Myeloproliferative neoplasms in Budd-Chiari syndrome and portal vein thrombosis: a meta-analysis

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Myeloproliferative neoplasms (MPNs) are the most common cause of Budd-Chiari syndrome (BCS) and nonmalignant, non-cirrhotic portal vein thrombosis (PVT). In this meta-analysis, we determined the prevalence of MPNs and their subtypes as well as JAK2V617F and its diagnostic role in these uncommon disorders. MEDLINE and EMBASE databases were searched. Prevalence of MPNs, JAK2V617F, and MPN subtypes were calculated using a random-effects model. A total of 1062 BCS and 855 PVT patients were included.

In BCS, mean prevalence of MPNs and JAK2V617F was 40.9% (95% CI, 32.9%-49.5%) and 41.1% (95% CI, 32.3%-50.6%), respectively. In PVT, mean prevalence of MPNs and JAK2V617F was 31.5% (95% CI, 25.1%-38.8%) and 27.7% (95% CI, 20.8%-35.8%), respectively. JAK2V617F and MPNs were more frequent in BCS compared with PVT (P = .03 and P = .09, respectively). Polycythemia vera was more prevalent in BCS than in PVT (P = .001). JAK2V617F screening in splanchic vein thrombosis (SVT) patients without typical hematologic MPN features identified MPN in 17.1% and 15.4% of screened BCS and PVT patients, respectively. These results demonstrate a high prevalence of MPNs and JAK2V617F in SVT patients and show differences in underlying etiology between these disorders.

The discovery of the JAK2V617F gain-of-function mutation in 2005, found in 95% of patients with polycythemia vera (PV) and in ~50% of patients with essential thrombocythemia (ET) and myelofibrosis (MF), represented a crucial advance in the diagnostic approach to MPNs.16-19 The close relationship between MPNs and BCS and PVT was confirmed by the high frequency of JAK2V617F among these patients, present in 30%-45%,20,21 and 17%-35%,11,20,21 respectively. Interestingly, JAK2V617F screening offered a new diagnostic tool to detect these so-called occult MPN patients. In this meta-analysis, we will focus exclusively on primary BCS and nonmalignant, noncirrhotic PVT.

Philadelphia-negative myeloproliferative neoplasms (MPNs) are the most frequent underlying prothrombotic factor in BCS and PVT, with a reported prevalence of 30%-50%4,9 and 15%-30%,2,6,10-12 respectively. Peripheral blood cell counts often remain within a normal range because of portal hypertension and its sequelae (splenomegaly, hemodilution, and iron deficiency). Despite suggestive features of an MPN, fulfillment of usual diagnostic criteria can therefore often be lacking, which is a notorious problem in MPN diagnostics in these patients. The term occult MPN has been used in the literature for patients who lack these typical hematologic features of MPN but who harbor clear features of MPN, for example, by means of bone marrow (BM) biopsy findings and growth of erythroid colonies in the absence of exogenous erythropoietin, referred to as spontaneous endogenous erythroid colonies, both of which have several limitations.12-14 BM biopsy is invasive, and the distinction between MPN and reactive BM is not unambiguous. Endogenous erythroid colony assays are performed only in specialized centers, are difficult to standardize, and offer the possibility of false positives in nonclonal causes of erythrocytosis and healthy controls.15

The aims of this study were: (1) to assess the prevalence of MPNs and JAK2V617F in BCS and PVT patients; (2) to determine...
the frequency of MPN subtypes in BCS and PVT patients; (3) to determine \( \text{JAK2} \text{V617F} \) prevalence in BCS and PVT patients without typical hematologic features of MPN; and (4) to evaluate the clinical relevance of the \( \text{MPL} \) and \( \text{JAK2} \) exon 12 mutations in BCS and PVT patients.

**Methods**

**Search strategy and selection criteria**

One of the authors (J.H.S.) searched Ovid MEDLINE and EMBASE from 1980 to August 1, 2011. The search strategy was restricted to published data and the English language using the subject headings presented in the Appendix. The search was supplemented by manually reviewing the reference list of retrieved articles and relevant reviews. Titles and abstracts were read in full by J.H.S. and F.W.G.L. Studies were selected when the reference list of retrieved articles and relevant reviews. Titles and abstracts were read in full by J.H.S. and F.W.G.L. Studies were selected when the following criteria were met: (1) patients were diagnosed with primary BCS or noncirrhotic, nonmalignant PVT, or patients with an underlying malignancy or cirrhosis were explicitly mentioned; (2) information on MPNs or noncirrhotic, nonmalignant PVT, or patients with an underlying malignancy or cirrhosis were explicitly mentioned; (3) clinicopathologic features were insufficiently collected, patients were designated as solitary \( \text{JAK2} \text{V617F} \) positive MPN. Studies that did not report on \( \text{JAK2} \text{V617F} \) were only included in the MPN subtype analysis and not in the MPN prevalence analysis, as this would result in an underestimation of MPN prevalence. Corresponding authors were contacted in case essential data were not mentioned, with a reminder sent after 2 weeks.

**Data extraction**

J.H.S. extracted data on each selected study (year of publication, study design, demographics, criteria for diagnosing MPNs, number of patients included). Patients with BCS in the presence of a malignancy and PVT or patients with an underlying malignancy or cirrhosis were explicitly mentioned; (2) information on MPNs and/or \( \text{JAK2} \text{V617F} \), \( \text{JAK2} \) exon 12, or \( \text{MPL} \) S1515 was provided; (3) the cohort consisted of patients in which patients with established MPNs or other thrombophilic factors were not excluded; (4) SVT was subdivided in BCS and PVT; and (5) a minimum of 10 patients were included. Disagreements were resolved after discussion or after having collected the opinion of a third reviewer (H.L.A.J.).

**Statistical analysis**

**Study identification and selection**

We included 822 potentially relevant publications: 256 from MEDLINE and 566 from EMBASE. A total of 109 studies were duplicate, and 665 studies were excluded after title and abstracts screening according to predefined inclusion criteria. The remaining studies were retrieved in full for detailed evaluation. Five additional studies were identified from reference lists. Figure 1 shows the study selection process.

Of the 53 retrieved studies, 21 were excluded because of the following reasons: in 2 studies, patients with malignancies or liver cirrhosis were not excluded or explicitly mentioned; 5 studies were based on selected cohorts in which patients with established MPNs or other thrombophilic factors were excluded; one study did not differentiate SVT into BCS and PVT; in 4 studies, MPN criteria were not acceptable or unclear; and 2 studies included < 10 patients. In addition, 7 studies contained duplicate data. This resulted in 32 studies eligible for inclusion.
Table 1. Baseline characteristics of studies, including BCS patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Y</th>
<th>Design</th>
<th>Male/ female</th>
<th>Median age, y (range)</th>
<th>Median follow-up, mo (range)</th>
<th>MPN criteria</th>
<th>MPN</th>
<th>JAK2V617F</th>
<th>Classification (PV/ET/MF/U/solitary JAK2)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eapen et al62</td>
<td>2006</td>
<td>RC</td>
<td>NA/NA</td>
<td>16-77</td>
<td>0-181</td>
<td>Not specified</td>
<td>17/61</td>
<td>28</td>
<td>NA</td>
</tr>
<tr>
<td>Smalberg et al9</td>
<td>2006</td>
<td>RC</td>
<td>14/26</td>
<td>18-53</td>
<td>7.1</td>
<td>WHO 2001, BM in nearly all patients</td>
<td>47/104</td>
<td>45</td>
<td>27/92/15/3</td>
</tr>
<tr>
<td>Uskudar et al59</td>
<td>2008</td>
<td>RC</td>
<td>40/35</td>
<td>14-72</td>
<td>18 (1-30)</td>
<td>BM if MPN was suspected</td>
<td>6/72</td>
<td>8</td>
<td>NA</td>
</tr>
<tr>
<td>Kiladjian et al20</td>
<td>2008</td>
<td>RC</td>
<td>69/35</td>
<td>36 (IQR 27-46)</td>
<td>47 (range NA)</td>
<td>BM in nearly all patients</td>
<td>47/104</td>
<td>45</td>
<td>17/30/270/45</td>
</tr>
<tr>
<td>Xiao et al60</td>
<td>2009</td>
<td>RC</td>
<td>11/20</td>
<td>33 (17-50)</td>
<td>51 (1-104)</td>
<td>WHO 2001, BM if MPN was suspected</td>
<td>8/31</td>
<td>26</td>
<td>NA</td>
</tr>
<tr>
<td>Janssen et al47</td>
<td>2001</td>
<td>CC</td>
<td>16/27</td>
<td>40 (19-60)</td>
<td>NA</td>
<td>BM if MPN was suspected</td>
<td>12/43</td>
<td>28</td>
<td>NA</td>
</tr>
<tr>
<td>Khuroo et al54</td>
<td>2005</td>
<td>RC</td>
<td>17/23</td>
<td>27 (1-12)</td>
<td>NA</td>
<td>BM if MPN was suspected</td>
<td>17/61</td>
<td>28</td>
<td>17/6/1300</td>
</tr>
<tr>
<td>Primignani et al52</td>
<td>2006</td>
<td>RC</td>
<td>4/11</td>
<td>34 (1-66)</td>
<td>NA</td>
<td>WHO 2001, based on BM only</td>
<td>9/20</td>
<td>45</td>
<td>8/2/0/0/0</td>
</tr>
<tr>
<td>DeStefano et al63</td>
<td>2007</td>
<td>RC</td>
<td>4/11</td>
<td>NA</td>
<td>48 (24-108)†</td>
<td>PVSG 2000</td>
<td>5/15</td>
<td>33</td>
<td>1/3/0/1</td>
</tr>
<tr>
<td>Bayraktar et al47</td>
<td>2010</td>
<td>RC</td>
<td>13/17</td>
<td>27 (19-70)†</td>
<td>NA</td>
<td>WHO 2001, based on BM only</td>
<td>17/42</td>
<td>40</td>
<td>11/5/1000</td>
</tr>
</tbody>
</table>

RC indicates retrospective cohort; CC, case-control; U, unclassifiable; solitary JAK2, solitary JAK2-positive; NA, not available; IQR, interquartile range; and BM, bone marrow biopsy.

aMPNs that became overt during follow-up were included in subtype analysis.
bMean age/follow-up (range) or ± SD.
cMedian follow-up of patients with JAK2V617F-positive MPNs without elevated blood counts.
dMedian time of diagnosis to overt MPNs.

Study characteristics and quality

Tables 1 and 2 summarize the characteristics of the included studies for BCS and PVT, respectively. Study size ranged between 10 and 237 patients. Nineteen studies, including 1062 patients, reported on MPNs and/or the JAK2V617F mutation in BCS patients. Fifteen studies, including 855 patients, reported on MPNs and/or the JAK2V617F mutation in PVT patients. Three studies, including 268 patients, reported on JAK2 exon 12 mutations. Two studies, including 305 patients, reported on MPL515 mutations.

Five studies included a healthy control population; all other studies were essentially retrospective cohort studies. Twenty of these studies enrolled patients consecutively. Fifty-three studies partly overlapped in 9 publications (ie, to some extent duplication of patients).

MPNs and JAK2V617F in BCS

A total of 1062 BCS patients were included in the analysis (Figure 2). Of these patients, 440 underwent a complete diagnostic workup.

Table 2. Baseline characteristics of studies including portal vein thrombosis patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Y</th>
<th>Design</th>
<th>Male/ female</th>
<th>Median age, y (range)</th>
<th>Median follow-up, mo (range)</th>
<th>MPN criteria</th>
<th>MPN</th>
<th>JAK2V617F</th>
<th>Classification (PV/ET/MF/U/solitary JAK2)*</th>
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<tbody>
<tr>
<td>Hoekstra et al43</td>
<td>2011</td>
<td>RC</td>
<td>13/31</td>
<td>48 (18-79)</td>
<td>70 (5-252)</td>
<td>WHO 2008 criteria</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rajani et al57</td>
<td>2010</td>
<td>RC</td>
<td>80/93</td>
<td>57 (15-94)</td>
<td>30 (0-116)</td>
<td>Not specified, BM in majority of patients</td>
<td>15/89</td>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>Orr et al56</td>
<td>2010</td>
<td>RC</td>
<td>80/93</td>
<td>57 (15-94)</td>
<td>30 (0-116)</td>
<td>Not specified, BM in majority of patients</td>
<td>15/89</td>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>Plessier et al22</td>
<td>2010</td>
<td>RC</td>
<td>50/52</td>
<td>48 (16-84)</td>
<td>20 (0-75)</td>
<td>BM if MPN was suspected</td>
<td>54/237</td>
<td>53</td>
<td>NA</td>
</tr>
<tr>
<td>Attweel et al44</td>
<td>2010</td>
<td>RC</td>
<td>7/15</td>
<td>24 (18-68)†</td>
<td>NA</td>
<td>BM if MPN was suspected</td>
<td>11/22</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td>Janssen et al57</td>
<td>2000</td>
<td>CC</td>
<td>16/27</td>
<td>40 (19-60)</td>
<td>BM if MPN was suspected</td>
<td>12/43</td>
<td>28</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Denninger et al50</td>
<td>2000</td>
<td>RC</td>
<td>NA/NA</td>
<td>16-77</td>
<td>0-181</td>
<td>Not specified</td>
<td>12/32</td>
<td>38</td>
<td>NA</td>
</tr>
<tr>
<td>Mahmood et al51</td>
<td>1996</td>
<td>RC</td>
<td>17/27</td>
<td>37 (19-70)†</td>
<td>NA</td>
<td>WHO 2001, based on BM only</td>
<td>17/42</td>
<td>40</td>
<td>11/5/1000</td>
</tr>
</tbody>
</table>

RC indicates retrospective cohort; CC, case-control; U, unclassifiable; solitary JAK2, solitary JAK2-positive; NA, not available; IQR, interquartile range; and BM, bone marrow biopsy.

†Mean age/follow-up (range) or ± SD.
‡Median follow-up of patients with JAK2V617F-positive MPNs without elevated blood counts.
§Median time of diagnosis to overt MPNs.
for MPN, including clinical, laboratory, and/or morphologic features of MPN as well as JAK2V617F mutation analysis. MPN was present in 40.9% (95% CI, 32.9%-49.5%) of these patients. Of the MPN patients, 80.3% were JAK2V617F-positive (95% CI, 63.5%-90.5%). The JAK2V617F mutation was present in 159 of 401 tested patients, for a mean prevalence of 41.1% (95% CI, 32.3%-50.6%). JAK2V617F screening in patients without typical hematologic features of MPN yielded diagnosis of MPN in 17.1% (95% CI, 7.9%-33.3%). Distribution of MPN subtypes was as follows: PV, ET, MF, unclassifiable MPNs, and solitary JAK2V617F-positive MPNs in 52.9% (95% CI, 42.2%-63.4%), 24.6% (95% CI, 18.0%-32.5%), 6.7% (95% CI, 3.7%-11.9%), 17.0% (95% CI, 9.8%-27.9%), and 6.5% (95% CI, 2.4%-16.3%), respectively (supplemental Figure 1).

Four studies made a distinction between diagnosis of MPN before or simultaneous to BCS, in which 13 of 50 patients were diagnosed with MPN before BCS, whereas BCS was the presenting symptom of MPN in 37 of 50 patients. Follow-up of JAK2V617F-positive MPNs without typical hematologic features of MPN, ranging from 0.7 to 7 years after diagnosis of BCS, yielded diagnosis of MPN in 15.4% (95% CI, 7.9%-33.3%) of screened PVT patients without characteristic hematologic features of MPNs, which would otherwise have been undiagnosed. Distribution of MPN subtypes was as follows: PV, ET, MF, unclassifiable MPNs, and solitary JAK2V617F-positive MPNs in 27.5% (95% CI, 19.0%-38.1%), 26.2% (95% CI, 19.1%-34.8%), 12.8% (95% CI, 8.0%-19.9%), 17.7% (95% CI, 9.9%-29.7%), and 24.0% (95% CI, 11.5%-43.3%), respectively (supplemental Figure 1).

Five studies differentiated between diagnosis of MPN before or simultaneous to PVT diagnosis, showing that 17 of 64 patients were diagnosed with MPN before PVT, whereas PVT was the presenting symptom of MPN in 47 of 64 patients. Follow-up of JAK2V617F-positive MPNs without typical hematologic features of MPN, ranging from 0.7 to 7 years after diagnosis of PVT, yielded diagnosis of MPN in 20.8% (95% CI, 12.8%-34.5%) of screened PVT patients without characteristic hematologic features of MPNs, which would otherwise have been undiagnosed. Distribution of MPN subtypes was as follows: PV, ET, MF, unclassifiable MPNs, and solitary JAK2V617F-positive MPNs in 26.2% (95% CI, 20.8%-32.5%), 22.2% (95% CI, 17.0%-27.9%), 12.8% (95% CI, 9.9%-19.9%), and 24.0% (95% CI, 17.7%-32.7%), respectively (supplemental Figure 1).
features counts was provided in 4 publications in which 6 of
48 patients (13%) developed characteristic laboratory or morpho-
logic features of MPN, ranging from 1-10 years after diagnosis of
PVT.31,56,60,63 One study described the long-term follow-up of
44 PVT patients with an underlying MPN.64 Five PV and 2 ET
patients developed secondary MF, 3 patients with MF progressed to
end-stage MF, and 4 patients developed acute myeloid leukemia
after a median period of 9.7 years (range, 1-17 years) after MPN
diagnosis. A total of 29% and 18% of the deaths in this cohort were
attributable to end-stage MF and progression to acute myeloid
leukemia, respectively.

**JAK2 exon 12 and MPL515 mutations in SVT**

A total of 268 SVT patients (ratio BCS/PVT unknown) were tested for
JAK2 exon 12 and 305 for MPL515 mutations. Three of these
patients were found to carry MPL515K mutation. The JAK2
exon 12 mutation was not present in any of these patients.

**Differences between BCS and PVT**

Prevalence of JAK2V617F and MPNs was higher in BCS than in
PVT ($P = 0.03$ and $P = 0.9$, respectively). With regards to the
subtype analysis, prevalence of PV and MF was higher in BCS than
in PVT patients ($P = 0.01$ and $P = 0.9$, respectively). Prevalence of
solitary JAK2V617F-positive MPNs was higher in PV in com-
pared with BCS ($P = 0.03$). There was no difference between the
prevalence of ET and MPNs unclassifiable ($P = 0.77$ and $P = 0.92$,
respectively). There was no difference in identification rate of
MPNs without typical features by means of JAK2V617F between
the 2 disorders (17.1% vs 15.4%, $P = 0.68$). All analyses were
repeated, including only publications since 2005 and excluding papers with potentially duplicated inclusion of patients, which
showed the same results (data not shown).

**I² and heterogeneity among studies**

A considerable heterogeneity among the studies was observed ($P < 0.5$). We therefore performed an additional analysis in which
we excluded one study per analysis. This analysis showed that no
single study significantly affected the point estimate of MPNs,
JAK2V617F, and its subtypes in both BCS and PVT.  

**Discussion**

In this meta-analysis, we assessed the role of MPNs in the etiology
of primary BCS and nonmalignant, noncirrhotic PVT. The results
showed a higher prevalence of MPNs and JAK2V617F in BCS
compared with PVT patients. Interestingly, our results indicate a
difference in the distribution of underlying MPN subtype between
BCS and PVT patients, PV being the most frequent MPN in BCS.
Finally, MPL515 mutations were present in < 1% of BCS and PVT
series, whereas JAK2 exon 12 mutations have never been published
so far in SVT patients.

Two meta-analyses have previously evaluated the impact of the
JAK2V617F mutation in SVT patients. In 2009, Dentali et al
assessed the role of JAK2V617F in patients with various venous
thrombosis, including SVT, deep vein thrombosis of the lower
extremities or pulmonary embolism, cerebral vein thrombosis, and
retinal vein thrombosis.65 In this study, a remarkable high preva-
ience of JAK2V617F in SVT was reported, whereas its prevalence
in other forms of VTE was similar to that of the general population.
SVT was not subdivided into BCS and PVT, which impedes
comparisons of MPNs and JAK2V617F prevalence between the
2 disorders. Qi et al calculated the prevalence of JAK2V617F in
BCS and PVT separately and assessed its prevalence after exclu-
sion of cases with preexisting MPNs.66 In contrast to those
previously published studies, we set out to provide a complete
overview of MPNs in the etiology of BCS and PVT. This included
assessment of the prevalence of MPNs and JAK2V617F as well as
the prevalence of MPN subtypes. In addition, we have compared
BCS and PVT for each of these variables, as it is increasingly
recognized that, despite several similarities, risk profiles are
different between these patients.57 To achieve this goal, we have
assessed all the publications regarding MPNs in SVT since 1980.

The results of this meta-analysis indicate a high prevalence of
MPNs in patients with SVT. The strong relation between MPNs
and SVT is confirmed by the high prevalence of JAK2V617F in
these patients. Interestingly, JAK2V617F and MPNs were more
prevalent in BCS compared with PVT patients, the latter showing a
statistical trend toward a significant difference. This difference
may be partially explained by the more prominent role of local risk
factors, such as focal inflammatory lesions and injury to the portal
venous system, in the development of PVT.68 This might contribute
to the relatively limited role of general prothrombotic conditions
reported in the etiology of PVT. Why MPNs and JAK2V617F are
so strongly related to thrombosis of the splanchnic veins remains an
unsolved issue. Further research is needed to identify associated
factors that could be involved in the pathogenesis of thrombosis at
these specific sites. In this respect, it has been speculated that
endothelial cells of the splanchnic veins may interact with activated
platelets and/or leukocytes and increased microparticles, which are
characteristic features of MPNs.69 In addition, these endothelial
cells have been shown to carry the JAK2V617F mutation and could
be part of the malignant process.70

We observed a marked difference between BCS and PVT patients
regarding the distribution of MPN subtypes. PV was clearly more
common in BCS compared with PVT. The prothrombo-
ctic effect of high hematocrit values in PV is well established.71
Under low-shear conditions, such as in the venous circulation, a
high hematocrit has a more important impact on blood viscosity
and causes a major disturbance to blood flow.72,73 This mechanism
may be mediated by the interaction between adhesion molecules
and red blood cells. Wautier et al described an increased adhesive-
ness of red blood cells in PV to human umbilical vein endothelial
cells and elegantly showed that adhesion was inversely related to
increasing shear stress (ie, adhesion proved particularly increased
at low shear rates).8 It is possible that variability in the expression
of these molecules along the vascular tree along with differences in
flow conditions might contribute to the site specificity of thrombo-
sis, as suggested by these authors.8 Indeed, the low-flow state in
the hepatic veins compared with the portal venous system may
participate in the higher frequency of PV in BCS. We also observed
a statistical trend toward increased frequency of MF in PVT
compared with BCS. Such difference could be the result of the
frequent presence of splenomegaly in MF, which may lead to
external compression of the portal venous system and subsequent
stasis of blood flow. Finally, solitary JAK2V617F-positive MPNs
were more frequent in PVT than in BCS patients. These are new
findings that deserve further evaluation in future studies.

This meta-analysis, for the first time, systematically assessed
the diagnostic yield of JAK2V617F screening in SVT patients
without typical hematologic MPN features. JAK2V617F screening
identified MPN in 17.1% and 15.4% of these BCS and PVT
patients, respectively, which would have remained undetected
before the JAK2V617F era. JAK2V617F was associated with
subsequent development of MPNs with typical hematologic MPN features in 41% and 14% of these BCS and PVT patients, respectively. These findings clearly substantiate inclusion of JAK2V617F in the routine diagnostic workup of all SVT patients, regardless of the absence of MPN hallmarks, such as elevated peripheral blood cell counts. Whether MPN specific treatment should be initiated in these patients, such as cytoreductive therapies or addition of aspirin to oral anticoagulant treatment, is a question that remains to be answered. One study described the long-term outcome of PVT patients with an underlying MPN.64 Twenty-nine and 18% of the deaths in this cohort were attributable to end-stage MF and progression to acute myeloid leukemia, respectively, indicating that risk of MPN progression is a clinical significant issue in these patients.

MPL515 mutations were reported in < 1% of SVT patients, whereas the JAK2 exon 12 could not be found at all. The JAK2 exon 12 mutation has been described only once in both a PVT and BCS patient, but this was a case study.29 These results indicate that both mutations are infrequent in SVT patients, in agreement with their low frequency in MPNs compared with the JAK2V617F mutation.23-27 We therefore conclude that, unlike JAK2V617F, screening for these mutations is dispensable in the routine diagnostic approach of SVT patients.

Our analysis has several potential limitations. First, because of the rarity of both diseases, only observational studies have been published and could be included in this analysis, with their inherent risks of bias. However, a prospective design for rare thrombotic manifestations as PVT and BCS is probably unachievable. Second, a considerable heterogeneity among the included studies was noticed. We therefore performed all analyses using a random-effects model, thereby accounting for between-study variance, next to within-study variance. In addition to the random-effects analysis, which generates a conservative estimate, we performed an analysis in which we excluded one study at a time to assess its individual impact on the results. This analysis showed that none of the included studies significantly affected the estimated prevalence of MPNs, JAK2V617F, and its subtypes in both BCS and PVT. Third, diagnostic criteria for MPNs were not similar across studies. Notably, BM biopsy was not always routinely performed, which may have resulted in an underestimation of the prevalence of MPNs. Because this applies to both BCS and PVT series, the effect on the comparison between these 2 groups is presumably small, if at all present. Lastly, since the discovery of JAK2V617F in 2005, an increase in larger and better quality studies was observed. We therefore repeated all analyses, including only publications from that time point. In addition, we excluded papers with potential overlap of patients. The same differences between BCS and PVT were observed.

In conclusion, this meta-analysis shows a high prevalence of MPNs and JAK2V617F in SVT patients. Prevalence of JAK2V617F and MPNs in BCS is higher compared with PVT, and differences in underlying MPN subtypes between these disorders exist. JAK2V617F screening identifies MPNs in patients without typical hematologic MPN features and should be included the routine diagnostic workup of SVT. On the contrary, JAK2 exon 12 and MPL515 mutations are extremely rare in SVT and should not be used in the routine diagnostic approach of SVT patients. Altogether, our results are in line with the advancing insight that, despite well-established similarities, marked differences in the etiology of BCS and PVT do exist.

Appendix: Medline search strategy

August 1, 2011

Database: Medline. Limits: English, limits publication date January 1, 1980 to August 1, 2011:

1. Myeloproliferative disorders [Mesh]: 23 690
2. Myeloproliferative neoplasms: 2798
3. Janus kinase 2 [Mesh]: 2880
4. MPL, protein, human [substance name]: 503
5. Colony-forming units assay: 13111
6. Budd-Chiari syndrome [Mesh]: 1539
7. Hepatic vein thrombosis: 2885
8. Hepatic venous thrombosis: 1544
9. Hepatic outflow obstruction: 295
10. Vascular liver disease: 11915
13. Portal vein thrombosis: 3158
15. Splanchnic vein thrombosis: 206
16. Splanchnic venous thrombosis: 163
17. Abdominal vein thrombosis: 2091
18. Abdominal venous thrombosis: 1587
19. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18: 19 561
20. 1 and 19: 214
21. 2 and 19: 45
22. 3 and 19: 57
23. 4 and 19: 3
24. 5 and 19: 12
25. 20 or 21 or 22 or 23 or 24: 255

The search was supplemented by manually reviewing the reference list of retrieved articles.

Authorship

Contribution: J.H.S. conceived and designed the study, collected, assembled, and interpreted the data, and wrote the manuscript; L.R.A. performed data analysis; J.-J.K. and D.C.V. interpreted the data and critically revised the article for important intellectual content; H.L.A.J. assisted in study selection and analysis of results and critically revised the article for important intellectual content; and F.W.G.L. designed the study, selected included studies, analyzed the results, and assisted with writing the manuscript.

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tients with portal and mesenteric venous throm-
24. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in myelofi-
36. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive sig-
39. Colaioco D, Amiratno L, Tisca GL, et al. The JAK2 V617F mutation frequently occurs in pa-
tients with portal and mesenteric venous throm-
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