*, *CALR,* and *MPL* mutations are exceedingly rare in MPN-SVT. Recent papers have successfully explored the application of NGS to SVTs, leading to diagnostic improvements and higher detection rates of MPNs among these patients. Although conventionally less sensitive compared to PCR, NGS identifies *JAK2* mutations and additional somatic mutations that might serve as proof of clonal hematopoiesis or molecular prognosticators, in a similar fashion to what is reported in conventional MPNs. Moreover, the application of ultrasensitive molecular techniques, such as Ultradeep NGS, might aid the recognition of SVT patients at risk of developing subsequent MPN (or with "incipient" MPN) by pointing out cases with low or "ultra-low" allele burden. Indeed, since early MPNs are presumably associated with low *JAK2*V617F VAF, low allele burden in MPN-SVTs reinforces SVT identification as a precocious manifestation of MPN. However, further studies are needed to deepen the contribution of low allele burden to MPNs in general and specifically to MPN-SVTs. Additionally, the combination of low/undetectable *JAK2*V617F allele burden with low blood counts secondary to SVT-related hypersplenism might dramatically hinder MPN diagnosis in SVT patients, or it may misleadingly suggest an MPN-U diagnosis. Therefore, the MPN-U category might also include a considerable group of MPN-SVTs. Further MPN-U series are required to fully uncover such aspects; moreover, the role of blood counts as well as *JAK2*V617F allele burden in specific MPN settings might need substantial revision, and techniques such as red cell mass and plasma volume measurements, although not easily accessible, might help to avoid underdiagnosing of MPN-SVT.

In summary, the integration of PCR, sequencing, and NGS methods has played a crucial role in uncovering the intricate molecular aspects of MPN and MPN-SVT. Continued research endeavors are expected to facilitate the development of a molecular theragnostic approach for MPN-SVT. This advancement will enhance diagnostic precision, identify prognostic and predictive factors, and ultimately aid in making informed decisions regarding treatment options.

Funding

This research received no external funding.

CRediT authorship contribution statement

Conceptualization, AI, UG, CP; methodology, CP, GL, DC; formal analysis, GL, DC; investigation, CP, GL; resources, CP, GL, DC, CB; data curation, CP, GL, DC; writing—original draft preparation, CP, GL; writing—review and editing, AI, UG, DC, CP, GL, CB; visualization, AI, UG, CP; supervision, AI, DC, UG. All authors reviewed the results and approved the final version of the manuscript.

Declaration of Competing Interest

U.G. received fees from Novartis Farma S.p.A. and Jazz Pharma as a consultant speaker and advisory board. A.I. and D.C. receive speaker honoraria from Novartis Farma S.p.A. All other authors declare no conflict of interest.

Acknowledgements

None.

References

[1] WHO Classification of Tumours, Haematolymphoid Tumours [Internet; beta version ahead of print], International Agency for Research on Cancer, Lyon (France), 2022.
[2] D.A. Arber, A. Orazi, R.P. Hasserjian, M.J. Borowitz, K.R. Calvo, H.-M. Kvasnicka, S.A. Wang, A. Bagg, T. Barbui, S. Branford, et al., International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data, Blood 140 (2022) 1200–1228, https://doi.org/10.1182/blood.2022015850.
[3] J. Thiele, H.M. Kvasnicka, A. Orazi, U. Gianelli, N. Gangat, A.M. Vannucchi, T. Barbui, D.A. Arber, A. Tefferi, The international consensus classification of myeloid neoplasms and acute Leukemias: myeloproliferative neoplasms, Am. J. Hematol. 98 (2023) 166–179, https://doi.org/10.1002/ajh.26751.
[4] U. Gianelli, J. Thiele, A. Orazi, N. Gangat, A.M. Vannucchi, A. Tefferi, H. M. Kvasnicka, International consensus classification of myeloid and lymphoid neoplasms: myeloproliferative neoplasms, Virchows Arch. 482 (2023) 53–68, https://doi.org/10.1007/s00428-022-03480-8.
[5] E.J. Duncavage, A. Bagg, R.P. Hasserjian, C.D. DiNardo, L.A. Godley, I. Iacobucci, S. Jaiswal, L. Malcovati, A.M. Vannucchi, K.P. Patel, et al., Genomic profiling for clinical decision making in myeloid neoplasms and acute leukemia, Blood 140 (2022) 2228–2247, https://doi.org/10.1182/blood.2022015853.
[6] M. Maddali, A. Venkatraman, U.P. Kulkarni, S. Mani, S. Raj, E. Sigamani, A. Korula, F.N. A, S.A. Lionel, S. Selvarajan, et al., Molecular characterization of triple-negative myeloproliferative neoplasms by next-generation sequencing, Ann. Hematol. 101 (2022) 1987–2000, https://doi.org/10.1007/s00277-022-04920-w.
[7] A. Iurlo, D. Cattaneo, U. Gianelli, Blast transformation in myeloproliferative neoplasms: risk factors, biological findings, and targeted therapeutic options, Int. J. Mol. Sci. 20 (2019) 1839.
[8] A. Tefferi, A.M. Vannucchi, Genetic risk assessment in myeloproliferative neoplasms, Mayo Clin. Proc. 92 (2017) 1283–1290, https://doi.org/10.1016/j.mayocp.2017.06.002.
[9] E. Valeriani, N. Riva, M. Di Nisio, W. Ageno, Splanchnic vein thrombosis: current perspectives, Vasc. Health Risk Manag 15 (2019) 449–461, https://doi.org/10.2147/vhrm.S197732.
[10] M. Ogren, D. Bergqvist, M. Björck, S. Acosta, H. Eriksson, N.H. Sternby, Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies, World J. Gastroenterol. 12 (2006) 2115–2119, https://doi.org/10.3748/wjg.v12.i13.2115.
[11] W. Ageno, F. Dentali, F. Pomero, L. Fenoglio, A. Squizzato, G. Pagani, R. Re, M. Bonzini, Incidence rates and case fatality rates of portal vein thrombosis and Budd-Chiari Syndrome, Thromb. Haemost. 117 (2017) 794–800, https://doi.org/10.1160/th16-10-0781.
[12] M. Hultcrantz, M. Björkholm, P.W. Dickman, O. Landgren, Å.R. Derolf, S. Y. Kristinsson, T.M.L. Andersson, Risk for arterial and venous thrombosis in patients with myeloproliferative neoplasms, Ann. Intern. Med. 168 (2018) 317–325, https://doi.org/10.7326/M17-0028.
[13] D. Tremblay, A.S. Vogel, E. Moshier, R. Hoffman, M. Kremyanskaya, S. Zhou, T. Schiano, J. Mascarenhas, Outcomes of splanchnic vein thrombosis in patients with myeloproliferative neoplasms in a single center experience, Eur. J. Haematol. 104 (2020) 72–73, https://doi.org/10.1111/ejh.13335.
[14] D. Tremblay, A. Winters, J.D. Beckman, L. Naymagon, R. Patel, J. Mascarenhas, T.D. Schiano, Splanchnic vein thrombosis associated with myeloproliferative neoplasms, Thromb. Res. 218 (2022) 8–16, https://doi.org/10.1016/j.thromres.2022.08.003.
[15] J.H. Smalberg, L.R. Arends, D.C. Valla, J.J. Kiladjian, H.L. Janssen, F.W. Leebeek, Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis, Blood 120 (2012) 4921–4928, https://doi.org/10.1182/blood-2011-09-376517.
[16] U. Gianelli, A. Iurlo, D. Cattaneo, A. Bossi, I. Cortinovis, C. Augello, A. Moro, F. Savi, R. Castelli, C. Brambilla, et al., Discrepancies between bone marrow histopathology and clinical phenotype in BCR-ABL1-negative myeloproliferative neoplasms associated with splanchnic vein thrombosis, Leuk. Res 39 (2015) 525–529, https://doi.org/10.1016/j.leukres.2015.03.009.
[17] B.L. Stein, S. Saraf, U. Sobol, A. Halpern, J. Shammo, D. Rondelli, L. Michaelis, O. Odenike, A. Rademaker, A. Zakarija, et al., Age-related differences in disease

characteristics and clinical outcomes in polycythemia vera, Leuk. Lymphoma 54 (2013) 1989–1995, https://doi.org/10.3109/10428194.2012.759656.
[18] F. Lussana, A. Carobbio, M.L. Randi, C. Elena, E. Rumi, G. Finazzi, I. Bertozzi, L. Pieri, M. Ruggeri, F. Palandri, et al., A lower intensity of treatment may underlie the increased risk of thrombosis in young patients with masked polycythaemia vera, Br. J. Haematol. 167 (2014) 541–546, https://doi.org/10.1111/bjh.13080.
[19] B.L. Stein, A. Rademaker, J.L. Spivak, A.R. Moliterno, Gender and vascular complications in the JAK2 V617F-positive myeloproliferative neoplasms, Thrombosis 2011 (2011), 874146, https://doi.org/10.1155/2011/874146.
[20] D. Colaizzo, G.L. Tiscia, V. Bafunno, L. Amitrano, P. Vergura, M.R. Lupone, E. Grandone, M.A. Guardascione, M. Margaglione, Sex modulation of the occurrence of jak2 v617f mutation in patients with splanchnic venous thrombosis, Thromb. Res. 128 (2011) 233–236, https://doi.org/10.1016/j.thromres.2011.03.024.
[21] J.H. Smalberg, E. Koehler, S. Darwish Murad, A. Plessier, S. Seijo, J. Trebicka, M. Primignani, M.P. de Maat, J.C. Garcia-Pagan, D.C. Valla, et al., The JAK2 46/1 haplotype in Budd-Chiari syndrome and portal vein thrombosis, Blood 117 (2011) 3968–3973, https://doi.org/10.1182/blood-2010-11-319087.
[22] J. Paes, G.A.V. Silva, A.M. Tarragô, L.P.S. Mourão, The contribution of JAK2 46/1 haplotype in the predisposition to myeloproliferative neoplasms, Int. J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms232012582.
[23] A. Tefferi, E. Rumi, G. Finazzi, H. Gisslinger, A.M. Vannucchi, F. Rodeghiero, M. L. Randi, R. Vaidya, M. Cazzola, A. Rambaldi, et al., Survival and prognosis among 1545 patients with contemporary polycythemia vera: an international study, Leukemia 27 (2013) 1874–1881, https://doi.org/10.1038/leu.2013.163.
[24] V. De Stefano, T. Za, A. Ciminello, S. Betti, E. Rossi, Causes of adult splanchnic vein thrombosis in the mediterranean area, Mediterr. J. Hematol. Infect. Dis. 3 (2011), e2011063, https://doi.org/10.4084/mjhid.2011.063.
[25] E. Sant'Antonio, P. Guglielmelli, L. Pieri, M. Primignani, M.L. Randi, C. Santarossa, E. Rumi, F. Cervantes, F. Delaini, A. Carobbio, et al., Splanchnic vein thromboses associated with myeloproliferative neoplasms: an international, retrospective study on 518 cases, Am. J. Hematol. 95 (2020) 156–166, https://doi.org/10.1002/ajh.25677.
[26] M. Yan, H. Geyer, R. Mesa, E. Atallah, J. Callum, J. Bartoszko, K. Yee, M. Maganti, F. Wong, V. Gupta, Clinical features of patients with philadelphia-negative myeloproliferative neoplasms complicated by portal hypertension, Clin. Lymphoma Myeloma Leuk. 15 (2015) e1–e5, https://doi.org/10.1016/j.clml.2014.04.004.
[27] T. Barbui, A. Carobbio, F. Cervantes, A.M. Vannucchi, P. Guglielmelli, E. Antonioli, A. Alvarez-Larrán, A. Rambaldi, G. Finazzi, G. Barosi, Thrombosis in primary myelofibrosis: incidence and risk factors, Blood 115 (2010) 778–782, https://doi.org/10.1182/blood-2009-08-238956.
[28] A. Enblom, E. Lindskog, H. Hasselbalch, D. Hersby, M. Bak, J. Tetu, F. Girodon, B. Andréasson, High rate of abnormal blood values and vascular complications before diagnosis of myeloproliferative neoplasms, Eur. J. Intern. Med. 26 (2015) 344–347, https://doi.org/10.1016/j.ejim.2015.03.009.
[29] D. Cattaneo, U. Gianelli, P. Bianchi, A. Cortelezzi, A. Iurlo, Heterogeneity among splanchnic vein thrombosis associated with myeloproliferative neoplasms, Eur. J. Intern. Med. 52 (2018) e25–e26, https://doi.org/10.1016/j.ejim.2018.03.009.
[30] V. De Stefano, A.M. Vannucchi, M. Ruggeri, F. Cervantes, A. Alvarez-Larrán, A. Iurlo, M.L. Randi, L. Pieri, E. Rossi, P. Guglielmelli, et al., Splanchnic vein thrombosis in myeloproliferative neoplasms: risk factors for recurrences in a cohort of 181 patients, e493-e493, Blood Cancer J. 6 (2016), https://doi.org/10.1038/bcj.2016.103.
[31] G. Greenfield, M.F. McMullin, Splanchnic venous thrombosis in JAK2 V617F mutation positive myeloproliferative neoplasms – long term follow-up of a regional case series, Thromb. J. 16 (2018), 33, https://doi.org/10.1186/s12959-018-0187-z.
[32] L. Drevon, N. Maslah, J. Soret-Dulphy, C. Dosquet, O. Ravdan, L. Vercellino, C. Belkhodja, N. Parquet, A.C. Brignier, M.H. Schlageter, et al., Anemia and hemodilution: analysis of a single center cohort based on 2,858 red cell mass measurements, Haematologica 106 (2021) 1167–1171, https://doi.org/10.3324/haematol.2020.249409.
[33] H.C. Hasselbalch, Time for revival of the red blood cell count and red cell mass in the differential diagnosis between essential thrombocythemia and polycythemia vera? Haematologica 104 (2019) 2119–2125, https://doi.org/10.3324/haematol.2019.229039.
[34] J.-J. Kiladjian, B. Cassinat, Myeloproliferative neoplasms and splanchnic vein thrombosis: contemporary diagnostic and therapeutic strategies, Am. J. Hematol. (2023), https://doi.org/10.1002/ajh.26896.
[35] A. Alvarez-Larrán, A. Pereira, M. Magaz, J.C. Hernández-Boluda, M. Garrote, B. Cuevas, F. Ferrer-Marín, M.T. Gómez-Casares, V. García-Gutiérrez, M.I. Mata-Vázquez, et al., Natural history of polycythemia vera and essential thrombocythemia presenting with splanchnic vein thrombosis, Ann. Hematol. 99 (2020) 791–798, https://doi.org/10.1007/s00277-020-03965-z.
[36] C. Noronha Ferreira, S. Seijo, A. Plessier, G. Silva-Junior, F. Turon, P.E. Rautou, A. Baiges, C. Bureau, J. Bosch, V. Hernández-Gea, et al., Natural history and management of esophagogastric varices in chronic noncirrhotic, nontumoral portal vein thrombosis, Hepatology 63 (2016) 1640–1650, https://doi.org/10.1002/hep.28466.
[37] S. Lavu, N. Szuber, M. Mudireddy, M. Yogarajah, N. Gangat, A. Pardanani, C. A. Hanson, R.P. Ketterling, A.A. Ashrani, P.S. Kamath, et al., Splanchnic vein thrombosis in patients with myeloproliferative neoplasms: The Mayo clinic experience with 84 consecutive cases, Am. J. Hematol. 93 (2018) E61–E64, https://doi.org/10.1002/ajh.24993.
[38] T. Barbui, A. Ghirardi, A. Masciulli, A. Carobbio, F. Palandri, N. Vianelli, V. De Stefano, S. Betti, A. Di Veroli, A. Iurlo, et al., Second cancer in Philadelphia negative myeloproliferative neoplasms (MPN-K). A nested case-control study, Leukemia 33 (2019) 1996–2005, https://doi.org/10.1038/s41375-019-0487-8.
[39] P.E. Debureaux, B. Cassinat, J. Soret-Dulphy, B. Mora, E. Verger, N. Maslah, A. Plessier, P.E. Rautou, I. Ollivier-Hourman, V. De Ledinghen, et al., Molecular profiling and risk classification of patients with myeloproliferative neoplasms and splanchnic vein thromboses, Blood Adv. 4 (2020) 3708–3715, https://doi.org/10.1182/bloodadvances.2020002414.
[40] T.C. Pearson, G. Wetherley-Mein, Vascular occlusive episodes and venous hæmatocrit in primary proliferative polycythæmlx, Lancet 312 (1978) 1219–1222, https://doi.org/10.1016/S0140-6736(78)92098-6.
[41] S. Sozer, M.I. Fiel, T. Schiano, M. Xu, J. Mascarenhas, R. Hoffman, The presence of JAK2V617F mutation in the liver endothelial cells of patients with Budd-Chiari syndrome, Blood 113 (2009) 5246–5249, https://doi.org/10.1182/blood-2008-11-191544.
[42] V. Rosti, E. Bonetti, G. Bergamaschi, R. Campanelli, P. Guglielmelli, M. Maestri, U. Magrini, M. Massa, C. Tinelli, G. Viarengo, et al., High frequency of endothelial colony forming cells marks a non-active myeloproliferative neoplasm with high risk of splanchnic vein thrombosis, PLoS One 5 (2010), e15277, https://doi.org/10.1371/journal.pone.0015277.
[43] R. Helman, Wd.O. Pereira, L.C. Marti, P.V. Campregher, R.D. Puga, N. Hamerschlak, C.S. Chiattone, F.Pd.S. Santos, Granulocyte whole exome sequencing and endothelial JAK2V617F in patients with JAK2V617F positive Budd-Chiari syndrome without myeloproliferative neoplasm, Br. J. Haematol. 180 (2018) 443–445, https://doi.org/10.1111/bjh.14327.
[44] A. Guadall, E. Lesteven, G. Letort, S. Awan Toor, M. Delord, D. Pognant, M. Brusson, E. Verger, N. Maslah, S. Giraudier, et al., Endothelial cells harbouring the JAK2V617F mutation display pro-adherent and pro-thrombotic features, Thromb. Haemost. 118 (2018) 1586–1599, https://doi.org/10.1055/s-0038-1667015.
[45] G. Alexandre, G.-L. Virginie, L. Nicolas Le, P. Claire, K. Badr, D. Juliana Vieira, D. Cécile, R. Marie-Ange, D. Cécile, V. Jean Luc, et al., Vascular endothelial cell expression of JAK2V617F is sufficient to promote a pro-thrombotic state due to increased P-selectin expression, Haematologica 104 (2019) 70–81, https://doi.org/10.3324/haematol.2018.195321.
[46] M. Castiglione, Y.P. Jiang, C. Mazzeo, S. Lee, J.S. Chen, K. Kaushansky, W. Yin, R. Z. Lin, H. Zheng, H. Zhan, Endothelial JAK2V617F mutation leads to thrombosis, vasculopathy, and cardiomyopathy in a murine model of myeloproliferative neoplasm, J. Thromb. Haemost. 18 (2020) 3359–3370, https://doi.org/10.1111/jth.15095.
[47] G. Giordano, M. Napolitano, M. Cellurale, P. Di Carlo, G. Musuraca, G. Micucci, A. Lucchesi, Circulating endothelial cell levels correlate with treatment outcomes of splanchnic vein thrombosis in patients with chronic myeloproliferative neoplasms, J. Pers. Med. 12 (2022), https://doi.org/10.3390/jpm12030364.
[48] T. Rusak, T. Misztal, J. Piszcz, M. Tomasiak, Nitric oxide scavenging by cell-free hemoglobin may be a primary factor determining hypertension in polycythemic patients, Free Radic. Res. 48 (2014) 230–238, https://doi.org/10.3109/10715762.2013.860225.
[49] K.J. Kim, S.H. Kwon, J.H. Yun, H.S. Jeong, H.R. Kim, E.H. Lee, S.K. Ye, C.H. Cho, STAT3 activation in endothelial cells is important for tumor metastasis via increased cell adhesion molecule expression, Oncogene 36 (2017) 5445–5459, https://doi.org/10.1038/onc.2017.148.
[50] L. Wang, M. Astone, S.K. Alam, Z. Zhu, W. Pei, D.A. Frank, S.M. Burgess, L. H. Hoeppner, Suppressing STAT3 activity protects the endothelial barrier from VEGF-mediated vascular permeability, Dis. Models Mech. 14 (2021), https://doi.org/10.1242/dmm.049029.
[51] M.K. Jensen, R. Riisbro, P. De Nully Brown, N. Brünner, H.C. Hasselbalch, Elevated soluble urokinase plasminogen activator receptor in plasma from patients with idiopathic myelofibrosis or polycythaemia vera, Eur. J. Haematol. 69 (2002) 43–49, https://doi.org/10.1034/j.1600-0609.2002.01732.x.
[52] I. Novitzky-Basso, F. Spring, D. Anstee, D. Tripathi, F. Chen, Erythrocytes from patients with myeloproliferative neoplasms and splanchnic venous thrombosis show greater expression of Lu/BCAM, Int. J. Lab Hematol. 40 (2018) 473–477, https://doi.org/10.1111/ijlh.12838.
[53] G. Finazzi, V. De Stefano, T. Barbui, Are MPNs vascular diseases? Curr. Hematol. Malig. Rep. 8 (2013) 307–316, https://doi.org/10.1007/s11899-013-0176-z.
[54] B.N. Reeves, J.D. Beckman, Novel pathophysiological mechanisms of thrombosis in myeloproliferative neoplasms, Curr. Hematol. Malig. Rep. 16 (2021) 304–313, https://doi.org/10.1007/s11899-021-00630-8.
[55] F. Dentali, A. Squizzato, L. Brivio, L. Appio, L. Campiotti, M. Crowther, A. M. Grandi, W. Ageno, JAK2V617F mutation for the early diagnosis of Ph-myeloproliferative neoplasms in patients with venous thromboembolism: a meta-analysis, Blood 113 (2009) 5617–5623, https://doi.org/10.1182/blood-2008-12-196014.
[56] N. Kumar, S. Sharma, J. Binota, J. Ahluwalia, N. Varma, S. Naseem, I. Chand, V. Uppal, S.K. Sinha, JAK2V617F mutation in patient with splanchnic vein thrombosis, Indian J. Hematol. Blood Transfus. 36 (2020) 700–704, https://doi.org/10.1007/s12288-020-01292-x.
[57] E.H. Yoo, J.H. Jang, K.J. Park, G.Y. Gwak, H.J. Kim, S.H. Kim, D.K. Kim, Prevalence of overt myeloproliferative neoplasms and JAK2 V617F mutation in Korean patients with splanchnic vein thrombosis, Int. J. Lab Hematol. 33 (2011) 471–476, https://doi.org/10.1111/j.1751-553X.2011.01308.x.
[58] J. How, A. Zhou, S.T. Oh, Splanchnic vein thrombosis in myeloproliferative neoplasms: pathophysiology and molecular mechanisms of disease, Ther. Adv. Hematol. 8 (2017) 107–118, https://doi.org/10.1177/2040620716680333.

[59] A.M. Vannucchi, E. Antonioli, P. Guglielmelli, G. Longo, A. Pancrazzi, V. Ponziani, C. Bogani, P.R. Ferrini, A. Rambaldi, V. Guerini, et al., Prospective identification of high-risk polycythemia vera patients based on JAK2V617F allele burden, Leukemia 21 (2007) 1952–1959, https://doi.org/10.1038/sj.leu.2404854.

[60] Y. Zhang, Y. Zhou, Y. Wang, G. Teng, D. Li, Y. Wang, C. Du, Y. Chen, H. Zhang, Y. Li, et al., Thrombosis among 1537 patients with JAK2V617F-mutated myeloproliferative neoplasms: Risk factors and development of a predictive model, Cancer Med. 9 (2020) 2096–2105, https://doi.org/10.1002/cam4.2886.

[61] P. Guglielmelli, G.G. Loscocco, C. Mannarelli, E. Rossi, F. Mannelli, F. Ramundo, G. Coltro, S. Betti, C. Maccari, S. Ceglie, et al., JAK2V617F variant allele frequency >50% identifies patients with polycythemia vera at high risk for venous thrombosis, Blood Cancer J. 11 (2021) 199, https://doi.org/10.1038/s41408-021-00581-6.

[62] F. Passamonti, E. Rumi, D. Pietra, C. Elena, E. Boveri, L. Arcaini, E. Roncoroni, C. Astori, M. Merli, S. Boggi, et al., A prospective study of 338 patients with polycythemia vera: the impact of JAK2 (V617F) allele burden and leukocytosis on fibrotic or leukemic disease transformation and vascular complications, Leukemia 24 (2010) 1574–1579, https://doi.org/10.1038/leu.2010.148.

[63] T.V. Makarik, A.O. Abdullaev, E.E. Nikulina, S.A. Treglazova, E.E. Stepanova, I. N. Subortseva, A.M. Kovrigina, A.L. Melikyan, S.M. Kulikov, A.B. Sudarikov, Low JAK2 V617F Allele Burden in Ph-negative chronic myeloproliferative neoplasms is associated with additional CALR or MPL gene mutations, Genes (Basel) 12 (2021), https://doi.org/10.3390/genes12040559.

[64] A. Iurlo, D. Cattaneo, U. Gianelli, E. Fermo, C. Augello, A. Cortelezzi, Molecular analyses in the diagnosis of myeloproliferative neoplasm-related splanchnic vein thrombosis, Ann. Hematol. 94 (2015) 881–882, https://doi.org/10.1007/s00277-014-2249-z.

[65] J. How, K.M. Trinkaus, S.T. Oh, Distinct clinical, laboratory and molecular features of myeloproliferative neoplasm patients with splanchnic vein thrombosis, Br. J. Haematol. 183 (2018) 310–313, https://doi.org/10.1111/bjh.14958.

[66] M. Magaz, A. Alvarez-Larrán, D. Colomer, M. López-Guerra, M. García-Criado, G. Mezzano, E. Belmonte, P. Olivas, G. Soy, F. Cervantes, et al., Next-generation sequencing in the diagnosis of non-cirrhotic splanchnic vein thrombosis, J. Hepatol. 74 (2021) 89–95, https://doi.org/10.1016/j.jhep.2020.06.045.

[67] L. Grunwald, C. Grosse-Thie, S. Sender, G. Knuebel, S. Krohn, C. Roolf, C. Junghanss, L. Henze, H. Murua Escobar, Ultradeep targeted sequencing reveals low allele frequencies of somatic JAK2 and MPL variants in patients with abdominal vein thromboses: results of an ongoing prospective prevalence study in Mecklenburg-West Pomerania, Biomark. Res. 8 (2020), 73, https://doi.org/10.1186/s40364-020-00254-9.

[68] I. Yonal, B. Pinarbası, F. Hindilerden, V.S. Hancer, M. Nalcaci, S. Kaymakoglu, R. Diz-Kucukkaya, The clinical significance of JAK2V617F mutation for Philadelphia-negative chronic myeloproliferative neoplasms in patients with splanchnic vein thrombosis, J. Thromb. Thrombolysis 34 (2012) 388–396, https://doi.org/10.1007/s11239-012-0738-2.

[69] V. De Stefano, A. Fiorini, E. Rossi, T. Za, G. Farina, P. Chiusolo, S. Sica, G. Leone, Incidence of the JAK2 V617F mutation among patients with splanchnic or cerebral venous thrombosis and without overt chronic myeloproliferative disorders, J. Thromb. Haemost. 5 (2007) 708–714, https://doi.org/10.1111/j.1538-7836.2007.02424.x.

[70] H.L. Janssen, F.W. Leebeek, JAK2 mutation: The best diagnostic tool for myeloproliferative disease in splanchnic vein thrombosis? Hepatology 44 (2006) 1391–1393, https://doi.org/10.1002/hep.21489.

[71] S. Karaköse, N. Oruç, M. Zengin, U.S. Akarca, G. Ersöz, Diagnostic value of the JAK2 V617F mutation for latent chronic myeloproliferative disorders in patients with Budd-Chiari syndrome and/or portal vein thrombosis, Turk. J. Gastroenterol. 26 (2015) 42–48, https://doi.org/10.5152/tjg.2015.5738.

[72] J.J. Kiladjian, F. Cervantes, F.W. Leebeek, C. Marzac, B. Cassinat, S. Chevret, D. Cazals-Hatem, A. Plessier, J.C. Garcia-Pagan, S. Darwish Murad, et al., The impact of JAK2 and MPL mutations on diagnosis and prognosis of splanchnic vein thrombosis: a report on 241 cases, Blood 111 (2008) 4922–4929, https://doi.org/10.1182/blood-2007-11-125328.

[73] M. Primignani, G. Barosi, G. Bergamaschi, U. Gianelli, F. Fabris, R. Reati, A. Dell'Era, P. Bucciarelli, P.M. Mannucci, Role of the JAK2 mutation in the diagnosis of chronic myeloproliferative disorders in splanchnic vein thrombosis, Hepatology 44 (2006) 1528–1534, https://doi.org/10.1002/hep.21435.

[74] D. Colaizzo, L. Amitrano, M.A. Guardascione, G.L. Tiscia, G. D'Andrea, V. A. Longo, E. Grandone, M. Margaglione, Outcome of patients with splanchnic venous thrombosis presenting without overt MPN: a role for the JAK2 V617F mutation re-evaluation, Thromb. Res. 132 (2013) e99–e104, https://doi.org/10.1016/j.thromres.2013.07.014.

[75] A. Pardanani, T.L. Lasho, K. Hussein, S.M. Schwager, C.M. Finke, R.K. Pruthi, A. Tefferi, JAK2V617F mutation screening as part of the hypercoagulable work-up in the absence of splanchnic venous thrombosis or overt myeloproliferative neoplasm: assessment of value in a series of 664 consecutive patients, Mayo Clin. Proc. 83 (2008) 457–459, https://doi.org/10.4065/83.4.457.

[76] G.M. Bergamaschi, M. Primignani, G. Barosi, F.M. Fabris, L. Villani, R. Reati, A. Dell'Era, P.M. Mannucci, MPL and JAK2 exon 12 mutations in patients with the Budd-Chiari syndrome or extrahepatic portal vein obstruction, 4418-4418, Blood 111 (2008), https://doi.org/10.1182/blood-2008-02-137687.

[77] A. Fiorini, P. Chiusolo, E. Rossi, T. Za, D.G. De Ritis, A. Ciminello, G. Leone, V. De Stefano, Absence of the JAK2 exon 12 mutations in patients with splanchnic venous thrombosis and without overt myeloproliferative neoplasms, Am. J. Hematol. 84 (2009) 126–127, https://doi.org/10.1002/ajh.21335.

[78] H. Andrikovics, S. Nahajevszky, M. Koszarska, N. Meggyesi, A. Bors, G. Halm, S. Lueff, N. Lovas, Z. Matrai, J. Csomor, et al., JAK2 46/1 haplotype analysis in myeloproliferative neoplasms and acute myeloid leukemia, Leukemia 24 (2010) 1809–1813, https://doi.org/10.1038/leu.2010.172.

[79] A. Pardanani, T.L. Lasho, C.M. Finke, N. Gangat, A.P. Wolanskyj, C.A. Hanson, A. Tefferi, The JAK2 46/1 haplotype confers susceptibility to essential thrombocythemia regardless of JAK2V617F mutational status-clinical correlates in a study of 226 consecutive patients, Leukemia 24 (2010) 110–114, https://doi.org/10.1038/leu.2009.226.

[80] S. Hermouet, M. Vilaine, The JAK2 46/1 haplotype: a marker of inappropriate myelomonocytic response to cytokine stimulation, leading to increased risk of inflammation, myeloid neoplasm, and impaired defense against infection? Haematologica 96 (2011) 1575–1579, https://doi.org/10.3324/haematol.2011.055392.

[81] D. Colaizzo, G.L. Tiscia, V. Bafunno, L. Amitrano, P. Vergura, E. Grandone, M. A. Guardascione, M. Margaglione, The JAK2 rs12343867 CC genotype frequently occurs in patients with splanchnic venous thrombosis without the JAK2V617F mutation: a retrospective study, J. Thromb. Haemost. 8 (2010) 413–416, https://doi.org/10.1111/j.1538-7836.2009.03691.x.

[82] L. Villani, G. Bergamaschi, M. Primignani, V. Rosti, A. Carolei, V. Poletto, P. Catarsi, A. Spolverini, A.M. Vannucchi, G. Barosi, JAK2 46/1 haplotype predisposes to splanchnic vein thrombosis-associated BCR-ABL negative classic myeloproliferative neoplasms, Leuk. Res. 36 (2012) e7–9, https://doi.org/10.1016/j.leukres.2011.08.008.

[83] S.-l Li, P.-j Zhang, G.-x Sun, Z.-j Lu, The JAK2 46/1 haplotype (GGCC) in myeloproliferative neoplasms and splanchnic vein thrombosis: a pooled analysis of 26 observational studies, Ann. Hematol. 93 (2014) 1845–1852, https://doi.org/10.1007/s00277-014-2134-9.

[84] L. Anelli, A. Zagaria, G. Specchia, F. Albano, The JAK2 GGCC (46/1) haplotype in myeloproliferative neoplasms: causal or random? Int. J. Mol. Sci. 19 (2018) https://doi.org/10.3390/ijms19041152.

[85] T. Klampfl, H. Gisslinger, A.S. Harutyunyan, H. Nivarthi, E. Rumi, J.D. Milosevic, N.C. Them, T. Berg, B. Gisslinger, D. Pietra, et al., Somatic mutations of calreticulin in myeloproliferative neoplasms, N. Engl. J. Med. 369 (2013) 2379–2390, https://doi.org/10.1056/NEJMoa1311347.

[86] P. Guglielmelli, G. Rotunno, T. Fanelli, A. Pacilli, G. Brogi, L. Calabresi, A. Pancrazzi, A.M. Vannucchi, Validation of the differential prognostic impact of type 1/type 1-like versus type 2/type 2-like CALR mutations in myelofibrosis, Blood Cancer J. 5 (2015), e360, https://doi.org/10.1038/bcj.2015.90.

[87] F. Turon, F. Cervantes, D. Colomer, A. Baiges, V. Hernández-Gea, J.C. Garcia-Pagán, Role of calreticulin mutations in the aetiological diagnosis of splanchnic vein thrombosis, J. Hepatol. 62 (2015) 72–74, https://doi.org/10.1016/j.jhep.2014.08.032.

[88] J. Poisson, A. Plessier, J.J. Kiladjian, F. Turon, B. Cassinat, A. Andreoli, E. De Raucourt, O. Goria, K. Zekrini, C. Bureau, et al., Selective testing for calreticulin gene mutations in patients with splanchnic vein thrombosis: a prospective cohort study, J. Hepatol. 67 (2017) 501–507, https://doi.org/10.1016/j.jhep.2017.04.021.

[89] K. Haslam, S.E. Langabeer, Incidence of CALR mutations in patients with splanchnic vein thrombosis, Br. J. Haematol. 168 (2015) 459–460, https://doi.org/10.1111/bjh.13121.

[90] M. Roques, J.-H. Park, A. Minello, J.N. Bastie, F. Girodon, Detection of the CALR mutation in the diagnosis of splanchnic vein thrombosis, Br. J. Haematol. 169 (2015) 601–603, https://doi.org/10.1111/bjh.13235.

[91] E.P. Plompen, P.J. Valk, I. Chu, S.D. Darwish Murad, A. Plessier, F. Turon, J. Trebicka, M. Primignani, J.C. Garcia-Pagán, D.C. Valla, et al., Somatic calreticulin mutations in patients with Budd-Chiari syndrome and portal vein thrombosis, Haematologica 100 (2015) e226–228, https://doi.org/10.3324/haematol.2014.120857.

[92] N. Castro, I. Rapado, R. Ayala, Martinez-Lopez J., CALR mutations screening should not be studied in splanchnic vein thrombosis, Br. J. Haematol. 170 (2015) 588–589, https://doi.org/10.1111/bjh.13314.

[93] E. Rumi, A.S. Harutyunyan, D. Pietra, J.D. Milosevic, I.C. Casetti, M. Bellini, N. C. Them, C. Cavalloni, V.V. Ferretti, C. Milanesi, et al., CALR exon 9 mutations are somatically acquired events in familial cases of essential thrombocythemia or primary myelofibrosis, Blood 123 (2014) 2416–2419, https://doi.org/10.1182/blood-2014-01-550434.

[94] H. Hauschner, M. Bokstad Horev, M. Misgav, M. Nagar, U. Seligsohn, N. Rosenberg, M. Koren-Michowitz, Platelets from Calreticulin mutated essential thrombocythemia patients are less reactive than JAK2 V617F mutated platelets, Am. J. Hematol. 95 (2020) 379–386, https://doi.org/10.1002/ajh.25713.

[95] D. Pietra, E. Rumi, V.V. Ferretti, C.A. Di Buduo, C. Milanesi, C. Cavalloni, E. Sant'Antonio, V. Abbonante, F. Moccia, I.C. Casetti, et al., Differential clinical effects of different mutation subtypes in CALR-mutant myeloproliferative neoplasms, Leukemia 30 (2016) 431–438, https://doi.org/10.1038/leu.2015.277.

[96] P. Guglielmelli, L. Calabresi, Chapter five - the MPL mutation, in: N. Bartalucci, L. Galluzzi (Eds.), International Review of Cell and Molecular Biology, vol. 365, Academic Press, 2021, pp. 163–178.

[97] A. Tefferi, Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management, Am. J. Hematol. (2023), https://doi.org/10.1002/ajh.26857.

[98] P.A. Beer, P.J. Campbell, L.M. Scott, A.J. Bench, W.N. Erber, D. Bareford, B. S. Wilkins, J.T. Reilly, H.C. Hasselbalch, R. Bowman, et al., MPL mutations in myeloproliferative disorders: analysis of the PT-1 cohort, Blood 112 (2008) 141–149, https://doi.org/10.1182/blood-2008-01-131664.

[99] D. Colaizzo, L. Amitrano, M.A. Guardascione, G. Favuzzi, G.L. Tiscia, G. D'Andrea, R. Santacroce, E. Grandone, M. Margaglione, Clinical utility of screening for CALR gene exon 9 mutations in patients with splanchnic venous thrombosis, Thromb. Haemost. 113 (2015) 1381–1382, https://doi.org/10.1160/TH14-12-1055.
[100] A. Jadli, B. Kulkarni, K. Ghosh, S. Shetty, Non conventional mutations associated with myeloproliferative disorders are absent in splanchnic venous thrombosis cases, Liver Int. 32 (2012) 1596–1597, https://doi.org/10.1111/j.1478-3231.2012.02851.x.
[101] L.V. Furtado, H.C. Weigelin, K.S. Elenitoba-Johnson, B.L. Betz, Detection of MPL mutations by a novel allele-specific PCR-based strategy, J. Mol. Diagn. 15 (2013) 810–818, https://doi.org/10.1016/j.jmoldx.2013.07.006.
[102] J.H. Jeong, H.T. Lee, J.Y. Seo, Y.H. Seo, K.H. Kim, M.J. Kim, J.H. Lee, J. Park, J. S. Hong, P.W. Park, et al., Screening PCR versus sanger sequencing: detection of CALR mutations in patients with thrombocytosis, Ann. Lab Med 36 (2016) 291–299, https://doi.org/10.3343/alm.2016.36.4.291.
[103] A.A. Mina, B. Stein, Next-generation sequencing in myeloproliferative neoplasms: is this indicated in all patients? Curr. Hematol. Malig. Rep. 14 (2019) 137–144, https://doi.org/10.1007/s11899-019-00514-y.
[104] N. Maslah, E. Verger, M.H. Schlageter, J.M. Miclea, J.J. Kiladjian, S. Giraudier, C. Chomienne, B. Cassinat, Next-generation sequencing for JAK2 mutation testing: advantages and pitfalls, Ann. Hematol. 98 (2019) 111–118, https://doi.org/10.1007/s00277-018-3499-y.
[105] S. Wu, P. Luo, Y. Yu, B. Xiong, Y. Wang, X. Zuo, Next-generation sequencing redefines the diagnosis of triple-negative myeloproliferative neoplasms, Ann. Hematol. 101 (2022) 705–708, https://doi.org/10.1007/s00277-021-04561-5.
[106] Z. Zuo, S. Li, J. Xu, M.J. You, J.D. Khoury, C.C. Yin, Philadelphia-negative myeloproliferative neoplasms: laboratory workup in the era of next-generation sequencing, Curr. Hematol. Malig. Rep. 14 (2019) 376–385, https://doi.org/10.1007/s11899-019-00534-8.
[107] M. Magaz, A. Alvarez-Larrán, D. Colomer, M. López-Guerra, M.Á. García-Criado, G. Mezzano, E. Belmonte, P. Olivas, G. Soy, F. Cervantes, et al., Next-generation sequencing in the diagnosis of non-cirrhotic splanchnic vein thrombosis, J. Hepatol. 74 (2021) 89–95, https://doi.org/10.1016/j.jhep.2020.06.045.
[108] A. Segura-Díaz, R. Stuckey, Y. Florido, J.M. González-Martín, J.F. López-Rodríguez, S. Sánchez-Sosa, E. González-Pérez, M.N. Sáez Perdomo, M.D. M. Perera, S. de la Iglesia, et al., Thrombotic risk detection in patients with polycythemia vera: the predictive role of DNMT3A/TET2/ASXL1 mutations, Cancers (Basel) 12 (2020), https://doi.org/10.3390/cancers12040934.
[109] R.H. Westbrook, N.C. Lea, A.M. Mohamedali, A.E. Smith, D.W. Orr, L.N. Roberts, N.D. Heaton, J.A. Wendon, J.G. O'Grady, M.A. Heneghan, et al., Prevalence and clinical outcomes of the 46/1 haplotype, Janus kinase 2 mutations, and ten-eleven translocation 2 mutations in Budd-Chiari syndrome and their impact on thrombotic complications post liver transplantation, Liver Transpl. 18 (2012) 819–827, https://doi.org/10.1002/lt.23443.
[110] D. Colaizzo, G.L. Tiscia, D. Pisanelli, V. Bafunno, L. Amitrano, E. Grandone, M. A. Guardascione, M. Margaglione, New TET2 gene mutations in patients with myeloproliferative neoplasms and splanchnic vein thrombosis, J. Thromb. Haemost. 8 (2010) 1142–1144, https://doi.org/10.1111/j.1538-7836.2010.03810.x.
[111] D. Cattaneo, C. Bucelli, A. Marchetti, M. Lionetti, E. Fermo, V. Bellani, C. De Magistris, A. Maeda, A. Marella, M. Primignani, et al., Pathological and genomic features of myeloproliferative neoplasms associated with splanchnic vein thrombosis in a single-center cohort, Ann. Hematol. (2023), https://doi.org/10.1007/s00277-023-05217-2.
[112] J.J. Kiladjian, P.E. Debureaux, A. Plessier, J. Soret-Dulphy, D. Valla, B. Cassinat, P.E. Rautou, Benefits of molecular profiling with next-generation sequencing for the diagnosis and prognosis of myeloproliferative neoplasms in splanchnic vein thrombosis, J. Hepatol. 74 (2021) 251–252, https://doi.org/10.1016/j.jhep.2020.07.043.
[113] J. Grinfeld, J. Nangalia, E.J. Baxter, D.C. Wedge, N. Angelopoulos, R. Cantrill, A. L. Godfrey, E. Papaemmanuil, G. Gundem, C. MacLean, et al., Classification and Personalized Prognosis in Myeloproliferative Neoplasms, N. Engl. J. Med. 379 (2018) 1416–1430, https://doi.org/10.1056/NEJMoa1716614.
[114] V. De Stefano, X. Qi, S. Betti, E. Rossi, Splanchnic vein thrombosis and myeloproliferative neoplasms: molecular-driven diagnosis and long-term treatment, Thromb. Haemost. 115 (2016) 240–249, https://doi.org/10.1160/th15-04-0326.
[115] L. Naymagon, Venous thrombosis of the liver: current and emerging concepts in management, Transl. Res. 225 (2020) 54–69, https://doi.org/10.1016/j.trsl.2020.04.012.
[116] H.L. Janssen, J.C. Garcia-Pagan, E. Elias, G. Mentha, A. Hadengue, D.C. Valla, Budd-Chiari syndrome: a review by an expert panel, J. Hepatol. 38 (2003) 364–371, https://doi.org/10.1016/s0168-8278(02)00434-8.
[117] S.K. Sarin, J.D. Sollano, Y.K. Chawla, D. Amarapurkar, S. Hamid, M. Hashizume, W. Jafri, A. Kumar, M. Kudo, L.A. Lesmana, et al., Consensus on extra-hepatic portal vein obstruction, Liver Int. 26 (2006) 512–519, https://doi.org/10.1111/j.1478-3231.2006.01269.x.
[118] L. Naymagon, D. Tremblay, N. Zubizarreta, E. Moshier, K. Troy, T. Schiano, J. Mascarenhas, The efficacy and safety of direct oral anticoagulants in noncirrhotic portal vein thrombosis, Blood Adv. 4 (2020) 655–666, https://doi.org/10.1182/bloodadvances.2019001310.
[119] T. Barbui, V. De Stefano, A. Carobbio, A. Iurlo, A. Alvarez-Larran, B. Cuevas, F. Ferrer Marín, A.M. Vannucchi, F. Palandri, C. Harrison, et al., Direct oral anticoagulants for myeloproliferative neoplasms: results from an international study on 442 patients, Leukemia 35 (2021) 2989–2993, https://doi.org/10.1038/s41375-021-01279-1.
[120] M. Di Nisio, E. Valeriani, N. Riva, S. Schulman, J. Beyer-Westendorf, W. Ageno, Anticoagulant therapy for splanchnic vein thrombosis, J. Thromb. Haemost. 18 (2020) 1562–1568, https://doi.org/10.1111/jth.14836.
[121] W. Ageno, N. Riva, S. Schulman, S.M. Bang, M.T. Sartori, E. Grandone, J. Beyer-Westendorf, G. Barillari, M.N. Di Minno, F. Dentali, Antithrombotic treatment of splanchnic vein thrombosis: results of an international registry, Semin Thromb. Hemost. 40 (2014) 99–105, https://doi.org/10.1055/s-0033-1363473.
[122] C. Kearon, E.A. Akl, A.J. Comerota, P. Prandoni, H. Bounameaux, S.Z. Goldhaber, M.E. Nelson, P.S. Wells, M.K. Gould, F. Dentali, et al., Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, Chest 141 (2012) e419S–e496S, https://doi.org/10.1378/chest.11-2301.
[123] A. Kaifie, M. Kirschner, D. Wolf, C. Maintz, M. Hänel, N. Gattermann, E. Gökkurt, U. Platzbecker, W. Hollburg, J.R. Göthert, et al., Bleeding, thrombosis, and anticoagulation in myeloproliferative neoplasms (MPN): analysis from the German SAL-MPN-registry, J. Hematol. Oncol. 9 (2016) 18, https://doi.org/10.1186/s13045-016-0242-9.
[124] L. Loffredo, D. Pastori, A. Farcomeni, F. Violi, Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis, e481, Gastroenterology 153 (2017) 480–487, https://doi.org/10.1053/j.gastro.2017.04.042.
[125] N.M. Intagliata, P. Davitkov, A.M. Allen, Y.T. Falck-Ytter, J.G. Stine, AGA technical review on coagulation in cirrhosis, Gastroenterology 161 (2021) 1630–1656, https://doi.org/10.1053/j.gastro.2021.09.004.
[126] M.G. Delgado, S. Seijo, I. Yepes, L. Achécar, M.V. Catalina, A. García-Criado, J. G. Abraldes, J. de la Peña, R. Bañares, A. Albillos, et al., Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis, Clin. Gastroenterol. Hepatol. 10 (2012) 776–783, https://doi.org/10.1016/j.cgh.2012.01.012.
[127] V. La Mura, S. Braham, G. Tosetti, F. Branchi, N. Bitto, M. Moia, A.L. Fracanzani, M. Colombo, A. Tripodi, M. Primignani, Harmful and beneficial effects of anticoagulants in patients with cirrhosis and portal vein thrombosis, e1144, Clin. Gastroenterol. Hepatol. 16 (2018) 1146–1152, https://doi.org/10.1016/j.cgh.2017.10.016.
[128] R. de Franchis, J. Bosch, G. Garcia-Tsao, T. Reiberger, C. Ripoll, Baveno VII - renewing consensus in portal hypertension, J. Hepatol. 76 (2022) 959–974, https://doi.org/10.1016/j.jhep.2021.12.022.
[129] G.M. Knight, J. Clark, J.R. Boike, H. Maddur, D.R. Ganger, A. Talwar, A. Riaz, K. Desai, S. Mouli, E. Hohlastos, et al., TIPS for adults without cirrhosis with chronic mesenteric venous thrombosis and EHPVO refractory to standard-of-care therapy, Hepatology 74 (2021) 2735–2744, https://doi.org/10.1002/hep.31915.
[130] L. Naymagon, D. Tremblay, N. Zubizarreta, E. Moshier, T. Schiano, J. Mascarenhas, Portal vein thrombosis patients harboring JAK2V617F have poor long-term outcomes despite anticoagulation, J. Thromb. Thrombolysis 50 (2020) 652–660, https://doi.org/10.1007/s11239-020-02052-4.
[131] T. Barbui, A. Tefferi, A.M. Vannucchi, F. Passamonti, R.T. Silver, R. Hoffman, S. Verstovsek, R. Mesa, J.-J. Kiladjian, R. Hehlmann, et al., Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet, Leukemia 32 (2018) 1057–1069, https://doi.org/10.1038/s41375-018-0077-1.
[132] G. Finazzi, V. De Stefano, T. Barbui, Splanchnic vein thrombosis in myeloproliferative neoplasms: treatment algorithm 2018, Blood Cancer J. 8 (2018), 64, https://doi.org/10.1038/s41408-018-0100-9.
[133] R. Marchioli, G. Finazzi, G. Specchia, R. Cacciola, R. Cavazzina, D. Cilloni, V. De Stefano, E. Elli, A. Iurlo, R. Latagliata, et al., Cardiovascular events and intensity of treatment in polycythemia vera, N. Engl. J. Med. 368 (2012) 22–33, https://doi.org/10.1056/NEJMoa1208500.
[134] G. Barosi, R. Mesa, G. Finazzi, C. Harrison, J.J. Kiladjian, E. Lengfelder, M. F. McMullin, F. Passamonti, A.M. Vannucchi, C. Besses, et al., Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project, Blood 121 (2013) 4778–4781, https://doi.org/10.1182/blood-2013-01-478891.
[135] G. Barosi, G. Birgegard, G. Finazzi, M. Griesshammer, C. Harrison, H. Hasselbalch, J.J. Kiladijan, E. Lengfelder, R. Mesa, M.F. Mc Mullin, et al., A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process, Br. J. Haematol. 148 (2010) 961–963, https://doi.org/10.1111/j.1365-2141.2009.08019.x.
[136] A. Quintás-Cardama, O. Abdel-Wahab, T. Manshouri, O. Kilpivaara, J. Cortes, A. L. Roupie, S.J. Zhang, D. Harris, Z. Estrov, H. Kantarjian, et al., Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon α-2a, Blood 122 (2013) 893–901, https://doi.org/10.1182/blood-2012-07-442012.
[137] A.M. Vannucchi, J.J. Kiladjian, M. Griesshammer, T. Masszi, S. Durrant, F. Passamonti, C.N. Harrison, F. Pane, P. Zachee, R. Mesa, et al., Ruxolitinib versus standard therapy for the treatment of polycythemia vera, N. Engl. J. Med. 372 (2015) 426–435, https://doi.org/10.1056/NEJMoa1409002.
[138] F. Passamonti, M. Griesshammer, F. Palandri, M. Egyed, G. Benevolo, T. Devos, J. Callum, A.M. Vannucchi, S. Sivgin, C. Bensasson, et al., Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study, Lancet Oncol. 18 (2017) 88–99, https://doi.org/10.1016/s1470-2045(16)30558-7.

[139] A. Iurlo, C. Bucelli, D. Cattaneo, Essential thrombocythemia in adolescents and young adults: clinical aspects, treatment options and unmet medical needs, Curr. Treat. Options Oncol. 24 (2023) 802–820, https://doi.org/10.1007/s11864-023-01099-8.

[140] B. Cassinat, E. Verger, J.J. Kiladjian, Interferon alfa therapy in CALR-mutated essential thrombocythemia, N. Engl. J. Med. 371 (2014) 188–189, https://doi.org/10.1056/NEJMc1401255.

[141] H. Gisslinger, M. Gotic, J. Holowiecki, M. Penka, J. Thiele, H.M. Kvasnicka, R. Kralovics, P.E. Petrides, Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial, Blood 121 (2013) 1720–1728, https://doi.org/10.1182/blood-2012-07-443770.

[142] G. Barosi, C. Besses, G. Birgegard, J. Briere, F. Cervantes, G. Finazzi, H. Gisslinger, M. Griesshammer, L. Gugliotta, C. Harrison, et al., A unified definition of clinical resistance/intolerance to hydroxyurea in essential thrombocythemia: results of a consensus process by an international working group, Leukemia 21 (2007) 277–280, https://doi.org/10.1038/sj.leu.2404473.

[143] F. Cervantes, B. Dupriez, A. Pereira, F. Passamonti, J.T. Reilly, E. Morra, A. M. Vannucchi, R.A. Mesa, J.L. Demory, G. Barosi, et al., New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment, Blood 113 (2009) 2895–2901, https://doi.org/10.1182/blood-2008-07-170449.

[144] F. Passamonti, F. Cervantes, A.M. Vannucchi, E. Morra, E. Rumi, M. Cazzola, A. Tefferi, Dynamic international prognostic scoring system (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis, Blood 116 (2010) 2857–2858, https://doi.org/10.1182/blood-2010-06-293415.

[145] N. Gangat, D. Caramazza, R. Vaidya, G. George, K. Begna, S. Schwager, D. Van Dyke, C. Hanson, W. Wu, A. Pardanani, et al., DIPSS plus: a refined dynamic international prognostic scoring system for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status, J. Clin. Oncol. 29 (2011) 392–397, https://doi.org/10.1200/jco.2010.32.2446.

[146] L. Pieri, C. Paoli, U. Arena, F. Marra, F. Mori, M. Zucchini, S. Colagrande, A. Castellani, A. Masciulli, V. Rosti, et al., Safety and efficacy of ruxolitinib in splanchnic vein thrombosis associated with myeloproliferative neoplasms, Am. J. Hematol. 92 (2017) 187–195, https://doi.org/10.1002/ajh.24614.

[147] G. Barosi, A. Buratti, A. Costa, L.N. Liberato, C. Balduini, M. Cazzola, V. Rosti, U. Magrini, E. Ascari, An atypical myeloproliferative disorder with high thrombotic risk and slow disease progression, Cancer 68 (1991) 2310–2318, https://doi.org/10.1002/1097-0142(19911115)68:10<2310::aid-cncr2820681034>3.0.co;2-2.

[148] G. Barosi, A.M. Vannucchi, V. De Stefano, F. Pane, F. Passamonti, A. Rambaldi, G. Saglio, T. Barbui, S. Tura, Identifying and addressing unmet clinical needs in Ph-neg classical myeloproliferative neoplasms: a consensus-based SIE, SIES, GITMO position paper, Leuk. Res. 38 (2014) 155–160, https://doi.org/10.1016/j.leukres.2013.09.008.

[149] V. De Stefano, E. Rossi, A. Carobbio, A. Ghirardi, S. Betti, G. Finazzi, A. M. Vannucchi, T. Barbui, Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splanchnic venous district. Pooled analysis of 1500 cases, Blood Cancer J. 8 (2018), 112, https://doi.org/10.1038/s41408-018-0151-y.

[150] J. Mascarenhas, H. Kosiorek, J. Prchal, A. Yacoub, D. Berenzon, M.R. Baer, E. Ritchie, R.T. Silver, C. Kessler, E. Winton, et al., A prospective evaluation of pegylated interferon alfa-2a therapy in patients with polycythemia vera and essential thrombocythemia with a prior splanchnic vein thrombosis, Leukemia 33 (2019) 2974–2978, https://doi.org/10.1038/s41375-019-0524-7.