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Low-hemoglobin Polycythemia Vera: Diagnostic Criteria and Clinico-pathological Characterization

Marta Garrote

garrote@clinic.cat

Hospital Clinic de Barcelona https://orcid.org/0000-0001-8571-1466

Paula Sastre

Hospital Clinic de Barcelona

Bárbara Tazón-Vega

Hospital del Mar

Marta Santaliestra

Hospital Universitari Mutua Terrassa

Monica Lopez-Guerra

HOSPITAL CLINIC

Raquel Longarón

Hospital del Mar - IMIM

Eduardo Arellano-Rodrigo

Hospital Clínic https://orcid.org/0000-0001-6236-7826

Julia Álvarez-Doral

Hospital Clinic de Barcelona

Francisco Campos Añón

Hospital Clinic de Barcelona

Inmaculada Romero-Zayas

Hospital Clinic de Barcelona

Concepción Fernández-Rodríguez

Hoapital del Mar

Ana Triguero

Hospital Clínic Barcelona

Adriana Cuartas

Hospital Clinic de Barcelona

Francesca Guijarro

Hospital Clinic https://orcid.org/0000-0001-6376-0929

Jose Álamo

Hematopathology Section, Pathology Department, CDB, Hospital Clínic of Barcelona

Sandra Castaño-Díez

Hospital Clinic de Barcelona

Gerard Frigola

Hospital Clinic de Barcelona https://orcid.org/0000-0001-6794-6456

Olga Balague

Hospital Clinic https://orcid.org/0000-0002-5099-3675

Cecilia Grandi

Hospital Clinic de Barcelona

Carmen Rodríguez-Miñón

Hospital Clinic de Barcelona

Dolors Colomer

Hospital Clinic, CIBERONC https://orcid.org/0000-0001-7486-8484

Beatriz Bellosillo

Hospital del Mar

Maria Rozman

Hospital Clinic

Alberto Alvarez-Larran

Hospital Clínic https://orcid.org/0000-0001-6387-4619

Article

Keywords:

Posted Date: August 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10625663/v1

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Additional Declarations: Yes there is potential conflict of interest.

Abstract

Criteria for the diagnosis of polycythemia vera (PV) require evidence of erythrocytosis, defined by increased hemoglobin and/or hematocrit. Although the International Consensus Classification also recognizes increased red cell mass (RCM), it is not included in the World Health Organization classification and is not widely available. We characterized a group of patients harboring *JAK2* mutation with increased RCM, but hemoglobin/hematocrit values below diagnostic thresholds – referred to as low-hemoglobin PV (lhPV) – and evaluated red blood cell (RBC) count as a surrogate marker of RCM.

We analyzed 288 patients: 79 essential thrombocythemia (ET), 31 lhPV and 178 PV. lhPV displayed features between ET and PV, but clustered closely with PV. Splenomegaly and thrombosis at diagnosis were more frequent in lhPV. *JAK2*variant allele frequency (VAF) and high molecular risk abnormalities increased progressively from ET to lhPV and PV. In women, RBC count identified increased RCM with greater accuracy (AUC, 0.93) than hemoglobin, hematocrit or *JAK2*VAF. RBC thresholds of >5.6×10^12/L (women) and >5.9×10^12/L (men) showed high diagnostic performance.

lhPV represents a form of PV, with features closer to PV than ET. RBC count is an accurate surrogate marker of RCM and can improve recognition of PV patients who do not meet hemoglobin/hematocrit criteria.

INTRODUCTION

According to World Health Organization (WHO) and International Consensus Classification (ICC) criteria (1–4), the diagnosis of polycythemia vera (PV) requires the evidence of erythrocytosis, defined by elevated hemoglobin (Hb) concentration (> 165 g/L in men and > 160 g/L in women) or hematocrit (Hct) (> 49% in men and > 48% in women), together with supporting features, such as bone marrow histology, *JAK2* mutation and low erythropoietin (EPO) level. The ICC also allows the diagnosis based on increased red cell mass (RCM) measured by isotopic dilution techniques (5); however, this method is no longer included in WHO criteria and is rarely available in clinical practice (2, 6).

Although Hb and Hct thresholds were lowered in 2016 to improve diagnostic sensitivity and reduce underdiagnosis of PV (7–9), exclusive reliance on these surrogate markers may still fail to identify patients with true erythrocytosis in the biological continuum between *JAK2*-mutated essential thrombocythemia (ET) and PV (10). PV may be misclassified as ET or myeloproliferative neoplasm, unclassifiable (MPN-U), especially in patients with borderline values, a situation that might be more common in the early stage of PV – usually referred as masked PV (mPV) – women and patients presenting with splanchnic vein thrombosis (SVT) (6, 8, 11, 12). This diagnostic gap may lead to an inadequate thrombotic risk assessment and suboptimal prophylactic strategies, such as Hct control (8, 13–17).

The aim of our study was to characterize patients with *JAK2* V617F and increased RCM but Hb and Hct lower than diagnostic thresholds – referred to as low-hemoglobin PV (lhPV) – and to compare them with

a cohort of patients with analytic values compatible with ET and PV. We further aimed to identify a surrogate marker for RCM elevation, in order to improve diagnostic accuracy in patients with suspected PV but non-diagnostic Hb/Hct values (6).

MATERIALS AND METHODS

Patient selection and data collection

We retrospectively selected all patients diagnosed at our institution with a *JAK2* V617F-mutated myeloproliferative neoplasm (MPN) who did not meet criteria for primary myelofibrosis, from 2000 to 2025, and for whom complete clinical information was available, including RCM assessment, excepting for some patients with overt erythrocytosis (Hb > 185 g/l or Hct > 55.5% in men and Hb > 165 g/l or Hct > 49.5% in women). In PV, BM biopsy was not routinely performed at diagnosis until the publication of WHO 2016 classification, when histology became a major criterion for PV diagnosis.

To define the lhPV group, we included all patients with Hb and Hct levels below the threshold required to fulfill the first diagnostic criterion of the WHO/ICC (Hb < 165 g/L and hematocrit < 49% in men; Hb < 160 g/L and hematocrit < 48% in women), but with increased RCM assessed by isotopic dilution technique. The ET group included patients with a platelet count ≥ 450 × 10^9/L, Hb and Hct levels below the WHO/ICC diagnostic thresholds for PV, and no increase in RCM by isotopic dilution technique. The PV group included patients with Hb and Hct levels above the WHO/ICC diagnostic thresholds, regardless of RCM values (supplemental Figure S1).

The diagnosis of PV and ET was based on the 2022 WHO/ICC diagnostic criteria. Clinical, laboratory, genomic, and histopathological data were obtained from medical records. Informed consent was obtained from all patients. The study was approved by the Ethics Committee of Hospital Clínic de Barcelona (ref. HCB/2022/0945) and conducted in accordance with the Declaration of Helsinki.

RCM assessment

RCM was measured by isotopic dilution of [99mTc]Tc-autologous red blood cells (RBC). The test consists of drawing 10 mL of blood from the patient and labeling it with 3.7 MBq of [99mTc]Tc. After reaching circulating equilibrium, a second blood draw is performed. By calculating the isotopic dilution, using samples of a standard of known volume corrected for capillary Hct, the total cell volume and the potential volume are determined indirectly. Finally, the percentage variation of total cell volume and potential volume with respect to the expected value for a person of the same age, sex, and height is estimated, considering an increased total cell volume, or increased RCM, when this value is ≥ 125%.

Molecular analysis

DNA from peripheral blood samples stored in the Hematopathology Collection (Biobank Hospital Clínic-IDIBAPS; R121004-094) was used for assessment of *JAK2* V617F status and molecular profiling. *JAK2* V617F was evaluated by droplet digital polymerase chain reaction (ddPCR) using the Bio-Rad (Berkeley, California, USA) platform. Molecular profile was assessed using myeloid-focused Next-Generation Sequencing (NGS) panels, and only pathogenic or likely pathogenic variants were considered for further analysis. Depending on availability during the study period, NGS was performed using one of the following panels: the Customized Myeloid Solution Panel MIC_v1 (Sophia Genetics, Rolle, Switzerland), the Oncomine Myeloid Assay (ThermoFisher Scientific, Waltham, Massachussetts, USA), or the Oncomine Myeloid Assay GX v2 (ThermoFisher Scientific).

Genomic classification proposed by Grinfeld et al (18) was applied to all cases based on mutational data. Patients were hierarchically assigned to four molecular categories: (1) *TP53* disruption or aneuploidy; (2) ≥ 1 genetic aberration in chromatin or spliceosome genes (including *EZH2*, *IDH1*, *IDH2*, *ASXL1*, *PHF6*, *CUX1*, *ZRSR2*, *SRSF2*, *U2AF1*, *KRAS*, *NRAS*, *GNAS*, *CBL*, chr7/7q LOH, chr4q LOH, *RUNX1*, *STAG2*, and *BCOR*); (3) homozygous *JAK2* mutation (we used variant allele frequency [VAF] ≥ 50% as a surrogate); and (4) heterozygous *JAK2* mutation (VAF < 50%). Patients were classified as high molecular risk (HMR) when they belonged to the first three categories. Further details regarding molecular analysis are provided in the Supplementary Data.

Statistical analysis

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Kruskal–Wallis test, with post-hoc pairwise comparisons adjusted using the Bonferroni correction.

Receiver operating characteristic (ROC) curves were generated separately by sex, and the area under the curve (AUC) was calculated for the prediction of increased RCM using RBC count, Hb level, Hct, and *JAK2* VAF. Ninety-five percent confidence intervals (95% CI) for AUCs and comparisons between curves were obtained using the bootstrap method. The Youden index was used to determine optimal cut-off values for each variable. Based on these results, clinically meaningful thresholds for RBC count were proposed, prioritizing specificity to minimize PV false positives.

Survival analyses were performed using the Kaplan–Meier method, with comparisons assessed by the log-rank test. Cumulative incidence was evaluated using a competing-risk framework, considering death as a competing event for thrombosis and transformation to myelofibrosis or acute leukemia.

All tests were two-sided, with statistical significance defined at $p < 0.05$. All analyses and figures were performed using R software, version RStudio 2024.12.1 + 563 "Kousa Dogwood" (R core Team, R Foundation for Statistical Computing, Vienna, Austria). ChatGPT (OpenAI, LLC, San Francisco, United States) was used to identify and correct coding errors in the statistical analysis scripts.

RESULTS

Baseline characteristics

A total of 288 patients were included in the study: 79 in the ET group, 31 in the lhPV group and 178 in the PV group. Patient baseline characteristics are summarized in Table 1. Concordance with the original clinical diagnosis was high across all groups: 89% of patients in the ET group had been clinically diagnosed with ET, whereas 97% and 89% of patients in the lhPV and PV groups, respectively, had been clinically diagnosed with PV.

The median age was 61 years, with no significant differences among groups. Notably, women were overrepresented in the ET and lhPV groups, whereas men predominated in the PV group.

Hb and Hct levels differed significantly among groups. Post hoc pairwise comparisons with Bonferroni correction confirmed that these differences were maintained between the PV group and both the ET and lhPV groups. RBC counts also differed significantly across the three groups, with all pairwise comparisons remaining significant after correction. White blood cell counts were significantly higher in the PV group, whereas platelet counts were higher in the ET and lhPV groups. Serum EPO levels were below the lower limit of normal in 72% and 76% of patients with lhPV and PV, respectively, compared with 30% of patients with ET ($p < 0.001$). Among the 167 patients (94%) with available RCM measurement in the PV group, increased RCM was documented in 135 (81%).

Palpable splenomegaly at diagnosis was more frequent in the lhPV and PV groups (23% and 17%, respectively) than in the ET group (5%). Thrombotic events at MPN diagnosis were particularly frequent in the lhPV group (32%), compared with the ET (10%) and PV (23%) groups. Notably, 6 of the 10 thrombotic events observed in the lhPV group involved the splanchnic territory. The occurrence of splanchnic thrombosis was significantly associated with increased RCM (odds ratio, 2.5; 95% CI, 1.3–5.8, $p = 0.01$).

Molecular profiling and classification

The mean *JAK2* V617F VAF obtained by ddPCR (median time from diagnosis: 0 days; interquartile range [IQR]: -24 to 157 days) was 17%, 32%, and 40% in the ET, lhPV, and PV groups, respectively. Although VAF differed significantly among groups, post hoc pairwise analysis with Bonferroni correction showed that the difference remained significant only between the ET and PV groups. Distribution of *JAK2* V617F VAF across study groups is displayed in Fig. 1.

NGS data were available for 254 patients (median time from diagnosis: 54 days; IQR: − 61 to 805 days). The mean number of pathogenic or likely pathogenic mutations per patient was 1.4, with no significant differences among groups. The distribution of additional gene mutations across study groups is shown in supplemental Figure S2.

HMR categories were uncommon in the ET group, being identified in only 6% of patients, all of whom belonged to the splicing/chromatin category. In contrast, HMR categories were more frequent in the

lhPV group, with 15% of patients classified in the splicing/chromatin category and 8% in the homozygous *JAK2* category. The highest prevalence of HMR features was observed in the PV group, where 3% of patients belonged to the *TP53*/aneuploidy category, 11% to the splicing/chromatin category, and 25% to the homozygous JAK2 category (Fig. 2).

ROC curve analysis

RCM measurements were available for 277 patients, including all patients in the ET and lhPV groups and 167 (94%) patients in the PV group. Using these data, ROC curve analyses were performed separately by sex to identify surrogate markers of increased RCM. ROC curves with 95% CI were generated for Hb, Hct, *JAK2* V617F VAF, and RBC count using the bootstrap method.

In women, RBC count showed the highest discriminative ability, with an AUC of 0.93 (95% CI, 0.89–0.97), which was significantly higher than the AUCs for Hb (0.83, 95% CI, 0.75–0.89; $p = 0.01$), Hct (0.85, 95% CI, 0.78–0.91; $p = 0.027$), and *JAK2* V617F VAF (0.78, 95% CI, 0.70–0.86; $p = 0.0005$).

In men, RBC count also yielded the highest AUC (0.84, 95% CI, 0.75–0.90); however, the differences compared with Hb (AUC 0.73, 95% CI, 0.64–0.81; $p = 0.07$), Hct (AUC 0.79, 95% CI, 0.71–0.86; $p = 0.41$), and *JAK2* V617F VAF (AUC 0.79, 95% CI, 0.70–0.87; $p = 0.42$) did not reach statistical significance.

The sensitivity, specificity, positive predictive value, negative predictive value, and false-positive rate (1 − specificity) of the Hb and Hct thresholds included in the WHO and ICC diagnostic criteria are shown in Table 2. ROC curves are presented in supplemental Figure S3 and Figure S4.

A RBC count > 5.6×10^{12}/L in women and > 5.9×10^{12}/L in men demonstrated greater diagnostic accuracy for increased RCM than the Hb and Hct thresholds currently included in the WHO and ICC diagnostic criteria (Table 2).

Bone marrow histology

Complete histologic information at diagnosis was available for 153 patients: 73 (92%) in the ET group, 15 (48%) in the lhPV group, and 65 (37%) in the PV group. A histological diagnosis of PV was reported in 33% and 43% of cases in the lhPV and PV groups, respectively, compared with only 5% in the ET group ($p < 0.001$). Post hoc analyses showed significant differences between ET and lhPV (adjusted $p = 0.02$), and between ET and PV (adjusted $p < 0.001$). Conversely, a histopathological diagnosis of ET was more frequent in the ET group (60%) than in the lhPV (40%) and PV (25%) groups ($p < 0.001$). In post hoc analyses, this difference remained significant only between the ET and PV groups.

Notably, bone marrow morphology was considered normal in 18%, 13%, and 20% of cases in the ET, lhPV, and PV groups, respectively, with no significant differences between groups. In addition, a substantial proportion of cases were classified as MPN without a definitive histological diagnosis, accounting for

16%, 13%, and 12% of cases in the ET, lhPV, and PV groups, respectively. Detailed findings are presented in Fig. 4 and supplemental Table S1.

Thrombosis, disease progression, and survival analysis

After a median follow-up of 7.0 years (IQR, 3.1–12.4), with no significant differences in follow-up duration between groups, a trend toward a higher incidence of thrombosis was observed in the lhPV and PV groups, although statistical significance was not reached (cumulative incidence of thrombosis accounting for the competing risk of death; Gray's test $p = 0.17$). The cumulative incidence of thrombosis at 5 years was 4.2%, 7.5%, and 12.6% in the ET, lhPV, and PV groups, respectively. A similar pattern was observed for progression to myelofibrosis (Gray's test $p = 0.06$). The cumulative incidence of myelofibrosis at 15 years was 3.3%, 16.9%, and 16.2% in the ET, lhPV, and PV groups, respectively. The cumulative incidence of transformation to acute leukemia was low across all three groups (Gray's test $p = 0.62$). At 5 years, the cumulative incidence was 0%, 3.9%, and 1.4%, whereas at 15 years it was 4.5%, 3.9%, and 8.5% in the ET, lhPV, and PV groups, respectively (supplemental Figures S5-S7).

Regarding overall survival, Kaplan-Meier analysis showed no significant differences between groups (log-rank test, $p = 0.085$). However, a trend toward shorter survival was observed in the lhPV and PV groups compared with ET, with median overall survival of 16 and 17 years, respectively, whereas median survival was not reached in ET (supplemental Figure S8).

HMR abnormalities were associated with a significantly increased risk of myelofibrotic transformation and trends toward higher cumulative incidences of thrombosis and leukemic transformation, as well as inferior overall survival (supplemental Figures S9-S12).

DISCUSSION

PV and ET harboring *JAK2* V617F constitute a biological continuum, and the distinction between these entities may be particularly challenging in patients with overlapping hematological and molecular characteristics (10, 12). The key clinical objective is to accurately identify patients according to their thrombotic risk, enabling appropriate therapeutic decisions, particularly regarding hematocrit control, which remains a cornerstone of PV management (15, 16). In the present study, we analyzed a large cohort of *JAK2*-mutated PV and ET patients, followed at a single institution. RCM, routinely used in our clinical practice, was included as a criterion for PV definition.

Patient classification based on Hb, Hct and RCM demonstrated high concordance with original clinical diagnosis, supporting the validity of this approach. In our work, we defined those with increased RCM but Hb/Hct below PV thresholds as lhPV, deliberately avoiding the term mPV, as this concept has been inconsistently defined across studies, frequently relying on bone marrow histology and Hb/Hct thresholds that have changed over time (6, 9, 19–22).

This approach identified three distinct groups: both ET and lhPV groups were markedly enriched in women, whereas overt PV showed a slight male predominance. Platelet counts were higher in ET and lhPV groups, as previously reported (12, 17, 22). At diagnosis, splenomegaly and thrombosis were significantly more frequent in lhPV and PV than in ET, in agreement with previous findings (17, 21). Moreover, molecular differences were observed across groups: *JAK2* VAF and the prevalence of HMR aberrations increased progressively from ET to lhPV and PV, supporting the intermediate position of lhPV between ET en PV, consistent with previous reports (6, 12, 17).

However, several of our observations strongly support classifying lhPV as PV in clinical practice. Firstly, lhPV exhibited true erythrocytosis as demonstrated by increased RCM. Secondly, this subgroup was predominantly female, and ROC analyses showed that conventional Hb and Hct thresholds have lower sensitivity in women than in men, as previously reported (6, 8). In the third place, thrombotic events at diagnosis occurred at frequencies comparable to, or even exceeding, those observed in PV. Taken together, these findings suggest the reliance on Hb/Hct alone may lead to under-recognition of PV.

Because RCM measurement is unavailable in many institutions and was removed from 2022 WHO diagnostic criteria, we explored RBC count as a surrogate marker of increased RCM. Of note, RBC count in women demonstrated superior diagnostic performance compared with Hb, Hct and *JAK2* VAF for identifying true erythrocytosis. Based on our data, a RBC count threshold > 5.6×10^12/L in women provided both sensitivity and specificity above 80%, whereas a threshold > 5.9×10^12/L in men achieved a high specificity (87%) despite lower sensitivity. These results support the incorporation of RBC count into future unified diagnostic criteria for PV. Such an approach may be particularly valuable in women, patients with iron deficiency and those presenting with SVT, all of whom may exhibit relatively low Hb/Hct values despite having true erythrocytosis and an increased thrombotic risk (11, 12, 22, 23).

Previous studies have consistently shown a higher *JAK2* VAF in PV than in ET, a difference attributed to loss of heterozygosity and the preferential expansion of the *JAK2*-mutated clone within hematopoiesis (12, 24, 25). In our cohort, lhPV displayed a mean *JAK2* VAF intermediate between ET and PV; however, its overall distribution more closely resembled that of PV, further supporting its biological proximity to the PV phenotype. These observations raise the possibility that *JAK2* VAF could contribute to future diagnostic algorithms. In particular, a *JAK2* VAF higher than 40% was identified as highly specific of true erythrocytosis in our series and therefore warrant consideration as a minor diagnostic criterion. Beyond *JAK2* VAF, the overall molecular profile may also provide valuable diagnostic information. In our cohort, HMR categories showed a distinct distribution across disease entities, consistent with previous reports (18). Whereas HMR was uncommon in ET (6%), it was more frequently observed in lhPV (23%) and PV (39%), suggesting that comprehensive molecular profiling may be helpful in distinguishing these entities.

The role of BM biopsy in PV diagnosis deserves particular attention. The concept of mPV has relied heavily on the identification of PV-like histological features despite Hb/Hct values below conventional diagnostic thresholds (6, 19, 22, 26). For this reason, we evaluated the histopathological findings within our cohort. Bone marrow data were available for a substantial proportion of patients, and although

biopsies were not centrally re-reviewed for the present study, most had originally been assessed in consensus by two expert hematopathologists at a referral center.

A notable observation was the relatively poor concordance between histological diagnosis and both clinical classification and study groups, particularly among lhPV and PV patients, supporting previous findings (27). While histological diagnosis of PV was exceptionally uncommon in ET group, supporting the role of BM biopsy in excluding PV in this setting, its sensitivity for confirming both lhPV and PV appeared limited. In contrast, low EPO levels showed substantially better concordance with clinical classification. These findings suggest that BM biopsy should not necessarily retain its current prominence among PV diagnostic criteria (1, 2). Patients with a thrombotic risk profile characteristic of PV may exhibit only subtle or non-specific marrow abnormalities, especially during early disease stages, as frequently observed in lhPV. Of note, BM biopsy retains an important role in excluding myelofibrosis in this context (9).

Accordingly, confirmation of erythrocytosis together with *JAK2* mutation should remain the cornerstone of diagnosis. In this context, a low serum EPO and/or a high *JAK2* VAF level may be sufficient as minor diagnostic criteria, potentially replacing the need for mandatory histological confirmation in many cases. Such an approach could reduce the number of patients who remain classified as ET or MPN-U, despite having biological and clinical features more consistent with PV.

Long-term outcomes further support this classification strategy. Overall survival and thrombotic outcomes were comparable across groups and remained favorable in a cohort in which RCM assessment enabled accurate recognition and management of patients with lhPV, consistent with prior observations (17). In our cohort we did not identify a higher incidence of transformation in lhPV compared to PV, as previously reported (19, 22), and our findings are congruent with the intermediate molecular profile (18).

One limitation of our study is that patient stratification was based exclusively on the first WHO/ICC diagnostic criterion (Hb and Hct thresholds or increased RCM), rather than on the complete set of diagnostic criteria. This approach was deliberately chosen to specifically evaluate the discriminatory value of this criterion and to explore the contribution of RCM measurement in the context of the most recent criteria. Consequently, a small proportion of patients in each group have been misclassified, potentially introducing a bias into the analyses. Another limitation is the incomplete availability of BM biopsy data, mainly among PV cases. A substantial proportion of these patients lacked BM histology because the biopsy had been performed at another institution or, more commonly, because it was a minor criterion before 2016. This may also have introduced a bias, as patients with the highest Hb/Hct values – those with an overt PV – were the ones in whom BM examination was least frequently performed. It should also be acknowledged that our institution is a referral center for patients with splanchnic thrombosis, which may have led to the overrepresentation of this subgroup in our cohort.

In conclusion, lhPV exhibits clinical, molecular, and hematological characteristics intermediate between ET and PV. Nevertheless, the overall integration of erythrocytosis evidence, thrombotic risk, molecular

features, and histopathological findings indicates that these patients are more appropriately classified as PV. Incorporation of RBC count into future diagnostic criteria, together with reconsideration of the role of BM morphology – potentially as a minor supportive criterion – and greater consideration of biological markers such as *JAK2* VAF and serum EPO levels, may improve diagnostic accuracy and ensure that patients receive management strategies aligned with their true thrombotic risk.

Declarations

Competing Interests: Marta Garrote has received honoraria for lectures from Novartis and travel support to attend scientific meetings. Beatriz Bellosillo has received honoraria for speaking and consultancy of advisory roles from Qiagen and ThermoFisher. The remaining authors declare no competing interests.

ACKNOWLEDGEMENTS

This work was funded by Instituto de Salud Carlos III (ISCIII) through the projects PI21/000231 and PI23/000626.

AUTHOR CONTRIBUTIONS

MG conceived and designed the study, collected data, performed statistical analyses, interpreted molecular and clinical data, and wrote the manuscript. PS contributed to data collection and data visualization. BTV, MLG, CFR, FG, SCD, and DC contributed to molecular data interpretation. MS, EAR, AT, AC, CG, and CRM contributed to data collection and clinical data interpretation. RL was responsible for sample management. JA, GF, OB, and MR contributed to bone marrow biopsy interpretation. BB contributed to molecular data interpretation and sample coordination. MLG, MR, and AAL contributed to manuscript writing. AAL conceived and designed the study, secured funding, contributed to data collection and interpretation, and supervised the project. All authors critically revised the manuscript and approved the final version for publication.

COMPETING INTERESTS

MG has received honoraria for lectures from Novartis and travel support to attend scientific meetings. BB has received honoraria for speaking and consultancy of advisory roles from Qiagen and ThermoFisher. The remaining authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Tables

Tables 1 and 2 are available in the supplementary files section

Figures

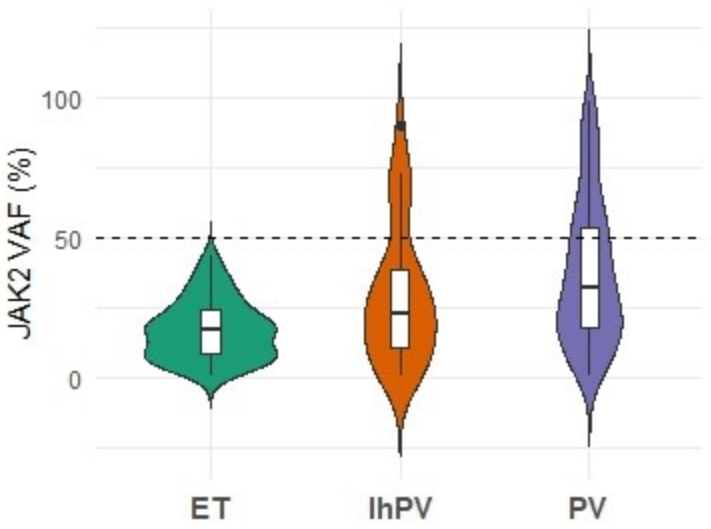


Figure 1

Distribution of *JAK2* V617F VAF across study groups

Violin plus boxplots showing the distribution of *JAK2* V617F VAF in patients in ET, lhPV and PV groups. A VAF ≥50% was not observed in the ET group, whereas it was observed in 17% of the lhPV group and in 30% of the PV group. Abbreviations: VAF, variant allele frequency; ET, essential thrombocythemia; lhPV, low hemoglobin polycythemia vera; PV, polycythemia vera.

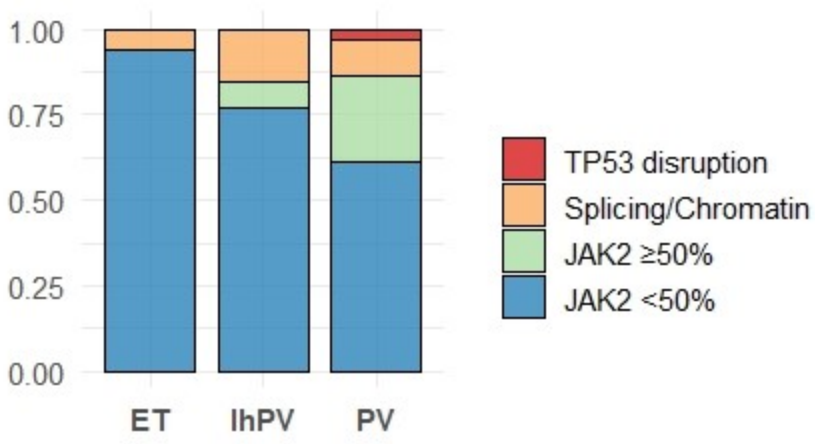


Figure 2

Proportion of patients in each genomic category across study groups

Proportion of patients in each genomic category. ET group: *TP53* disruption, 0%; Splicing/Chromatin, 6%; *JAK2* ≥50%, 0%; *JAK2* <50%, 94%. LhPV group: *TP53* disruption, 0%; Splicing/Chromatin, 15%; *JAK2* ≥50%, 8%; *JAK2* <50%, 77%. PV group: *TP53* disruption, 3%; Splicing/Chromatin, 11%; *JAK2* ≥50%, 25%; *JAK2* <50%, 62%. TP53 disruption, aberration in chromatin or spliceosome genes and JAK2 allele frequency ≥50% were considered high molecular risk categories. Abbreviations: ET, essential thrombocythemia; lhPV, low hemoglobin PV; PV, polycythemia vera.

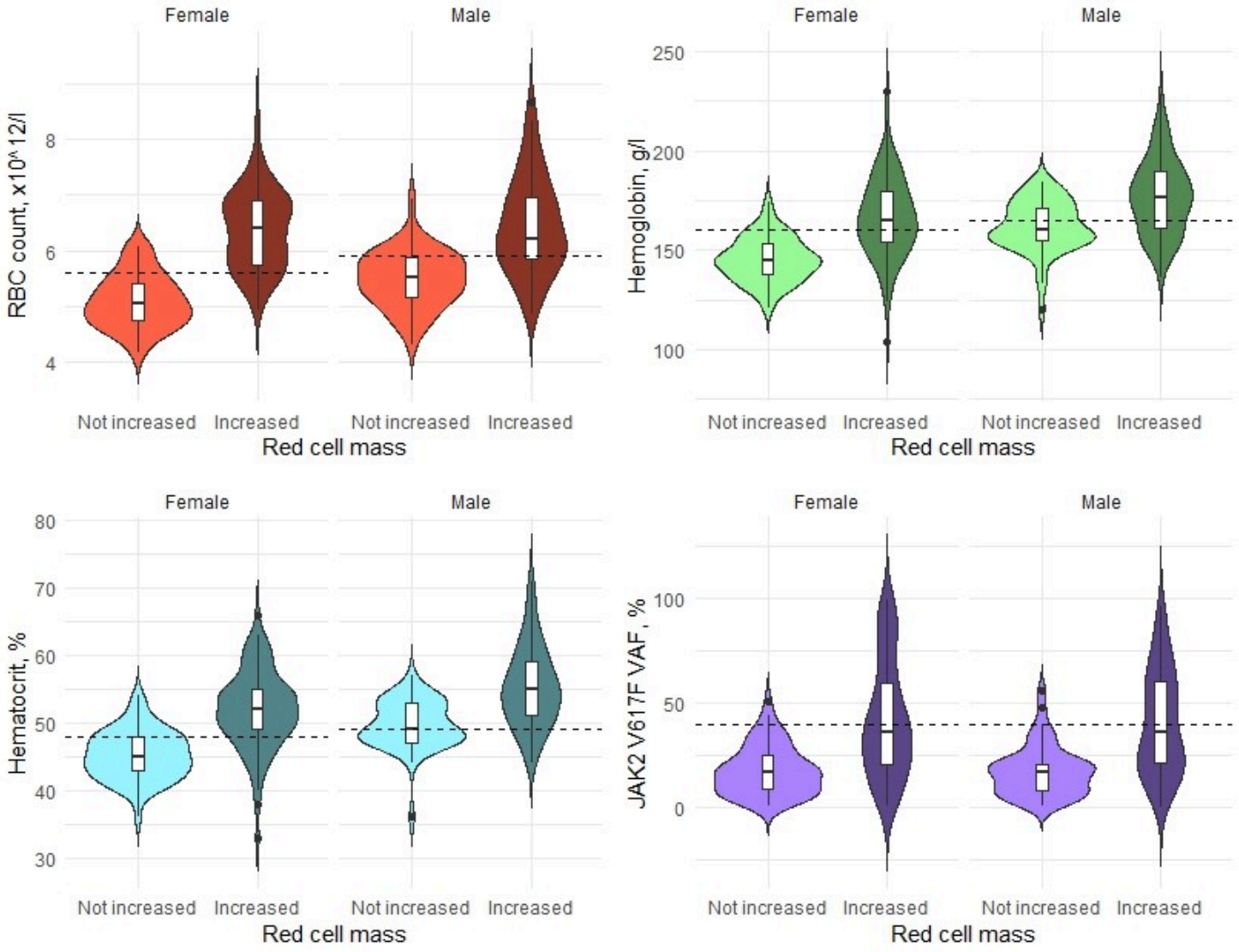


Figure 3

Distribution of the studied surrogate markers for increased red cell mass according to sex

Violin and box plots illustrating the distribution of RBC count, hemoglobin, hematocrit, and *JAK2* V617F VAF according to the presence or absence of increased red cell mass. As most of these variables are sex-dependent, distributions are shown separately for women and men.

Dashed lines indicate the current diagnostic thresholds for Hb (160 g/L in women and 165 g/L in men) and Hct (48% in women and 49% in men), as well as the proposed cut-off values that may aid in the differential diagnosis of PV and ET for RBC count (5.6×10^{12}/L in women and 5.9×10^{12}/L in men) and *JAK2* V617F VAF (40%).

Abbreviations: RBC, red blood cells; VAF, variant allele frequency; PV, polycythemia vera; ET, essential thrombocythemia.

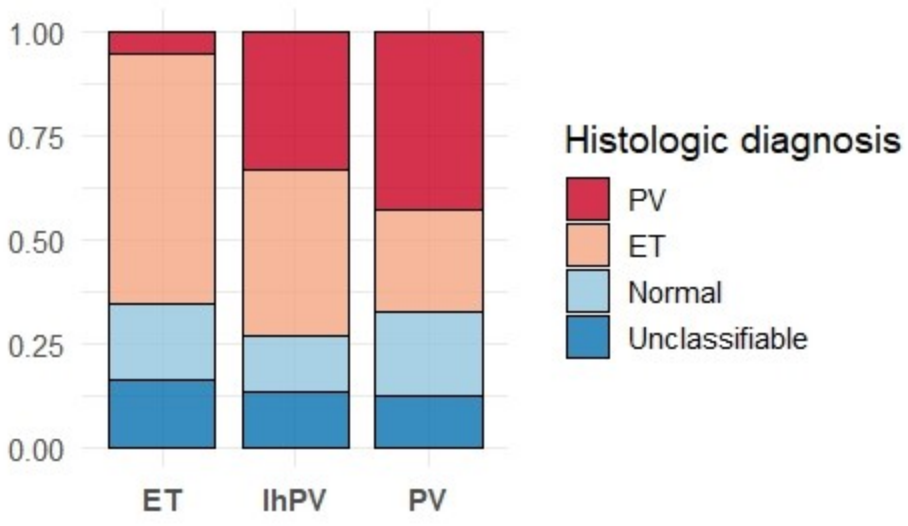


Figure 4

Proportion of patients with each histological diagnosis across the study groups

Bar plot showing the distribution of histological diagnoses according to the study groups. A histological diagnosis of PV was uncommon in the ET group (5%) compared with the lhPV and PV groups (33% and 43%, respectively). Notably, the majority of patients fulfilling the first diagnostic criterion for PV (lhPV and PV groups) did not have a definitive histopathological diagnosis of PV on bone marrow biopsy.

Bone marrow morphology was considered normal in a substantial proportion of patients, accounting for 18%, 13%, and 20% of cases in the ET, lhPV, and PV groups, respectively. In addition, a considerable proportion of biopsies showed features consistent with a MPN but without sufficient characteristics to establish a specific histological subtype, representing 16%, 13%, and 12% of cases in the ET, lhPV, and PV groups, respectively.

Abbreviations: ET, essential thrombocythemia; lhPV, low hemoglobin polycythemia vera; PV, polycythemia vera; MPN, myeloproliferative neoplasm.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- GarroteetalSupplementarydata.pdf
- GarroteetalTable1.xlsx
- GarroteetalTable2.xlsx