

JAK2V617F mutation for the early diagnosis of Ph⁻ myeloproliferative neoplasms in patients with venous thromboembolism: a meta-analysis

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Recent studies suggested that *JAK2V617F* mutation is frequent in patients with splanchnic vein thrombosis (SVT) but not in patients with other venous thromboembolic events (VTE). However, whether screening for the *JAK2V617F* mutation in VTE patients is justified remains unclear. Therefore, we performed a systematic review to assess the frequency of JAK2 mutation in VTE patients and the role of *JAK2V617F* mutation in the diagnosis of myeloproliferative neoplasms. MEDLINE and EMBASE data-

bases were searched. Two reviewers independently performed study selection and extracted study characteristics. Pooled odds ratios of case-control studies and weighted mean proportion of the prevalence of *JAK2V617F* mutation of uncontrolled series were calculated. Twenty-four studies involving 3123 patients were included. Mean prevalence of JAK2 mutation was 32.7% (95% confidence interval, 25.5%-35.9%) in SVT patients. JAK2 mutation was associated with increased risk of SVT (odds ratio, 53.98;

95% confidence interval, 13.10-222.45). Mean prevalence of JAK2 mutation in other VTE patients was low (range, 0.88%-2.57%). Presence of *JAK2V617F* mutation in SVT patients was associated with a subsequent diagnosis of myeloproliferative neoplasm in many patients. JAK2 mutation is strongly associated with SVT, and routine screening of JAK2 mutation appears to be indicated in these patients. (Blood. 2009;113:5617-5623)

Venous and arterial thrombosis are important causes of morbidity and mortality in patients with Philadelphia-negative (Ph⁻) myeloproliferative neoplasms (MPNs), polycythemia vera (PV), and essential thrombocythemia (ET).¹ In particular, splanchnic vein thromboses (SVTs), which include portal vein thrombosis, mesenteric vein thrombosis, and thrombosis of the hepatic veins causing Budd-Chiari syndrome, are frequently the first manifestation of PV and ET.² Overall, Ph⁻ MPNs are among the commonest causes of Budd-Chiari syndrome and portal vein thrombosis, being found in up to 50% and 25% of the patients, respectively.³

The identification of occult MPNs in patients with venous thromboembolism (VTE) has traditionally been based on bone marrow biopsy findings and endogenous erythroid colony formation assessment.⁴ Both tests have significant limitations: bone marrow biopsy is invasive and its interpretation is, at best, semiquantitative; endogenous erythroid colony assessment is performed in only a few specialized centers, and its significance as a unique anomaly in patients with SVT has been disputed.⁵ These limitations have hindered diagnosis of underlying MPN and assessment of its influence on the outcome of VTE patients, particularly those with SVT.

The discovery of the gain-of-function *JAK2V617F* mutation, found in approximately 95% of patients with PV and in 50% of those with ET or primary myelofibrosis, has modified the diagnostic approach to Ph⁻ MPNs.^{6,7} Several small series have suggested that *JAK2V617F* is found frequently in patients with SVT patients but not in VTE patients; many such patients have no other manifestations of an MPN.⁸ However, whether screening for the *JAK2V617F* mutation in patients presenting with venous thrombosis without overt MPD is justified remains unclear.

The aims of our systematic review were to assess the prevalence of the *JAK2V617F* mutation in patients' lower limb deep venous

thrombosis and pulmonary embolism, and in patients with VTE in unusual sites (SVT, cerebral sinus, and vein thrombosis [CVT], upper limb deep venous thrombosis, and retinal vein occlusion [RVO]). Furthermore, we sought to examine the role of this mutation in the diagnosis of nonovert MPNs.

Methods

A protocol for this review was developed prospectively, detailing the specific objectives, criteria for study selection, approach to assess study quality, outcomes, and statistical methods.

Study identification

We attempted to identify all published studies that evaluated the prevalence of the JAK2 V617F mutation (homozygote and heterozygote) in patients with VTE in usual and unusual sites using the MEDLINE⁹ (1966 to October, week 2, 2008) and EMBASE¹⁰ (1980 to October, week 2, 2008) electronic databases. The search strategy was developed without any language restriction and used the subject headings presented in the "Appendix." We supplemented our search by manually reviewing abstract books from the Congress of the American Society of Hematology and the International Society on Thrombosis and Hemostasis (2005-2007), the reference lists of all retrieved articles, and contacting content experts for additional published or unpublished trials.

Study selection

Two reviewers (L.B., L.A.) performed study selection independently, with disagreements resolved through discussion and by the opinion of a third reviewer (F.D.), if necessary. Studies were included if they met the following criteria: (1) analysis of JAK2 mutation was performed according to established and commonly accepted criteria¹¹; (2) patients were 18 years of age or older; and (3) at least 10 patients were included. To assess the agreement between reviewers for study selection, we used the κ statistic, which measures agreement beyond chance.¹²

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Study validity assessment

The same 2 unmasked investigators independently completed the assessment of study validity. Because the use of quality scoring systems or quality scales in observational studies is controversial,¹³ the internal validity of each case-control study was evaluated considering 2 potential sources of bias.¹⁴ Studies were considered of low quality when subjects were arbitrarily excluded from either the case or control groups and when baseline characteristics of the control group (age, sex) were not matched with the characteristics of the patient group. Otherwise, studies were considered of higher quality.

Data extraction

L.A. and L.B. independently extracted data on study (year of publication, design, study center) and patient characteristics (number of subjects studied, mean age, variation in age, sex, and race). Furthermore, the prevalence of *JAK2V617F* mutation was assessed in all the studies in which a population of patients with VTE was considered. Disagreement was resolved by consensus and by opinion of a third reviewer (F.D.), if necessary. If the required data could not be located in the published report, we contacted the corresponding author, with a reminder sent after 15 days. The definition of overt or nonovert MPN and the definition of idiopathic or nonidiopathic SVT were based on the definitions used in each selected study.

Statistical analysis

Weighted mean proportion of the prevalence of JAK2 mutation was calculated using random-effects model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated when studies compared the prevalence of JAK2 mutation in VTE patients and in controls. These data were pooled using a fixed-effects model (Mantel-Haenszel method)¹⁵ and comparing these findings with results obtained using a random-effects model (DerSimonian and Laird method).¹⁶ Statistical heterogeneity was evaluated using the I^2 statistic, which assesses the appropriateness of pooling the individual study results.¹⁷ The I^2 value provides an estimate of the amount of variance across studies resulting from heterogeneity rather than chance. P less than .05 was considered to denote statistically significant heterogeneity. When heterogeneity was present, we repeated the analyses removing one study at a time to assess the source of heterogeneity. The proportion of VTE in the different populations that could be attributed to JAK2 mutation (population-attributable risk) was estimated as follows:

Population-attributable risk = 100

$$\times [\text{prevalence}(\text{OR} - 1) / \text{prevalence}(\text{OR} - 1) + 1]$$

For this calculation, we used the fixed-effects model, and we estimated the prevalence of exposure as the genotype frequency among control subjects. The presence of publication bias was explored using funnel plots of effect size against SE.¹⁸

Results

Study identification and selection

We identified 1036 potentially relevant studies from the following databases: 691 from EMBASE, 295 from MEDLINE, and 50 from abstracts books from the American Society of Hematology and International Society on Thrombosis and Hemostasis Congress. A total of 220 studies were duplicated, and 782 studies were excluded after title and abstract screening using predefined inclusion and exclusion criteria; the remaining 34 studies were retrieved in full for detailed evaluation.^{10,19-51} One additional study was identified through manual review of references.⁵² The study identification and selection progression are summarized in Figure 1.

Of the 35 retrieved studies, 11 were excluded for the following reasons: 7 contained duplicated data^{19,22,26,28,29,32,39-50} and 3^{20,33,38} included fewer than 10 patients. Twenty-four studies were therefore included in this systematic review.^{10,21,23,25,27,30,33,37,40-49,51,52} Interobserver agreement for study selection was excellent ($\kappa = 0.96$).

Study characteristics

Baseline characteristics of patients included in the studies are summarized in Table 1. All studies were written in English, and all studies analyzed the V617F mutation of JAK2; other mutations of JAK2 were not assessed. Studies ranged in size from 11 to 560 patients; a total of 3508 patients were included. Six case-control studies^{10,23,25,27,35,40} and 18 retrospective cohort studies^{21,24,30,31,34,36,37,41-49,51,52} were included in our systematic review. Five studies enrolled patients consecutively.^{35,42,44,46,51} A few studies differentiated between patients with homozygote and heterozygote *JAK2V617F* mutation,^{24,34,35,41,43,44,49} and 2 studies provided data on patients with homozygote mutation *JAK2V617F*.²⁴⁻³⁵ Sixteen studies,^{10,21,23-25,30,35-37,40,43,44,46,47,49,53} including a total 831 patients, assessed the prevalence of *JAK2V617F* mutation in patients with SVT. Eight studies,^{21,27,34,37,40-42,47} including 1293

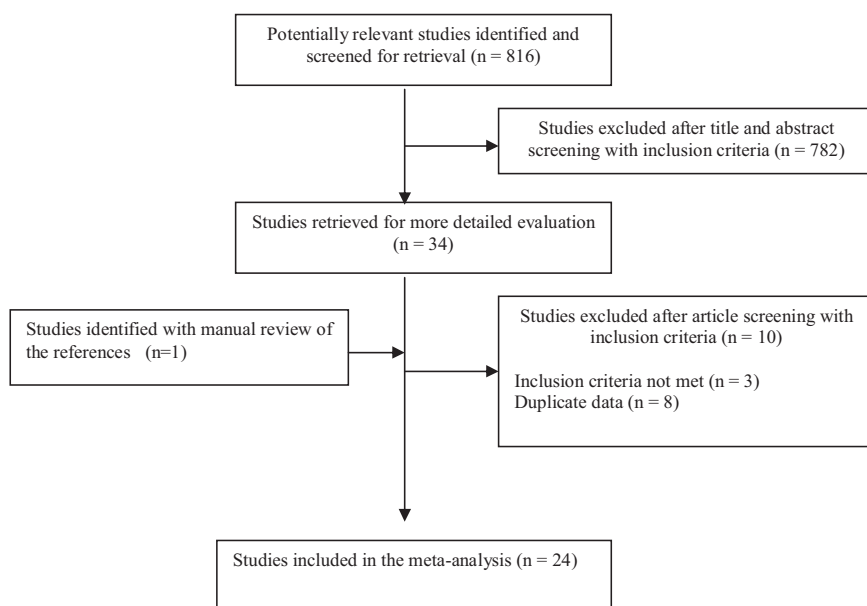


Figure 1. Study selection progression.

patients, assessed the prevalence of *JAK2V617F* mutation in patients with deep vein thrombosis of the leg or pulmonary embolism. Six studies,^{21,24,40,41,45,51} for a total 241 patients, assessed the prevalence of *JAK2V617F* mutation in patients with CVT. Finally, 6 studies^{21,31,40,41,47,48} with a total 153 patients assessed the prevalence of *JAK2V617F* mutation in patients with RVO. No study assessed the *JAK2V617F* mutation in patients with upper limb deep venous thrombosis.

Study quality

Two case-control studies enrolled patients consecutively.^{23,35} Age and sex of cases and controls were similar in 2 studies,^{25,40} whereas in the other 3 studies^{10,23,35} baseline characteristics of controls were not specified.

Patients with SVT

A total of 280 of 831 patients with SVT had the *JAK2V617F* mutation, for a mean prevalence of 32.7% (95% CI, 25.5%-35.9%). Five studies provided the prevalence of the *JAK2V617F* mutation in patients with idiopathic SVT^{10,21,36,37,49}; the mutation was present in 49.0% (95% CI, 32.9%-65.1%) of such patients. Ten studies^{21,23,25,35,37,40,43,44,52} provided separate data on the rate of diagnosis of myeloproliferative disorder in patients with *JAK2* mutation at the time of diagnosis of SVT (77 of 131 patients; mean prevalence, 59.5%; 95% CI, 51.3%-67.5%), and 5 studies provided data on the rate of diagnosis of myeloproliferative disorder during the follow-up period in patients with *JAK2* mutation without a diagnosis of myeloproliferative disorder at the time of SVT diagnosis (21 of 41 patients; mean rate, 52.4%; 95% CI, 38.0%-66.5%).^{21,23,25,40,49}

Four case-control studies evaluated the association between *JAK2V617F* mutation and SVT.^{10,23,35,40} Cases were composed by patients with SVT, whereas controls were composed by healthy subjects and by subjects with nonthrombotic liver and pancreatic disease. These studies included 297 cases and 363 controls. The *JAK2V617F* mutation was found significantly more often in patients with SVT than those without (OR, 53.98; 95% CI, 13.10-222.45; Figure 2), suggesting a strong association between the mutation and SVT. There was no heterogeneity among the studies ($I^2 = 0\%$). The analysis was repeated using the random-effects model, which yielded similar results (OR, 46.88; 95% CI, 11.21-196.15). The estimated attributable risk of SVT conferred by *JAK2V617F* mutation was 12.74% in this pooled cohort.

Patients with VTE in other sites

Ten of 1293 patients with deep vein thrombosis of the lower limbs or pulmonary embolism were found to have *JAK2V617F* mutation for a mean prevalence of 0.88% (95% CI, 0.44%-1.45%).^{21,27,34,37,40,42,47} Eight of 248 patients with CVT had *JAK2V617F* mutation, for a mean prevalence of 2.57% (95% CI, 0.97%-4.91%).^{21,24,40,41,45,51} One of 153 patients with RVO had *JAK2V617F* mutation, for a mean prevalence of 0.99% (95% CI, 0.05%-3.20%).^{21,31,40,41,47,48}

Discussion

This is the first systematic review and meta-analysis that assessed the role of *JAK2* mutation in patients with venous thrombosis. The results of this study indicate that the prevalence of this mutation is high in patients with SVT. On the other hand, we found the mutation to be no more common in patients with venous thrombosis at other sites than it is in patients with neither venous thrombosis

nor known MPN.⁵³ The meta-analysis of case-control studies found a strong association between *JAK2V617F* mutation and SVT, with an OR greater than 50.0, suggesting that a high proportion of SVTs can be associated with the presence of *JAK2* mutation. Finally, the concomitant presence of *JAK2* mutation in patients with SVT was associated with a subsequent diagnosis of an occult myeloproliferative disease in a large proportion of patients both at the time of SVT diagnosis and after long-term follow-up, suggesting both the role of the presence of *JAK2* mutation as a marker of latent myeloproliferative disorders and that SVT commonly occurs as the first manifestation of MPN.

Taken together, these results suggest that, in general, patients with VTE should not be screened for the presence of *JAK2* mutation. This screening appears to be justified in the population of patients with SVT, in whom the presence of *JAK2* mutation is higher than 30% and in whom the finding of this mutation is a strong predictor of a subsequent diagnosis of an MPN. This is particularly relevant given that, in these patients, the concomitant presence of portal hypertension and hypersplenism could mask the increase in blood cell counts, even in the presence of ongoing myeloproliferation, thus making clinical suspicion more difficult.⁵⁴ Whether the screening for *JAK2* mutation could be justified also in patients with CVT remains controversial. Our results suggest a slight increase in the prevalence of the mutation in this patient population; however, the number of evaluated patients is small and the CI is thus too wide to allow any meaningful conclusion. Larger studies would be required to confirm or refute such an association.

Searching for an occult MPN in patients presenting with SVT, in particular, when other, major triggering factors are absent appears appropriate given that several studies have found MPN as one of the most common causes of SVT.⁵⁵ However, routine screening with invasive and expensive procedures, such as bone marrow biopsy and endogenous erythroid colony formation assessment, may not be cost-effective if proposed to all such patients, in particular, in the absence of other specific signs of MPN, such as changes in blood cell counts. Routine testing for *JAK2* mutation should identify those patients for whom additional investigation is warranted and may also prevent the need for additional investigation in some circumstances. Furthermore, according to the revised World Health Organization diagnostic criteria, invasive tests are not strictly necessary to diagnose PV in the presence of *JAK2* mutation, and the presence of high hematocrit values in concomitance with serum erythropoietin level below the reference range for normal may be sufficient.⁵⁶

Why the *JAK2* mutation is so strongly associated with SVT is unknown. The mutation causes the constitutive activation of *JAK2*, which in turn results in cytokine-independent myeloproliferation, mobilization of blood cell progenitors, and the spontaneous formation of endogenous erythroid colonies leading to the development of a myeloproliferative disorder.⁵⁷ Whether all these abnormalities also induce a hypercoagulable state will need to be determined by future studies. The reason for the specific association between *JAK2* mutation and this unusual site of thrombosis could also be explained by the effects of the disease in the splanchnic system, possibly affecting the flow of the splanchnic venous bed. However, the exact mechanisms underlying these changes remain to be established.

Our systematic review has several potential limitations. First, our meta-analysis was restricted to case-control studies, and the application of formal meta-analytic methods to observational studies is controversial because bias implicit in the study design may misrepresent the strength of associations within the

Table 1. Baseline characteristics of patients included in the studies

Study, date (reference no.)	Study type	Selected population	Median age, y (range)	No. of patients	JAK2 mutation (homozygous or heterozygous)	Population controls
Rossi et al, 2007 (19)	Retrospective cohort	Patients with idiopathic VTE (absence of: known conditions of inherited or acquired thrombophilia; common acquired risk factors for VTE, malignancy, surgery, pregnancy, estrogen consumption, liver failure, and nephritic syndrome; overt Ph ⁻ CMPD).	48 (5-84)	139 (F/M 81/58)	3 of 139 JAK2V617F (lower limb DVT 0 of 61, CVT 0 of 13, RVO 0 of 6, SVT 3 of 6, PE 0 of 53)	—
McMahon et al, 2007 (21)	Case-control	Patients with catastrophic intraabdominal venous thrombosis.	47.5 (18-64)	24† (F/M 10/14)	5 of 24 JAK2V617F	30 patients with hereditary pancreatitis (mutation in the PRSS1 gene); 0 of 30 JAK2V617F
De Stefano et al, 2007 (22)	Retrospective cohort	Patients with idiopathic SVT or CVT, excluding overt cancer.	—	139 (94 SVT + 45 CVT)	37 of 139 JAK2V617F (32 of 94 SVT and 5 of 45 CVT*) (27 of 37 were sequenced)	—
Regina et al, 2007 (23)	Case-control	Patients with HVT or EHPVO in whom liver cirrhosis, infection, and neoplastic disease were excluded. Patients with spontaneous DVT of the lower limbs.	39 (22-76)	44 (F/M 21/23)	8 of 44 JAK2V617F	—
Remacha et al, 2007 (25)	Case-control	Patients with thrombosis in common locations (consecutive patients with a first thrombotic event < 70 years, excluding those with neoplastic disease, liver failure, nephrotic syndrome).	39 (22-76) 48 ± 14	44 (F/M 21/23) 295 (F/M 162/133)	0 of 44 JAK2V617F 1 of 295 JAK2V617F	65 patients with other hematologic non-CMPD; 0 of 65 JAK2V617F
Boissinot et al, 2006 (28)	Retrospective cohort	Patients with SVT.	46.8*	45 (F/M 21/24)	14 of 45 JAK2V617F	—
Patel et al, 2006 (8)	Case-control	Patients with idiopathic BCS, excluding secondary etiology: adult polycystic liver and renal disease, hepatic vein stenosis, inferior vena cava stenosis, Bechet disease, carcinoid tumor, malignant infiltration, hepatocellular carcinoma, pregnancy, sickle cell disease, ulcerative colitis, PV, hydatid liver disease.	35.5 ± 13.3*	41 (F/M 26/15)	24 of 41 JAK2V617F, during follow-up, 11 of 41 developed CMPD; 10 of 11 JAK2V617F	27 patients with nonthrombotic liver disease (autoimmune, acetaminophen overdose, Gilbert syndrome, and Wilson disease); 0 of 27 JAK2V617F
Héron et al, 2007 (29)	Retrospective cohort	Patients with a first or recurrent central or branch RVO, excluding traumatic, inflammatory, or tumor-related local cause of RVO; history of cancer, CMPD, systemic immunoinflammatory disease, and overt organ failure.	46.1 ± 11.5* (25-58)†	11	0 of 11 JAK2V617F	—
Ugo et al, 2007 (32)	Retrospective cohort	Patients with first unprovoked VTE without major acquired risk factor: surgery, plaster cast, pregnancy or delivery in the past 3 months, cancer.	73 (18-96)	394 (F/M 226/168)	6 of 394 JAK2V617F	—
Primignani et al, 2006 (33)	Case-control	Consecutive patients with EHPVO or BCS, excluding neoplastic disease and liver cirrhosis. None of the patients had prior history of CMPD.	38 (13-72)	93 (20 BCS + 73 EHPVO) (F/M 56/37)	34 of 93 JAK2V617F (26 heterozygous, 8 homozygous)	20 healthy subjects; 0 of 20 JAK2V617F
Kiladjian et al, 2008 (34)	Retrospective cohort	Patients with EHPVO or BCS, excluding neoplastic disease and liver cirrhosis.	BCS: 36 (27-46) PVT: 42 (30-57)	241 (104 BCS + 137 EHPVO) (F/M 129/112)	94 of 241 JAK2V617F (47 of 104; 47 of 137)	—
Abel et al, 2008 (35)	Retrospective cohort	Patients with documented venous thrombosis (DVT, PE, SVT), excluding neoplastic disease, CMPD, or HIT within 1 year of thrombosis.	—	52	1 of 52 JAK2V617F (0 of 45 DVT of PE 1 of 7 SVT)	—
Colaizzo et al, 2007 (38)	Case-control	Patients with SVT, RVO, CVT, or DVT, excluding cirrhosis or hepatocellular carcinoma.	SVT: 47 (10-86) RVO: 51 (20-81) CVT: 40 (13-55) DVT: 49 (12-81)	139 SVT (F/M 83/56); 93 RVO (F/M 42/51); 45 CVT (F/M 31/14); 110 DVT (F/M 51/59)	27 of 139 JAK2V617F (0 of 93 RVO, 0 of 45 CVT, 0 of 110 DVT)	286 healthy subjects (F/M 163/119; median age, 44 years; range, 21-73 years); 0 of 286 JAK2V617F

Table 1. Baseline characteristics of patients included in the studies (continued)

Study, date (reference no.)	Study type	Selected population	Median age, y (range)	No. of patients	JAK2 mutation (homozygous or heterozygous)	Population controls
Pardanani et al, 2008 (39)	Retrospective cohort	Patients with non-SVT and non-CMPD.	56 (17-93)†	303 (114 DVT, 95 PE, 50 DVT and PE, 10 RVO, 7 CVT, 27 other thromboses)	4 of 303 JAK2V617F (1 of 10 RVO, 1 of 7 CVT and PE, 1 of 50 DVT and PE, 1 of 95 PE)	—
Sène et al, 2008 (40)	Retrospective cohort	Consecutive patients with venous thrombosis (lower limbs, inferior vena cava, arm, pulmonary arteries).	45.8 ± 18	44 (F/M 23/21)	0 of 44 JAK2V617F	—
Bayraktar et al, 2008 (41)	Retrospective cohort	Patients with chronic noncirrhotic PVT (chronic PVT: partial or total occlusion of the portal system known for > 6 months or as the presence of portal vein cavernous transformation). Patients with acute or subacute PVT (within 3 months), cirrhosis, or liver malignancy were excluded.	44.9* (24-73)	25 (F/M 16/9)	6 of 25 JAK2V617F; all were heterozygous	—
Colaizzo et al, 2008 (42)	Retrospective cohort	Consecutive patients with BCS.	35 (14-66)	32 (F/M 23/9)	11 of 32 JAK2V617F	—
Bellucci et al, 2008 (43)	Retrospective cohort	Patients with CVT without overt CMPD	35.4 ± 12.9	87 (F/M 68/19)	1 of 87 JAK2V617F	—
Garcés-Eisele et al, 2008 (44)	Retrospective cohort	Patients with at least 1 episode of venous thrombosis confirmed by phlebography or Doppler in the previous 30 days. Patients with overt malignancy, pregnancy, puerperium, oral contraceptives, or other conditions associated with secondary thrombophilia were excluded.	37.5§	36	0 of 36 JAK2 V617 F (0 of 30 DVT; 0 of 2; 0 of 2 RVO; 0 of 2 SVT)	—
Karimi et al, 2008 (45)	Retrospective cohort	Thrombotic IBD patients (22 CD and 26 UC).	51* (20-80)	31 (F/M 17/14)	0 of 31 JAK2V617F	—
Hermans et al, 2008 (46)	Retrospective cohort	Patients with idiopathic RVO.	41 (24-76)	19	14 of 19 JAK2V617F; all were heterozygous	—
Goulding et al, 2008 (47)	Retrospective cohort	Patients with HVT (10) and PVT (10). Patients with thrombophilia, pregnancy, malignancy, sepsis, OC, preexisting cirrhosis, and patients with overt CMPD at the time of diagnosis of thrombosis were excluded.	28 (15-65)	44 (F/M 30/14)	0 of 44 JAK2V617F	—
Xavier et al, 2008 (49)	Retrospective cohort	Consecutive CVT patients without overt CMPD.	26.3	17 (F/M 10/7)	7 of 17 JAK2V617F	—
Smalberg et al, 2006 (50)	Retrospective cohort	Patients with BCS.	—	—	—	—

SVT indicates splanchic vein thrombosis; BCS, Budd-Chiari syndrome; EHPVO, extrahepatic portal vein obstruction; CMPD, chronic myeloproliferative disease; PV, polycythemia vera; CVT, cerebral venous thrombosis; HVT, hepatic venous thrombosis; DVT, deep vein thrombosis; MVT, mesenteric vein thrombosis; VTE, venous thromboembolism; PMVT, portal and mesenteric venous thrombosis; RVO, retinal vein occlusion; HIT, heparin-induced thrombocytopenia; US, ultrasonography; CT, computed tomography; MR, magnetic resonance; PE, pulmonary embolism; MF, idiopathic myelofibrosis; CML, chronic myeloid leukemia; PVT, portal vein thrombosis; ET, essential thrombocythemia; IBD, inflammatory bowel disease; CD, Crohn disease; UC, ulcerative colitis; F, female; M, male; and —, not applicable.

*Mean or mean ± SD.
 †Age referred to 12 patients.
 ‡Referred to 439 patients.
 §Median age of onset of IBD.
 ¶Two patients had also arterial superior mesenteric thrombosis.
 **Data on patients with CVT were supplemented with data of a more recent publication; 6 of 52 patients with CVT were positive for JAK2 V617F mutation (xx).

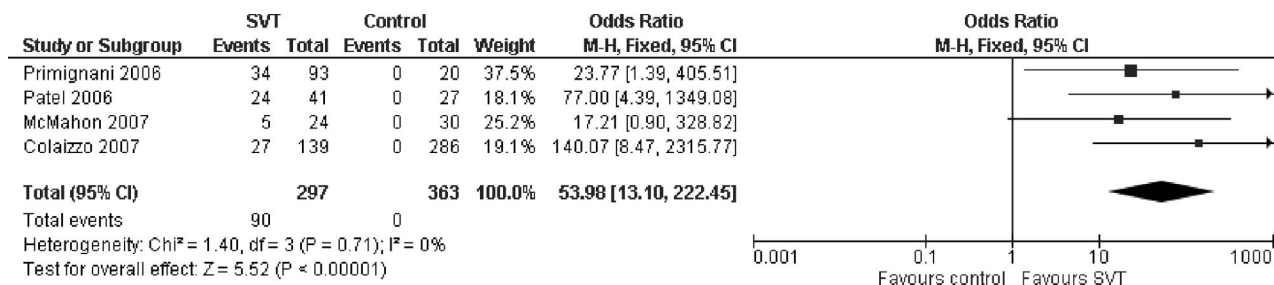


Figure 2. Odds ratio for the association between splanchnic vein thrombosis and JAK2 V617F mutation.

data.¹⁷ Second, studies included in our meta-analysis have different inclusion and exclusion criteria, and to combine results across studies may be inappropriate. However, the heterogeneity between the studies, calculated using the I^2 statistic, was extremely low. Furthermore, when we repeated the analysis using a random-effects model, an approach that accounts for some of the variance between studies, we found similar results. Third, the importance of other inherited or acquired risk factors for thrombosis (in addition to the JAK2 mutation) could not be assessed as relevant data were not reported in the contributing articles. Thus, whether the presence of other risk factors contributes to the risk of SVT in patients with the JAK2 mutation remains unknown. Fourth, there are too few studies to assess the role of other less frequent mutations of JAK2 and to distinguish the risk of venous thrombosis in patients with heterozygous and homozygous V617F mutation of JAK2. Furthermore, given the low quality of case-control studies included in our systematic review, our findings should be interpreted with caution. Last, because there were too few case-control studies, the presence of publication bias could not be evaluated. However, given the magnitude of the association and the homogeneity of results in different studies, it is extremely doubtful that unpublished studies that did not find an association between SVT and JAK2 mutation, if really exist, could substantially modify our results.

In conclusion, the JAK2 mutation is strongly associated with SVT. Because the presence of JAK2 mutation is also a strong predictor of a subsequent diagnosis of occult MPNs and MPNs are among the most common causes of SVT, routine screening of JAK2 mutation appears to be indicated in patients presenting with SVT. This suggestion does not apply to patients presenting with VTE in other sites because the observed prevalence of this mutation was similar to the prevalence reported in the general population. Future studies are necessary to evaluate why SVT occurs in patients with MPN, the association of SVT, and other less frequent mutations of JAK2, and to better define the risk of venous thrombosis in patients with heterozygous and homozygous V617F mutation of JAK2.

Authorship

Contribution: F.D. handled conception and design, analyzed and interpreted the data, drafted the article, critically revised the

article for important intellectual content, gave final approval of the article, provided administrative, technical, or logistic support, and collected and assembled the data; A.S. and W.A. handled conception and design, analyzed and interpreted the data, drafted the article, critically revised the article for important intellectual content, and gave final approval of the article; L.B. and L.A. drafted the article, gave final approval of the article, and collected and assembled the data; and L.C., M.C., and A.M.G. drafted the article, critically revised the article for important intellectual content, and gave final approval of the article.

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Appendix: Medline search strategy

Database: Ovid MEDLINE(R), 1950 to October (Week 2) 2008

1. Janus Kinase 2/ (2301)
2. Portal Vein/ (15 338)
3. Budd-Chiari Syndrome/ (2472)
4. Mesenteric Veins/ (3651)
5. Mesenteric Vascular Occlusion/ (3661)
6. Venous Thrombosis/ (12 123)
7. Venous Thromboembolism/ (433)
8. Thromboembolism/ (17 903)
9. Thrombosis/ (46 277)
10. Pulmonary Embolism/ (26 470)
11. Pulmonary Embolism/ (26 470)
12. Intracranial Thrombosis/ (1059)
13. Cardiovascular Diseases/ (65 129)
14. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (179271)
15. 1 and 14 (74)
16. Polycythemia Vera/ (4496)
17. Thrombocytopenia, Hemorrhagic/ (1711)
18. 16 or 17 (5833)
19. 1 and 18 (264)
20. 15 or 19 (295)

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