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**Prevalence of the activating JAK2 tyrosine kinase mutation
in chronic porto-splenomesenteric venous thrombosis**

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3 Prevalence of the activating *JAK2* tyrosine kinase mutation in chronic porto-
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5 splenomesenteric venous thrombosis
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3 MPD - Myeloproliferative disorders
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5 PSMVT - Portal, splenic and mesenteric venous thrombosis
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8 PRV - Polycythemia rubra vera
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10 ET - Essential Thrombocythemia
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12 IMF - Idiopathic myelofibrosis
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14 CML - Chronic myelogenous leukaemia
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17 BCS - Budd Chiari Syndrome
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19 JAK - Janus Kinase 2 gene
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22 JH 2 - Janus Homology 2
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25 CT - Computed tomography
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27 MRI - Magnetic resonance imaging
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29 PV - Portal Vein
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31 APCR - Activated protein C resistance
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34 AT - Antithrombin
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36 PC - Protein C
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38 PS - Protein S
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40 PNH - Paroxysmal nocturnal hemoglobinuria
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43 BM - Bone Marrow
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3 Abstract:

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5 Background: Occult myeloproliferative disorders (MPD) are present in 25% of
6 patients with chronic portal, splenic and mesenteric venous thrombosis (PSMVT). A
7 somatic mutation of JAK2 (JAK2V617F) can be used to identify patients with latent
8 MPD.
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11 Aims: We evaluated the prevalence and clinical significance of JAK2V617F in
12 patients with chronic PSMVT.
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15 Methods: Allele specific PCR was performed to screen for JAK2V617F.
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18 Results: Thirty-five patients were tested for JAK2V617F. The underlying pro-
19 coagulant condition was MPD in 7/35 (20.0%); other aetiologies included hereditary
20 thrombophilia (n=5), chronic pancreatitis (n=2), liver abscess (n=1) and umbilical
21 vein sepsis (n=3). The remainder were labelled idiopathic 17/35 (48.6%).
22 JAK2V617F was detected in 16/35 (45.7%) patients; 7/7 (100%) with MPD; 2/11
23 (18.1%) with non-MPD acquired conditions and 7/17 (41.2%) with 'idiopathic'
24 chronic PSMVT. Mean haemoglobin concentration (p=0.04), haematocrit (p=0.04),
25 white cell count (p=0.002) and platelet count (p=0.05) were significantly higher in
26 patients with JAK2V617F. None of the 7 patients with latent MPD have progressed to
27 overt MPD over median follow up of 85-months.
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31 Conclusion: JAK2V617F occurs in a 41% of patients with idiopathic chronic
32 PSMVT, confirming the presence of latent MPD and should form part of the routine
33 pro-coagulant screen.
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Introduction

Chronic portosplenic mesenteric thrombosis (PSMVT) is an uncommon event and is associated with pro-coagulant conditions such as cancer, cirrhosis and intra-abdominal inflammatory and infectious processes.(1, 2) The myeloproliferative disorders (MPD) carry with them a significant risk of developing venous thrombosis which can occur at any site. The MPD comprise a heterogeneous group of disorders including, polycythemia rubra vera (PRV), essential thrombocythemia (ET), idiopathic myelofibrosis (IMF), and chronic myelogenous leukaemia (CML). PRV and ET are the commonest intrinsic risk factors for the development of the Budd Chiari Syndrome (BCS) and PSMVT.(3-5) Until recently, the natural history of chronic PSMVT has been poorly defined. Previous work from our group has shown that the 1- and 5-year survival of these patients was 81.6%, and 78.3% respectively, with morbidity and mortality attributable to variceal bleeding, thrombotic complications and the underlying pro-coagulant disease.(6) In that series of patients with PSMVT, a MPD was identified in 18.3%, whereas no pro-coagulant condition was identified in 28.3% of patients with PSMVT.(6)

Many patients with thrombosis of the splanchnic vessels are labelled as having 'idiopathic' thrombosis but subsequently develop clinically apparent MPD over long term follow-up.(7) A recently described mutation of the Janus Kinase 2 gene (JAK2) has been identified in 65-97% patients with PRV, 23-57% with ET and 50-57% with IMF.(8, 9) This single point mutation of guanine to thymine which in turn exchanges valine to phenylalanine at position 617 (V617F), results in loss of the inhibitory function of the Janus Homology 2 (JH2) domain, over the active kinase domain (JH1). This gain-of-function mutation, which confers erythropoietin hypersensitivity and growth factor independence,(10) appears important in the pathogenesis of MPD and has also been associated with an increased frequency of haemorrhagic and thrombotic complications.(8)

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The aim of this study was to assess the prevalence and clinical significance of JAK2V617F in patients with chronic PSMVT and subsequently identify patients who are at high risk of developing MPD in future years.

For Peer Review

Patients and Methods.

Patients with non-cirrhotic, non-cancer related chronic PSM venous thrombosis were assessed for the presence of JAK2V617F. A well characterised cohort was identified.(6) Briefly PSMVT was confirmed on the basis of computerized tomography (CT), magnetic resonance imaging (MRI) and/or aortopography. Patients were deemed to have chronic thrombosis if there was radiological apparent thrombosis of the PSM venous system of more than three months duration. Supportive evidence of chronic thrombosis was the presence of extensive intra-abdominal venous collaterals, cavernous transformation of the portal vein (PV) and splenomegaly. Clinical and laboratory data was recorded on all subjects.

Assessment for haematological pro-coagulant conditions included genotyping for Factor V Leiden and Prothrombin Gene mutation (PT20210A) along with phenotypic studies for activated protein C resistance (APCR), antithrombin (AT), protein C (PC), free protein S (PS), anti-cardiolipin antibodies and lupus anticoagulant. Paroxysmal nocturnal hemoglobinuria (PNH) was screened for by performing an Acidified-Serum Test prior to 1996 and thereafter by standard flow cytometry techniques using fluorescent-labelled antibodies against erythrocyte CD59 and neutrophil CD66b. Patients were diagnosed with neonatal umbilical vein sepsis, on the basis of a history of complicated umbilical vein cannulation, where no other aetiology was apparent.

DNA testing for JAK2V617F was performed on DNA which was extracted from archival bone marrow (BM) films or blood samples obtained in the context of this study. DNA was extracted from BM samples by removing cover slips after soaking slides in xylene and then transferring cells into a high salt buffer. Proteinase K, RNase A and sodium dodecyl sulfate were added. Cells were incubated at 37°C overnight prior to phenol extraction and ethanol precipitation. DNA extraction from blood samples was done using standard phenol/chloroform extraction.

An allele specific polymerase chain reaction (AS-PCR) was used to detect the guanine to thymine mutation in exon 12 of *JAK2*. PCR primers (Geneservice, Cambridge, UK) were used which flank the point mutation forward and reverse to verify the specificity of

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3 the allele specific PCR as previously described. The histological diagnosis of MPD was
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5 reviewed as per the World Health Organization criteria.(11) The study received local ethical
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7 committee approval. All testing was confidential and was linked to patient information with
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9 the use of a system of unique identifiers.
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11 12 13 14 Statistical Analysis.

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16 For quantitative data, analysis was performed using the Mann-Whitney U test for 2
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18 independent groups. The Kruskal-Wallis test was used for the comparison of more than 2
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20 groups. Difference in proportions of categorical data was performed using Fisher's exact test
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22 when the number of subjects was <5 , and by Chi-square test for 2x2 tables when the number
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24 of subjects in each cell was ≥ 5 . Data is expressed as means or median and ranges where
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26 appropriate. *P* values less than 0.05 were considered significant. All analysis was performed
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28 using SPSS 13.0[®] (SPSS Inc., Chicago, IL).
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Results.

The study group was comprized of 35 patients, 21 female, 14 male. The median age at the time of diagnosis of PSMVT was 43 years (range, 18-72). Twenty-five of 35 (71.4%) were of Northern European ethnicity, 6 (17.1%) from the Indian subcontinent and 4 (11.4%) of African ethnicity. Median follow-up was 51 months (range, 10-300). The presenting features were variceal bleeding in 18/35 (51.4%), abdominal pain in isolation in 4/35 (11.4%), abdominal pain with gut ischaemia in 4/35 (11.4%), abdominal pain with ascites in 4/35 (11.4%), and 5/35 (14.3%) cases were discovered incidentally. Out of the five cases which were discovered incidentally, 2 were identified during investigation of abnormal liver enzymes, whereas the other patients were undergoing investigation of liver abscess, anaemia and splenomegaly during pregnancy.

Etiology of PSMVT

The majority of patients (33/35, 94.3%) were assessed for AT, PC, PS, APCR, factor V Leiden, Prothrombin Gene mutation, anticardiolipin antibodies and lupus anticoagulant. Twenty four of 35 (68.6%) were assessed for PNH. Urine samples from the patients not investigated for PNH (11/35 patients) demonstrated no haematuria, rendering the diagnosis of PNH unlikely. Eight patients had a bone marrow examination, which confirmed the diagnosis of MPD in 3 cases, whereas, the other 5 samples were either normal, or without the typical findings of MPD. Only one of these biopsies was performed on a patient who was *JAK2V617F* positive.

The etiology of PSMVT and results of *JAK2V617F* analysis is shown in table 1. In total, 16/35 (45.7%) of patients were *JAK2V617F* positive. The most common identified etiology of PSMVT was MPD (7/35, 20%). All patients with MPD were *JAK2V617F* positive (none were homozygous for the mutant allele). MPD was diagnosed in 5/7 patients at presentation of their PSMVT. Three patients were diagnosed on bone marrow biopsy, and two on the basis of haematological indices and *JAK2V617F* in keeping with World Health Organisation guidelines. One further patient was diagnosed with essential thrombocythemia,

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3 3 years prior to presenting with features of mesenteric thrombosis; the other patient was
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5 diagnosed with myelofibrosis 10 years after the diagnosis of PSMVT.
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8 A significant proportion of patients (17/35, 48.6%) had previously no identifiable
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10 thrombophilic etiology attributed. Of these patients, 7/17 (41.2%) were *JAK2V607F* positive,
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12 consistent with latent MPD. Three patients were Factor V Leiden heterozygous, two of whom
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14 had concomitant thrombotic risk factors (antiphospholipid syndrome and acute pancreatitis).
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16 The patient thought to have isolated Factor V Leiden heterozygosity was also *JAK2V617F*
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18 positive. Other risk factors for thrombosis in patients who did not have the *JAK2* mutation
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20 were protein S deficiency, antiphospholipid syndrome, chronic pancreatitis and liver
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22 abscesses. None of the patients diagnosed with congenital or umbilical vein sepsis were
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24 *JAK2V617F* positive.
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29 Clinical and Laboratory Analysis: *JAK2V617F* versus Wild-Type.
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32 When comparing the clinical presentations between *JAK2V617F* positive patients and
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34 wild-type, no significant difference was identified. Variceal bleeding occurred in 9/16
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36 (56.3%) and 10/19 (52.6%) respectively, abdominal pain in 4/16 (25.0%) and 4/19 (21.1%),
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38 abdominal pain and ascites in 3/16 (18.8%) and 1/19 (5.3%) and incidental detection in 0/16
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40 (0.0%) and 4/19 (21.1%).
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43 The laboratory variables at presentation are shown in table 2. The mean hemoglobin
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45 concentration (12.5g/L vs. 11.3g/L, $p=0.04$), hematocrit (0.38 vs. 0.35, $p=0.04$); white cell
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47 count ($10.0 \times 10^6/L$ vs. $5.1 \times 10^6/L$, $p=0.002$) and platelet count ($290 \times 10^3/L$ vs. $171 \times 10^3/L$,
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49 $p=0.04$) were significantly higher in patients with *JAK2V617F*. No significant difference
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51 between the haematological indices of patients diagnosed with MPD with patients with latent
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53 MPD was identified. Patients with the *JAK2V617F* mutation presented with worse liver
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55 synthetic function with a higher mean bilirubin levels, 30.0 $\mu\text{mol/L}$ vs. 13.9 $\mu\text{mol/L}$ ($p=0.02$)
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57 and INR 1.18 vs. 1.06 ($p=0.01$). There was no significant difference in serum albumin levels
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59 (37.9g/L vs. 38.5g/L, $p=NS$) or liver enzymes at presentation. Table 3 summarizes
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haematological indices between patients with confirmed MPD compared to those with latent

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3 MPD. No significant differences were evident between the two groups. Liver histology was
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5 available in 16 patients. The indications for liver biopsy included assessment for cirrhosis or
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7 concerns regarding additional hepatic pathology. Six were normal, 5 showed stage 1 fibrosis,
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9 2 showed nodular regenerative hyperplasia with minimal fibrosis and 3 revealed mild fibrosis
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11 with sinusoidal dilatation. The 3 patients with sinusoidal dilatation had no evidence of Budd-
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13 Chiari Syndrome with normal ultrasound doppler flow and CT contrast enhancement of the
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15 hepatic veins.
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20 Outcome

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23 None of the 7 patients with latent MPD progressed to overt MPD over a mean follow-
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25 up duration of 85 months (range 10-300 months). One patient with myelofibrosis who was
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27 initially termed 'idiopathic thrombosis' was diagnosed with MPD 10-years after their
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29 presentation with mesenteric thrombosis. Patients with MPD were more likely to be anti-
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31 coagulated with warfarin compared to patients with latent MPD (6/7, 85.7% vs. 3/9, 33.3%,
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33 $p=0.06$). Of the wild-type patients, 5/19 (26.3%) were anti-coagulated, of whom 4/5 (80.0%)
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35 of these patients had another recognized pro-coagulant condition.
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38 Four patients died between 61 and 300 months after diagnosis. Two died from
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40 variceal bleeding, one from small bowel infarction, and the other from non-thrombotic
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42 etiology. The four patients were all initially labelled as 'idiopathic thrombosis' and none were
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44 treated with wafarin. All subsequently tested positive for JAK2V617F. The liver biopsies of
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46 the three patients who died from complications of PSMVT showed mild fibrosis (stage 1),
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48 and 1 patient with sinusoidal dilatation.
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Discussion

Complete occlusion of the portal, splenic and mesenteric veins represents a rare, but clinically significant condition, the etiology of which is complex and multi-factorial in nature. In this study we have identified that the presence of the *JAK2V617F* mutation accounts for 41% of patients previously labelled as 'idiopathic'. Moreover recently patients identified with previously established 'minor' pro-coagulant conditions were also at risk of concomitant latent MPD as evidenced by the presence of *JAK2V617F*. One patient with factor V Leiden and one with prothrombin mutation also tested positive for *JAK2V617F* mutation, indicating that all patients with PSMVT should be tested for the mutation and not just 'idiopathic cases'. Other case series have reported a similar prevalence of *JAK2V617F* in patients with PMSVT. (12-15). Primigani et al. report a prevalence of *JAK2V617F* in 35.6% in patients presenting with PSMVT,(16) but a separate study by Colaizzo et al. reported a lower prevalence at 17.2%. (17)

None of the patients with latent MPD fulfilled the diagnostic criteria for MPD and no significant differences between the haematological indices were identified when comparing the 2 groups. However both MPD and latent MPD patients had significantly higher haemoglobin, haematocrit, white cell count and platelet counts when compared to other identifiable pro-coagulant conditions. Six out of 7 patients with MPD presented with a complication related to portal hypertension. The mean platelet count and haematocrit in the latent MPD and MPD patients was within the normal range, suggesting that they do not develop thrombotic complications due to thrombocytosis or haemostasis due to an elevated hematocrit. Moreover the development of hypersplenism resulting in a reduction of the platelet count and hematocrit does not appear to be protective against progression of mesenteric thrombosis.

The initial discovery of the *JAK2V617F* mutation, identified in greater than 90% of patients with PRV and 50% of patients with ET and MF, (8-10) is evidence of genetic heterogeneity. Although not all patients with MPD have the *JAK2V617F* mutation, all of the MPD patients (7/7, 100%) in our cohort were *JAK2V617F* positive. The presence of this

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3 mutation may predict a more aggressive phenotype with an increased risk of thrombosis.
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5 Kravolics et al. reported an increased risk of both haemorrhagic and thrombotic complications
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7 in patients with MPD and the *JAK2* mutation, with thrombotic complications in MPD patients
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9 with the *JAK2V617F* mutation reported at 26% versus 15% in wild-type patients (p=0.03).
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11 However, other retrospective analyses have not confirmed this finding. (18, 19)
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14 The pathogenesis of thrombosis in patients with *JAK2V617F* remains to be defined.
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16 Activation of platelets and leucocytes assessed in patients with ET has shown baseline levels
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18 of platelet p-selectin expression, a constituent of platelet aggregation, and leukocyte
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20 activation were increased. Additionally there is increased production of monocyte tissue
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22 factor increasing fibrin deposition, thereby conferring an increased risk of thrombosis in
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24 *JAK2V617F*. (20) During long-term follow-up, 4 patients died, all of whom were
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26 retrospectively diagnosed with latent MPD. Two patients died due to uncontrolled variceal
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28 bleeding, 1 patient from gut infarction and one death was unrelated to the underlying
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30 thrombosis. This equates to an overall mortality rate of 11%, but of 25% in those patients who
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32 subsequently tested positive for *JAK2* mutation. This increased mortality may be as a
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34 consequence of less frequent anticoagulation, in a group previously diagnosed with
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36 'idiopathic mesenteric thrombosis'. Without anticoagulation, thrombotic extension in the
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38 portomesenteric vessels or collateral vessels increases the risk of variceal bleeding, or gut
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40 infarction. Retrospective case controlled studies demonstrate that anticoagulation reduces
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42 mortality without significantly increasing the incidence or risk of death from variceal
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44 bleeding (21, 22)
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49 In this study 10/35 (28.6%) of patients had no identifiable thrombophilia. Mutations
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51 in the *JAK2* locus at exon 12, in patients negative for *JAK2V617F* with PCV or idiopathic
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53 erythrocytosis have been identified. These appear to confer the 'gain-of-function' with
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55 preliminary evidence suggesting that these mutations, in addition to the *JAK2V617F* should
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57 be assessed. (8, 23, 24) With recognition that other unidentified mutations exist, all patients
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59 with idiopathic thrombosis should also be considered for long term anticoagulation. Patients
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who are unlikely to benefit from long term anticoagulation are those with a defined period of

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3 illness resulting in chronic mesenteric thrombosis, notably patients with intra-abdominal
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5 inflammatory conditions as they will have likely have normal underlying hemostasis and
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7 fibrinolysis.
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10 The finding on liver biopsy of sinusoidal dilatation in 2/8 (25%) of JAK2V617F
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12 patients, despite radiological investigations confirming patent hepatic veins, may represent an
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14 important finding. The observed sinusoidal dilatation may be due to microthromboses of the
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16 hepatic venules in view of the absence of other features of nodular regenerative hyperplasia.
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18 MPD and latent MPD are the most frequent causes of BCS. (25) Sinusoidal dilatation without
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20 occlusion of the hepatic veins in patients with PSMVT may represent early BCS or part of the
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22 spectrum of progression to acute BCS. Subclinical BCS may in-part explain the worse liver
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24 synthetic function and increased mortality observed in patients with JAK2V617F associated
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26 disease even in the absence of overt BCS.
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30 In conclusion, the *JAK2V617F* mutation is frequently identified in patients previously
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32 labelled a having 'idiopathic thrombosis' of the portomesenteric veins. The *JAK2V617F*
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34 mutation places these patients at increased risk of thrombus extension causing gut ischemia
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36 and worsening portal hypertension without anticoagulation. Anticoagulation may reduce the
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38 risk of life-threatening variceal haemorrhage by prevention of thrombus extension in the
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40 mesenteric and collateral circulation. Identification of latent MPD may also be useful in
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42 identifying patients who require regular screening to monitor for progression to overt MPD.
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Tables:

Table 1. Etiology of Chronic PSM Venous Thrombosis and prevalence of *JAK2V617F*.

Etiology of PSMVT thrombosis	<i>JAK2V617F</i>	
	<i>n</i>	(%)
Myeloproliferative	7/7	(100%)
PRV	2	
ET*	3	
IMF	1	
MPD (unclassified)	1	
Idiopathic	7/17	(41.2%)
Congenital/ Umbilical vein sepsis	0/3	(0.0%)
Factor V Leiden*	1/3	(33.3%)
G/A Prothrombin mutation*	1/1	(100%)
Other*	0/4	(0.0%)
Total	16/35	(45.7%)

* 4 Patients on oral contraceptive pill at presentation.

Abbreviations: PRV polycythemia rubra vera, ET essential thrombocytosis,
MF myelofibrosis, MPD myeloproliferative disorder.

Table 2. Laboratory investigations at presentation comparing *JAK2V617F* vs Wild-type.

Laboratory variable (range)	<i>JAK2V617F</i> (<i>n</i> =16)	Wild-type (<i>n</i> =19)	<i>p</i> value
Mean Hemoglobin (g/dL)	12.5 (9.2-15.2)	11.3 (8.0-15.1)	0.04
Mean Hematocrit	0.38 (0.30-0.46)	0.35 (0.27-0.45)	0.04
Mean white cell count (x10 ⁹ /L)	10.0 (2.6-24.3)	5.1 (1.4-11.6)	0.002
Mean neutrophil count (x10 ⁹ /L)	7.7 (1.6-20.8)	3.4 (0.7-8.9)	0.001
Mean platelet count (x10 ⁹ /L)	290 (75-712)	171 (24-455)	0.05
Mean Bilirubin (μmol/L)	30.0 (5-182)	13.9 (2-29)	0.02
Mean Albumin (g/L)	37.9 (27-44)	38.5 (31-43)	0.43
Mean INR	1.18 (1.0-1.8)	1.06 (0.9-1.4)	0.01
Mean AST (U/L)	34 (16-70)	32 (21-55)	0.96

Table 3. Hematological investigations at presentation comparing latent MPD vs MPD

Laboratory variable	Latent MPD (<i>n</i> =9)	MPD (<i>n</i> =7)	<i>p</i> value
Mean Hemoglobin (g/dL)	12.9	11.9	0.27
SD (range)	1.2(11.2-15.2)	1.6 (9.2-14.0)	
Mean Hematocrit	0.39	0.37	0.40
SD (range)	0.03 (0.33-0.43)	0.06 (0.31-0.45)	
Mean white cell count (x10 ⁹ /L)	9.0	11.3	0.84
SD (range)	4.6 (2.6-18.1)	7.2 (4.5-24.3)	
Mean platelet count (x10 ⁹ /L)	267	320	0.63
SD (range)	192 (75-684)	236 (82-712)	

Table 4: Complications and outcome *JAK2V617F* vs Wild-type

Complication	<i>JAK2V617F</i>	Wild-type	<i>p</i> -value
1 ⁰ Variceal Bleed	10/16 (62.5%)	13/19 (68.4%)	0.73
2 ⁰ Variceal Bleed	3/16 (18.8%)	6/19 (31.6%)	0.46
Choledochal varices	4/16 (25.0%)	2/19 (10.5%)	0.38
Bowel infarction	2/16 (12.5%)	0/19 (0.0%)	0.20
Extrahepatic/PSMV thrombosis	2/16 (12.5%)	2/19 (10.5%)	1.00
Latent MPD to MPD	1/9 (11.1%)	0/19 (0.0%)	0.90
Death	4/16 (25.0%)	0/19 (0.0%)	0.04

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