Polycythemia vera: Emerging diagnostic and risk stratification criteria

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Disclosure

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Introduction to polycythemia vera (PV)

- A Philadelphia chromosome–negative myeloproliferative neoplasm (MPN)\(^1,2\)
- Characterized by trilineage hyperproliferation\(^3\)


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Clinical features of PV at presentation

Most patients present with 1 of 3 clinical scenarios:\(^1\)

- Diagnosis after a thrombotic event
- Diagnosis following presentation with disease-related symptoms
- Diagnosis by chance after routine blood work


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Erythrocytosis is the most prominent characteristic of PV\textsuperscript{1}

In 1,545 patients with PV, in addition to erythrocytosis\textsuperscript{2}:

- 49\% presented with leukocytosis
- 53\% presented with thrombocytosis


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# PV diagnostic criteria: Erythrocytes

## World Health Organization (WHO)

<table>
<thead>
<tr>
<th>Hemoglobin (Hb) levels</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb &gt;18.5 g/dL</td>
<td></td>
<td>&gt;16.5 g/dL or Hb or Hct &gt;99th percentile of reference range for age, sex, or altitude of residence or Hb &gt;17 g/dL (men) or &gt;15 g/dL (women) if associated with a sustained increase of ≥2 g/dL from baseline that cannot be attributed to correction of iron deficiency or Elevated red cell mass &gt;25% above mean normal predicted value</td>
</tr>
</tbody>
</table>

## British Committee for Standards in Haematology (BCSH)

<table>
<thead>
<tr>
<th>Hematocrit (Hct) levels</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct ≥60% (men) or ≥56% (women) in the absence of JAK2 mutation or Elevated red cell mass &gt;25% above mean normal predicted value</td>
<td>Men &gt;52%</td>
<td>Women &gt;48%</td>
</tr>
</tbody>
</table>

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Hb and Hct are surrogates for red cell mass (RCM)\(^1\)

RCM and plasma volume may vary independently of each other\(^2\)

- As the RCM expands, the plasma volume may also expand
- Hb and Hct levels might appear normal despite elevated RCM
- PV might not be apparent, even though the RCM may be elevated


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Patients may have an elevated RCM without meeting Hb or Hct criteria for PV

<table>
<thead>
<tr>
<th>Patients With RCM 25% Higher Than the Mean Predicted Value but not Meeting Hb or Hct Criteria for PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansson et al, 2005¹</td>
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<td>Cassinat et al, 2008²</td>
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<tr>
<td>Alvarez-Larrán et al, 2012³</td>
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<tr>
<td>Alvarez-Larrán et al, 2012³</td>
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<tr>
<td>Silver et al, 2013⁴</td>
</tr>
</tbody>
</table>


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Proposed revisions to diagnostic criteria for PV\textsuperscript{1}

**Major**

- Hb >16.5 g/dL for men, >16 g/dL for women
- Hct >49% for men, >48% for women
- Elevated RCM >25% above mean normal predicted value
- Bone marrow trilineage myeloproliferation with pleomorphic megakaryocytes
- Presence of \textit{JAK2V617F} or \textit{JAK2} exon 12 mutation

**Minor**

- Subnormal serum erythropoietin level

If adopted, PV diagnosis would require meeting either all 3 major criteria or the first 2 major criteria and 1 minor criterion.


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Stratification to predict risk for thrombosis and guide disease management

• High risk
  – Age >60 years or
  – Previous thrombotic event

• Low risk
  – Age ≤60 years and
  – No history of thrombosis

Does not predict survival, disease progression, or risk for leukemic/fibrotic transformation

* In the absence of extreme thrombocytosis (platelets >1,000 × 10⁹/L).


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## Emerging evidence for additional risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocytosis</td>
<td>Marchioli et al, 2013&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Landolfi et al, 2007&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Gangat et al, 2007&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Chou et al, 2013&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>Lim et al, 2015&lt;sup&gt;5&lt;/sup&gt;</td>
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<td></td>
<td>Bonicelli et al, 2013&lt;sup&gt;6&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Marchioli et al, 2013&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Tefferi et al, 2013&lt;sup&gt;7&lt;/sup&gt;</td>
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<td>Barbui et al, 2015&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td>Leukocytosis</td>
<td>Alvarez-Larrán et al, 2012&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Thrombocytosis</td>
<td>Vannucchi et al, 2007&lt;sup&gt;10&lt;/sup&gt;</td>
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<td></td>
<td>Passamonti et al, 2010&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>Mutational profile</td>
<td>Alvarez-Larrán et al, 2012&lt;sup&gt;9&lt;/sup&gt;</td>
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<tr>
<td>Hydroxyurea resistance</td>
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Conclusions

• Revised diagnostic criteria that lower thresholds for Hb and Hct levels may identify PV in some patients with borderline red cell parameters who may be at increased risk for thrombotic events

• Standard risk factors (age >60 years and history of thrombosis) will maintain their significance but are not prognostic for disease progression or overall survival

• Investigators continue to explore the associations of various potential risk factors with outcomes in PV

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